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# Treatment of Adult Patients With Chronic Immune Thrombocytopenia After Failure of First-Line Therapies

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# Table of Contents

<b>Abbreviations .....</b>	<b>7</b>
<b>Key Messages.....</b>	<b>8</b>
<b>Executive Summary.....</b>	<b>9</b>
Background and Policy Context .....	9
Clinical Evidence.....	9
Economic Evidence .....	9
Limitations .....	9
Conclusions and Implications for Decision-Making or Policy-Making .....	10
<b>Introduction and Rationale .....</b>	<b>10</b>
Background and Rationale.....	10
Summary of Patient Group Input.....	12
<b>Objectives.....</b>	<b>15</b>
<b>Policy Questions .....</b>	<b>15</b>
<b>Research Questions.....</b>	<b>15</b>
Clinical Evaluation .....	15
Economic Analysis .....	15
<b>Methods.....</b>	<b>15</b>
<b>Opportunities for Stakeholder Feedback.....</b>	<b>16</b>
<b>Clinical Review .....</b>	<b>16</b>
Literature Search Methods .....	16
Eligibility Criteria.....	17
Population and Subgroups .....	18
Intervention and Comparators.....	18
Outcomes Definition.....	19
Study Designs .....	19
Study Selection Process .....	19
Quality Assessment .....	19
Data Analyses and Synthesis .....	20

<b>Results of Clinical Evaluation .....</b>	<b>21</b>
Selection of Primary Studies .....	21
Study and Patient Characteristics .....	21
Summary of Critical Appraisal .....	28
Data Analysis and Synthesis .....	30
<b>Economic Analysis .....</b>	<b>31</b>
Economic Evaluation .....	31
<b>Discussion .....</b>	<b>32</b>
Summary of Evidence .....	32
<b>Conclusions and Implications for Decision-Making or Policy-Making .....</b>	<b>34</b>
<b>References .....</b>	<b>36</b>
<b>Appendix 1: Literature Search Strategy .....</b>	<b>39</b>
<b>Appendix 2: Statistical Analysis Plan .....</b>	<b>46</b>
<b>Appendix 3: List of Included Studies .....</b>	<b>53</b>
<b>Appendix 4: List of Excluded Studies During Data Extraction .....</b>	<b>54</b>
<b>Appendix 5: Network Meta-Analysis .....</b>	<b>55</b>
<b>Appendix 6: Summary Tables of Studies With Eltrombopag as Intervention .....</b>	<b>57</b>
<b>Appendix 7: Summary Tables of Studies With Avatrombopag as Intervention ...</b>	<b>72</b>
<b>Appendix 8: Summary Tables of Studies With Romiplostim as Intervention .....</b>	<b>79</b>
<b>Appendix 9: Summary Tables of Studies With Interventions Other Than TPO-RA .....</b>	<b>92</b>
<b>Appendix 10: Critical Appraisal .....</b>	<b>100</b>
<b>Appendix 11: Economic Evaluation .....</b>	<b>107</b>

## List of Tables

Table 1: Immunosuppressive Drugs Without Guideline Recommendations.....	11
Table 2: Selection Criteria.....	17
Table 3: High-Level Study Characteristics.....	24
Table 4: Outcomes Assessing Platelet Count Response .....	25
Table 5: Additional Outcomes .....	26
Table 6: Syntax Guide .....	39
Table 7: List of Excluded Studies During Data Extraction .....	54
Table 8: Details of Included Studies – Eltrombopag as Intervention (N = 4 Studies) .....	57
Table 9: Patient Characteristics – Eltrombopag as Intervention (N = 4 Studies).....	60
Table 10: Patient Disposition – Eltrombopag as Intervention (N = 4 Studies) .....	62
Table 11: Summary of Key Efficacy Outcomes – Eltrombopag as Intervention (N = 4 Studies) .....	65
Table 12: Summary of Key Harms Outcomes – Eltrombopag as Intervention (N = 4 Studies) .....	69
Table 13: Details of Included Studies – Avatrombopag as Intervention (N = 1 Study) .....	72
Table 14: Patient Characteristics – Avatrombopag as Intervention (N = 1 Study) .....	73
Table 15: Patient Disposition – Avatrombopag as Intervention (N = 1 Study).....	74
Table 16: Summary of Key Efficacy Outcomes – Avatrombopag as Intervention (N = 1 Study) .....	76
Table 17: Summary of Key Harms Outcomes – Avatrombopag as Intervention (N = 1 Study) .....	77
Table 18: Details of Included Studies – Romiplostim as Intervention (N = 3 studies) .....	79
Table 19: Patient Characteristics – Romiplostim as Intervention (N = 3 studies).....	81
Table 20: Patient Disposition – Romiplostim as Intervention (N = 3 studies).....	81
Table 21: Summary of Key Efficacy Outcomes – Romiplostim as Intervention (N = 3 Studies) .....	85
Table 22: Summary of Key Harms Outcomes – Romiplostim as Intervention (N = 3 Studies) .....	89
Table 23: Details of Included Studies – Interventions other than TPO-RA (N = 2 Studies) .....	92
Table 24: Patient Characteristics – Interventions Other Than TPO-RA (N = 2 Studies).....	93
Table 25: Patient Disposition – Interventions Other Than TPO-RA (N = 2 Studies).....	94
Table 26: Summary of Key Efficacy Outcomes – Interventions Other Than TPO-RA (N = 2 Studies).....	97
Table 27: Summary of Key Harms Outcomes – Interventions Other Than TPO-RA (N = 2 Studies).....	98
Table 28: Critical Appraisal of Included Studies .....	100
Table 29: Summary of ITP Decision-Analytic Models.....	108

Table 30: Model Input Parameters That Were Successfully Identified and Sourced.....	111
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Table 31: Treatment Costs That Were Successfully Identified and Sourced .....	112
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## List of Figures

Figure 1: Flow Chart of the Selection Process .....	22
---	----

Figure 2: Network for Platelet Count Response Using the Most Encompassing Threshold (20 Thousand or More Platelets) .....	30
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Figure 3: Risk of Bias Assessments Per Outcome Within Each Study (Jurczak, Arnold, Yang, Ghanima, Shirasugi) .....	104
--	-----

Figure 4: Risk of Bias Assessments Per Outcome Within Each Study (Kuter 2010, Bussel 2018, Eisai, Cheng) .....	105
--	-----

Figure 5: Risk of Bias Assessments Per Outcome Within Each Study (Tomiyaama, Kuter 2008, Kuter 2009, Kuter, 2010, Kuter 2011, Bussel 2009) .....	106
--	-----

Figure 6: Diagram of the Ideal Model.....	110
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## Abbreviations

<b>AE</b>	adverse event
<b>DB</b>	double blind
<b>HRQoL</b>	health-related quality of life
<b>HTA</b>	health technology assessment
<b>ITP</b>	immune thrombocytopenia
<b>ITT</b>	intent to treat
<b>IVIG</b>	IV immunoglobulin
<b>NMA</b>	network meta-analysis
<b>OL</b>	open label
<b>RCT</b>	randomized controlled trial
<b>SAE</b>	serious adverse event
<b>TPO-RA</b>	thrombopoietin receptor agonist

## Key Messages

- **What is the issue?**
  - Immune thrombocytopenia (ITP) is an autoimmune disorder characterized by low platelets and an increase in bleeding risk. It has an incidence rate of 3.3 per 100,000 adults per year.
  - After first-line corticosteroid treatment, there is limited evidence on the best subsequent-line therapies based on evidence of low certainty. Subsequent therapies after failure of corticosteroid use include several treatments, such as rituximab, eltrombopag, romiplostim, fostamatinib, avatrombopag, and splenectomy.
  - The goal of treatment is to reduce bleeding and prolong life. Increases in platelet count are considered a surrogate to these treatment goals.
- **What did we do?**
  - We conducted a narrative review of 15 publications (10 randomized controlled trials) found through a systematic literature search.
  - The review addressed the following policy questions:
    - What treatment(s) should be used in adult patients with ITP who have failed first-line treatments?
    - What is the place in therapy of splenectomy in adult patients with ITP?
- **What did we find?**
  - We found that eltrombopag and romiplostim increased platelet count response and improved ITP symptoms and health-related quality of life compared to placebo.
  - Interpretation of the effectiveness of avatrombopag, rituximab, and fostamatinib was inconclusive due to the limited availability of evidence and varying risks of bias in the trials.
  - There was a lack of evidence in specific subgroups of patients and on the role of splenectomy in the sequency of subsequent-line therapies.
  - Further research is needed to compensate for clinical data gaps to inform an appropriate and relevant economic evaluation.
- **What does this mean?**
  - CADTH suggests that jurisdictions may consider requesting that an implementation advice panel be conducted to bring together clinical experts to suggest measures (e.g., discontinuation criteria) to manage the clinical and economic uncertainty identified in this report.



## Executive Summary

### Background and Policy Context

Immune thrombocytopenia (ITP) is an autoimmune disorder characterized by low platelets and an increase in bleeding risk,<sup>1-4</sup> with a reported incidence rate varying between 2 and 4 per 100,000 adults per year according to various epidemiological studies around the world.<sup>5</sup> Severe bleeding, such as in the gastrointestinal tract or in the brain, is seen in approximately 10% of adults.<sup>6,7</sup> First-line therapy is a short course of corticosteroids;<sup>8</sup> alternatively, IV immunoglobulin (IVIG) and anti-D immunoglobulin may be used in patients who are unresponsive or have a contraindication to taking corticosteroids.<sup>8</sup> Recommendations for subsequent-line therapies are based on evidence of low certainty.<sup>8</sup> Therefore, a systematic review was undertaken at the request of public drug plans to determine the efficacy and safety of subsequent-line therapies – that is, rituximab, eltrombopag, romiplostim, fostamatinib, avatrombopag, and splenectomy – in adult patients with ITP who have failed first-line treatments.

### Clinical Evidence

The research protocol was developed a priori, by engaging with patient groups, and the systematic review used robust methodology. A total of 15 publications met the final inclusion criteria, reporting findings from 10 unique trials. The study populations in the trials were considered generalizable to most ITP patients and the concomitant use of other ITP medications was allowed. A narrative synthesis was conducted due to clinical heterogeneity between studies and methodological constraints that precluded a network meta-analysis (NMA).

Findings from 4 randomized controlled trials (RCTs) showed that, compared to placebo, eltrombopag generated a long-lasting platelet count response (at least 6 weeks and up to 6 months) and improved health-related quality of life (HRQoL), in addition to reducing bleeding events and the need for rescue medication. In 3 RCTs, romiplostim increased platelet count response, improved ITP symptoms and HRQoL, and reduced the need for rescue medication compared to placebo or standard of care. Interpretation of the effectiveness of avatrombopag, rituximab, and fostamatinib was inconclusive due to the limited availability of evidence, which was 1 single trial for each intervention, with varying risks of bias.

Due to a scarcity of evidence, conclusions could not be drawn for the clinically meaningful outcomes of emergency department visits, hospitalization, and treatment-free remission.

### Economic Evidence

An economic evaluation could not be conducted due to significant clinical data gaps, including the methodological limitations precluding assessment of comparative treatment efficacy in an NMA. Therefore, the comparative cost-effectiveness of treatments for ITP is unknown.

### Limitations

No head-to-head study, or study with comparisons to splenectomy, was identified from the literature search. Methodological consideration prevented an NMA from being conducted. As such, direct comparisons of

effectiveness between ITP treatments cannot be made. Similarly, there was insufficient evidence to inform the efficacy or sequence of subsequent-line therapies in subgroups of adult patients with ITP or the role of splenectomy in the sequency of subsequent-line therapies.

The narrative review was limited by availability of evidence. The risk of bias across the 10 studies ranged from low<sup>9-11</sup> to high.<sup>12-15</sup> An overall limitation of the included trials was the small sample size, which limited the level of precision and affected the certainty in the findings.

## Conclusions and Implications for Decision-Making or Policy-Making

Considering that the evidence of a clinical benefit was restricted to eltrombopag or romiplostim, public drug plans may want to consider revisiting reimbursement criteria for ITP. CADTH suggests that interested jurisdictions request an implementation advice panel to suggest strategies (e.g., discontinuation criteria) to manage the clinical and economic uncertainty identified in the report.

## Introduction and Rationale

### Background and Rationale

ITP is an autoimmune disorder characterized by low platelets and an increase in bleeding risk due to increased platelet destruction and impaired platelet production.<sup>1-4</sup> It was previously called “idiopathic thrombocytopenic purpura,” but is no longer considered to be an idiopathic disease.<sup>1,4</sup> The specific cause of ITP is unknown but may be a mix of genetic and environmental factors.<sup>16</sup> In addition, not all patients will experience bleeding symptoms such as purpura (hemorrhages in the skin and mucous membranes).<sup>16</sup> Symptoms associated with ITP are excessive bruising, superficial bleeding that appears as reddish spots on the skin (petechiae), bleeding from the gums or nose, blood in urine or stool, and unusually heavy menstrual flow; however, ITP may present with no signs or symptoms.

Primary ITP is defined as isolated thrombocytopenia — that is, peripheral blood platelet count less than  $100 \times 10^9/L$  — in the absence of other causes or disorders that may be associated with thrombocytopenia.<sup>1</sup> The disorder falls into 1 of the following 3 disease groups according to disease duration:

- Newly diagnosed ITP: active disease duration of 0 to 3 months
- Persistent ITP: active disease duration of 3 to 12 months, including those patients who do not reach spontaneous remission or do not maintain complete response of therapy<sup>1</sup>
- Chronic ITP: ongoing, active disease lasting longer than 12 months<sup>1</sup>

Spontaneous remission may occur when there is an improved platelet count in the absence of ongoing or recent therapy, which occurs in 45% of adults at 6 months and 49% of adults at 12 months. Among those with chronic ITP, 30% of adults achieve spontaneous remission at 24 months.<sup>17</sup>

ITP has a reported incidence rate varying between 2 and 4 per 100,000 adults per year according to various epidemiological studies around the world.<sup>5</sup> Bleeding symptoms are often present, including severe bleeding

(such as in the gastrointestinal tract or the brain) in approximately 10% of adults.<sup>6,7</sup> At least 1 comorbid condition is reported in more than 30% of patients.<sup>7</sup>

First-line therapy for newly diagnosed adult patients, according to both the *American Society of Hematology 2019 Guidelines for Immune Thrombocytopenia*<sup>8</sup> and the *Updated international consensus report on the investigation and management of primary immune thrombocytopenia*,<sup>18</sup> is a short course (approximately 6 weeks) of corticosteroids. For patients with ITP who are unresponsive or have a contraindication to taking corticosteroids, other first-line therapies include IVIG and anti-D immunoglobulin.<sup>8</sup> The international standardized definition<sup>1</sup> of a platelet response is a platelet count of  $30 \times 10^9/L$  or higher with at least a 2-fold increase in platelet count from baseline and an absence of bleeding, while a platelet count of  $100 \times 10^9/L$  or higher would typically be considered a complete response as long as there is an absence of bleeding.<sup>1</sup>

Patients who do not respond to first-line treatment within the first 3 months, or who are corticosteroid-dependent, will have a disease duration that falls within the persistent ITP category and may benefit from second-line treatment options.<sup>19</sup> These include thrombopoietin receptor agonists (TPO-RA) romiplostim and eltrombopag, as well as rituximab.<sup>19</sup> After 12 months of ongoing, active disease, patients are considered to have chronic disease and, in addition to second-line treatment options, become candidates for splenectomy.<sup>8</sup> The choice of treatment will be based on patient preferences, such as whether they prefer a durable response, or if they would rather avoid long-term medication or avoid surgery.

Refractory ITP is characterized by nonresponse to splenectomy, or relapse after surgery, and either severe ITP or a high risk of bleeding that requires continued subsequent therapy.<sup>1</sup> Treatments may include 1 of the following: TPO-RAs (i.e., eltrombopag, avatrombopag, or romiplostim), spleen tyrosine kinase inhibitor fostamatinib, or rituximab.<sup>18</sup>

There are other second-line treatment options, including azathioprine, cyclophosphamide, cyclosporine, danazol, dapsone mycophenolate mofetil, and the vinca alkaloids; however, guidelines such as that of the American Society of Hematology do not provide recommendations on these drugs due to limitations in the current evidence, mainly the small sample sizes of studies and heterogeneous patient populations.<sup>8</sup> A brief summary of the reported efficacy of immunosuppressive drugs without American Society of Hematology guideline recommendations can be found in [Table 1](#).

**Table 1: Immunosuppressive Drugs Without Guideline Recommendations**

Immunosuppressive drug	Reported efficacy	Reported safety concerns
Azathioprine	<ul style="list-style-type: none"> <li>Several months until full effect</li> <li>Durable response rate of 51% and 64% in 2 trials</li> <li>Half of responders required ongoing therapy</li> </ul>	<ul style="list-style-type: none"> <li>Major AEs: nausea, infection, liver function abnormalities, neutropenia, anemia</li> <li>0.25% of the population lacks enzyme to degrade drug</li> </ul>
Cyclophosphamide	<ul style="list-style-type: none"> <li>Slow onset of effect</li> <li>Highly variable response rate at 1 month based on 2 trials (from 10 to 70%)</li> <li>Durable response rate of 60% in 2 trials</li> </ul>	<ul style="list-style-type: none"> <li>Major AEs: bone marrow suppression, infection, infertility, secondary malignancies, and hemorrhagic cystitis</li> </ul>

Immunosuppressive drug	Reported efficacy	Reported safety concerns
<b>Cyclosporine A</b>	<ul style="list-style-type: none"> <li>Variable response rate at 1 month (from 38 to 57%)</li> <li>Durable response rate from 23% (off therapy) to 44% (ongoing therapy)</li> </ul>	<ul style="list-style-type: none"> <li>Major AEs: gingival hyperplasia, hypertension, nephrotoxicity, and nausea</li> </ul>
<b>Danazol</b>	<ul style="list-style-type: none"> <li>Variable response rate at 1 month (24% to 58%)</li> <li>Durable response rate (10% to 96%) with differences between trials in response definitions, follow-up, and therapy status</li> </ul>	<ul style="list-style-type: none"> <li>Major AEs: androgenic effects, elevated liver function tests, weight gain, acne, rash, mood change, amenorrhea, and virilization</li> </ul>
<b>Dapsone</b>	<ul style="list-style-type: none"> <li>Highly variable response rate at 1 month (36% to 63%)</li> <li>Durable response rate (0% to 55%)</li> </ul>	<ul style="list-style-type: none"> <li>Well tolerated</li> <li>Major AEs: nausea/vomiting and mild hemolysis</li> <li>Screen for G6PD deficiency and monitor for methemoglobinemia</li> </ul>
<b>Mycophenolate mofetil</b>	<ul style="list-style-type: none"> <li>Relatively slow effect</li> <li>Response rate at 1 month (around 50%)</li> <li>Durable response rate (57% to 62%)</li> </ul>	<ul style="list-style-type: none"> <li>Major AEs: diarrhea, neutropenia, anemia, and viral infections</li> <li>Prolonged use associated with small increased risk of malignancy, PML, and pure red aplasia</li> </ul>
<b>Vinca alkaloids</b>	<ul style="list-style-type: none"> <li>Highly variable response rate at 1 month (as low as 18%)</li> <li>Durable response rate (0% to 42%)</li> </ul>	<ul style="list-style-type: none"> <li>Significant toxicity</li> <li>Major AEs: vincristine neuropathy, vinblastine-associated bone marrow suppression, constipation, hyponatremia, and infusion site vesication</li> </ul>

AE = adverse event; G6PD = glucose-6-phosphate dehydrogenase; PML = progressive multifocal leukoencephalopathy.

Note: All data presented are reported in Neunert et al. (2019).<sup>8</sup> Studies had small sample sizes and heterogeneous patient populations; disease duration, disease severity, and previous treatments received may vary substantially from current clinical practice.<sup>8</sup>

Source: American Society of Hematology 2019 Guidelines for Immune Thrombocytopenia.<sup>8</sup>

It is unclear which treatments are most appropriate for adult patients with chronic ITP who have failed first-line treatments. The federal, provincial, and territorial public drug plans have requested an evaluation on the comparative evidence of available treatments for adults with ITP who have already received first-line therapies (i.e., corticosteroids, IVIG, and/or anti-D immunoglobulin) and the place in therapy of splenectomy.

## Summary of Patient Group Input

### Lived Experience of Chronic ITP

CADTH welcomed feedback from the patient community on the proposed project entitled “Treatment of Adult Patients With Chronic ITP After Failure of First-Line Therapies.” The Platelet Disorder Support Association encouraged its patient community to contribute feedback. Twenty people living with chronic ITP shared their experiences and expectations of ITP therapies, in addition to the information provided by the Platelet Disorder Support Association. Many contributors were in their 50s, 60s, and 70s, with a few contributors in their early 30s. Many had lived with ITP for more than 10 years, with a range of 12 months to 55 years. Most contributors identified that they were from Ontario or British Columbia.

Several contributors described living with the fear of serious or fatal bleeds and the exhaustion associated with low platelets. “Having ITP and living with the fear of bleeding is a very stressful and unpredictable situation. I am not able to work full-time owing to the fatigue associated with ITP. I cannot travel or participate in overly vigorous activities because of the fear of a sudden drop in platelets and bleeding.”

### **Patients’ Experiences of Therapies for ITP**

Contributors described a wide range of experiences of therapies: corticosteroids, including prednisone and dexamethasone; IVIG; rituximab; TPO-RAs, including romiplostim and eltrombopag; immunosuppressants, including cyclosporine and azathioprine; and/or splenectomy.

Contributors described trying multiple therapies over the years. “After trying prednisone — did not respond; IVIG which did respond; then splenectomy which did not work; IVIG only lasted a few weeks; rituximab, only last a few weeks; cyclosporine which proved to be the best medication for controlling ITP for the next 11 years. Now on Revolade for the past 4 years, which has worked well.”

Temporary and/or waning effectiveness were concerns shared by contributors. “IVIG treatments which are a lifesaver but temporary.” Time spent in hospital or spent receiving IV therapy was another concern. “During the first six months, I was admitted to the hospital on 5 separate occasions with platelet readings of between 0k and 3k, accompanied by various indications (e.g., unexplained bruises, blood blisters, slight nose bleeds and bleeding gums), with an average stay of 3-5 days in each case.” “I opted for a watch and wait approach because I hated the side effects of prednisone, and the amount of school I was missing for IVIG treatments every 3-4 weeks was not sustainable.”

Many contributors described the side effects they experienced using corticosteroids. “I had terrible side effects from the steroids including manic-like episodes, weight gain, heart racing, insomnia, and eye disturbances. I have had to take bone health supplements and have regular bone scans to monitor bone loss due to long term use of steroids.” One person described being unable to work due to side effects of prednisone, while others described permanent side effects of “brain fog” and osteonecrosis, as a consequence of steroids. A few contributors described a willingness to use steroids only if platelets were extremely low, for example: “I do respond to steroids and have used prednisone but will only use them in an emergency—platelets at 10 or less—as I have a great deal of difficulty dealing with the side effects.”

One person shared their experience of 28 years of remission following removal of their spleen. When ITP returned, use of prednisone and dexamethasone raised platelets levels temporarily until an accessory spleen was found and removed, allowing the person to return to remission. Other contributors shared that splenectomy had not helped them. One person described experiencing portal vein thrombosis, resulting in 2 emergency surgeries and an intensive care unit stay; deep vein thrombosis; bowel resection; permanent daily incontinence; reduced immune system response; and a reliance on blood thinners as a consequence of splenectomy that did not offer remission, to access rituximab, which was also not effective. For this person, only prednisone has been effective.

## Rationale Behind Treatment Decisions

Outside of Alberta, patients with chronic ITP must try splenectomy to be eligible for public funding of second-line drug treatments. Many contributors described how they faced an uncertain disease path, uncertain benefit of splenectomy in the short term and long term, and knowledge that the removal of their spleen was permanent, required surgery, and increased their risk of infection.

I have been highly resistant to the idea of a splenectomy for a number of reasons, including uneven record of success in treating ITP; surgical risks including long term effects of general anaesthetic; availability of alternative noninvasive medications.

Once the spleen is gone, it is gone forever.

I ended up having a splenectomy that, within a few months, indicated that it had failed. In hindsight I would not have had a splenectomy. But I felt I did not have a choice, as I could not access the more expensive treatments like Rituxan or the TPOs without having first “failed” three other lines of treatment.

Given the variability and unpredictability of the disease, some respondents described refusing splenectomy and the potential for remission, to accept the risks of bleeding and to treat only serious episodes with first-line therapy. “As there is no cure for ITP, I decided that I would rather live with what I know than a whole new batch of side effects with treatment that may or may not help bring my platelets up.”

## Patients’ Expectations for ITP Treatment

A desire to see different types of therapies accessible to patients in Canada — including avatrombopag, fostamatinib, eltrombopag, romiplostim, rituximab, and oral veltuzumab — was expressed by contributors. “I understand this is a rare condition but, to me, it feels like there is really no treatment for me because what is available is so very inadequate.”

One contributor asked for public funding of TPO-RA medications. Another emphasized that health care providers should explain to patients and their families the full range of treatments available for ITP, even if not all are publicly funded. “As other new treatment advances are made, more favourable medications should constantly be re-evaluated in terms of coverage and accessibility. For now, I remain in a position where my only next treatment option is the same one offered over 100 years ago.”

Many contributors expressed a desire to avoid surgery (splenectomy) and the side effects associated with the long-term use of steroids. “It seems like an inhumane choice to force surgery to remove an organ before access to other treatments, especially when splenectomy is less often successful the older a patient is and does not have a high percentage of success in the ITP population as a whole.”

Several sought public funding of the use of indium white blood cell screening, to gauge the likelihood that splenectomy would be successful for the individual, before considering surgery.

The collection of patient perspectives highlighted the unmet need for treatment options for adult patients with chronic ITP after failure of first-line therapies.

## Objectives

CADTH undertook a Health Technology Assessment (HTA) to review the effectiveness and cost-effectiveness of treatments for ITP in adults after failure of first-line treatments. A secondary objective was to determine the place of splenectomy in therapy.

## Policy Questions

The following policy questions were addressed with this project:

1. What treatment(s) should be used in adult patients with ITP who have failed first-line treatments?
2. What is the place in therapy of splenectomy in adult patients with ITP?

## Research Questions

The project addressed the following research questions. Details on the specific interventions and outcomes are included in [Table 2](#).

### Clinical Evaluation

1. What is the comparative effectiveness and safety of subsequent-line therapies in adult patients with ITP who have failed first-line treatments?
2. What is the comparative effectiveness and safety of splenectomy compared with second-line therapies (rituximab, fostamatinib, or TPO-RA [romiplostim, eltrombopag, avatrombopag]) in adult patients with ITP?

### Economic Analysis

1. What is the cost-effectiveness of therapies in adult patients with ITP who have failed first-line treatments?
2. What is the cost-effectiveness of splenectomy compared with second-line therapies (rituximab, fostamatinib, or TPO-RA [romiplostim, eltrombopag, avatrombopag]) in adult patients with ITP?

## Methods

To inform the conduct of this HTA, a preliminary informal scoping of the existing literature was conducted. A protocol was written a priori and was followed throughout the study process. The project is an HTA that includes clinical and economic reviews. Stakeholder feedback was solicited at key steps. The key elements of the project, including the population of interest, the interventions and comparators, and the main outcomes of interest, are outlined in [Table 2](#). The protocol was registered ([registration number: CRD42021276565](#)) in PROSPERO.<sup>20</sup> No deviations in the protocol occurred.



## Opportunities for Stakeholder Feedback

The project scope was posted on the CADTH website for 10 days and feedback from the patient community was reviewed and summarized. The collection of patient perspectives enabled the research team to consider the evidence found in the literature alongside an understanding of the wider experiences of patients and family caregivers. In addition, the draft list of included studies in the review, the statistical analyses plan, and a draft of the report were also posted on the CADTH website and all stakeholders (e.g., patient community, clinician groups, industry) were given the opportunity to provide written feedback.

## Clinical Review

This clinical evaluation was designed as a systematic review and an NMA to answer the first and second research questions. The systematic review and NMA of the primary studies focused on the clinical effectiveness, comparative clinical effectiveness, safety, and comparative safety of ITP medications, as well as on the clinical effectiveness, comparative clinical effectiveness, safety, and comparative safety of splenectomy in ITP. The systematic review was conducted following standard methodology and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement,<sup>21</sup> with consideration of relevant elements of PRISMA-NMA.<sup>22</sup> The NMA was conducted in accordance with the Professional Society for Health Economics and Outcomes Research (ISPOR) guidelines for NMAs.<sup>23</sup>

### Literature Search Methods

An information specialist developed and conducted a literature search for clinical studies using a peer-reviewed search strategy according to CADTH's [PRESS Peer Review of Electronic Search Strategies checklist](#).<sup>24</sup> The complete search strategy is presented in [Appendix 1](#).

Published literature was identified by searching the following bibliographic databases: MEDLINE via Ovid, Embase via Ovid, and the Cochrane Central Register of Controlled Trials (CENTRAL) via Ovid. All Ovid searches were run simultaneously as a multifile search. Duplicates were removed using Ovid deduplication for multifile searches, followed by manual deduplication in EndNote. The search strategy comprised both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. Search concepts were developed based on the elements of the PICOS (Population(s), Intervention(s), Comparator(s), Outcome(s), Study Design(s)) framework and research questions. The main search concepts were rituximab, fostamatinib, TPO-RAs (romiplostim, eltrombopag, avatrombopag), or splenectomy and ITP. Clinical trials registries with results were searched: the US National Institutes of Health's clinicaltrials.gov, WHO's International Clinical Trials Registry Platform (ICTRP) search portal, Health Canada's Clinical Trials Database, and the European Union Clinical Trials Register.

[CADTH-developed search filters](#) were applied to limit retrieval to HTAs, systematic reviews, meta-analyses, or NMAs, RCTs, or controlled clinical trials. Systematic reviews were included in the literature search to inform



the initial scoping of the project. Retrieval was not limited by publication date but was limited to the English or French language. Conference abstracts were excluded from the search results.

The initial search was completed on July 23, 2021. Regular alerts updated the database literature searches until July 26, 2022. The clinical trials registries search was updated before the completion of the stakeholder feedback period. Studies meeting the selection criteria of the review and identified in the alerts before the completion of the stakeholder feedback period were incorporated into the analysis of the final report. Any studies that were identified after the stakeholder feedback period are described in the discussion, with a focus on comparing the results of these new studies with the results of the analysis conducted for this report.

Grey literature (literature that is not commercially published) was identified by searching sources listed in relevant sections of [Grey Matters: A Practical Tool For Searching Health-Related Grey Literature](#), which includes the websites of regulatory agencies, HTA agencies, clinical guideline repositories, systematic review repositories, patient-related groups, and professional associations. Google was used to search for additional internet-based materials. These searches were supplemented by screening articles identified by clinical experts and by industry following the stakeholder feedback period.

## Eligibility Criteria

Studies were included if they met the eligibility criteria, including the specific population, intervention, comparators, and study designs, presented in [Table 2](#). Drug regimens eligible for inclusion in the review were those that have been approved by Health Canada for ITP or were considered of clinical relevance based on expert advice or international clinical practice guidelines. The inclusion criteria were informed by the informal scoping review of the existing literature, patient engagement, stakeholder feedback, and consultation with the clinical experts. Studies were excluded if they did not report outcomes of interest. The language of publications was limited to English and French, with no limitation on publication date, and conference abstracts were excluded.

**Table 2: Selection Criteria**

Criteria	Description
<b>Population</b>	<p>Adult patients (<sup>3</sup> aged 18 years or older) with ongoing, active ITP who have failed first-line treatments</p> <p>Subgroups of interest:</p> <ul style="list-style-type: none"> <li>• Duration of disease (i.e., chronic ITP versus persistent ITP)</li> <li>• Adult patients who have previously failed at least 1 second-line therapy</li> </ul>
<b>Interventions</b>	<ul style="list-style-type: none"> <li>• Rituximab<sup>a,b</sup></li> <li>• Eltrombopag</li> <li>• Romiplostim</li> <li>• Fostamatinib</li> <li>• Avatrombopag</li> <li>• Splenectomy</li> </ul>

Criteria	Description
<b>Comparators</b>	<ul style="list-style-type: none"> <li>• Above-noted interventions against each other</li> <li>• IVIG</li> <li>• Immunosuppressants (i.e., azathioprine, cyclosporine, cyclophosphamide, mycophenolate mofetil, danazol, dapsone)</li> <li>• Corticosteroids</li> <li>• Placebo and/or standard of care</li> </ul>
<b>Outcomes</b>	<p>Clinical effectiveness:</p> <ul style="list-style-type: none"> <li>• Platelet count response</li> <li>• Time to platelet response</li> <li>• Bleeding events</li> <li>• Emergency department visits</li> <li>• Hospitalization</li> <li>• Health-related quality of life</li> <li>• Symptoms (e.g., fatigue)</li> <li>• Treatment-free remission</li> <li>• Need for rescue medication (e.g., IVIG, corticosteroids)</li> <li>• Reduction or discontinuation of corticosteroids</li> </ul> <p>Safety:</p> <ul style="list-style-type: none"> <li>• Adverse events, serious adverse events, withdrawal due to adverse events, mortality</li> <li>• Notable harm: infection</li> </ul>
<b>Study design</b>	Phase III and phase IV randomized controlled trials

ITP = immune thrombocytopenia; IVIG = IV immunoglobulin.

\*Rituximab dose for ITP: 375 mg/m<sup>2</sup> IV infusion once a week for 4 weeks (4 total doses; days 1, 8, 15, and 22). There is also a lower dose that can be used for ITP: 100 mg IV infusion once a week for 4 weeks (4 total doses; days 1, 8, 15, and 22).

<sup>b</sup>Includes biosimilars.

## Population and Subgroups

The patient population included in the review consisted of adults with ongoing, active ITP who did not respond to first-line treatments. Relevant subgroups included duration of disease as persistent ITP (between 3 and 12 months) or chronic ITP (more than 12 months), and previous failure of at least 1 second-line therapy. Patients were eligible for inclusion in the studies if they were adults with a diagnosis of ITP that was either newly diagnosed, persistent, or chronic, depending on the study inclusion criteria. Platelet count was typically required to be less than  $30 \times 10^9/L$ . It was standard for patients to be excluded from the studies if they had significant comorbidities such as other blood disorder, history of thrombosis, cardiovascular disease, or active malignancy.

## Intervention and Comparators

All currently available subsequent-line therapies for ITP were considered potentially relevant interventions and comparators, including rituximab, eltrombopag, romiplostim, fostamatinib, avatrombopag, and splenectomy. Comparators also included placebo and/or standard of care (IVIG; immunosuppressants, including azathioprine, cyclosporine, cyclophosphamide, mycophenolate mofetil, danazol, dapsone; and

corticosteroids). Recognizing that rescue therapies are sometimes given in combination with these drugs, no distinction was made between monotherapy or combination therapy for any of the included treatments.

It should be noted that standard of care was included as a background treatment, or as an add-on treatment to any of the included second-line therapies because the clinical expert noted that standard of care is generally given to all patients. IVIG, immunosuppressants (azathioprine, cyclosporine, cyclophosphamide, mycophenolate mofetil, danazol, dapsone), or corticosteroids were considered as standard of care.

## Outcomes Definition

In consultation with a clinical expert, outcomes were selected to assess the clinical effectiveness and safety of the interventions, including platelet count response, bleeding events, emergency department visits, hospitalization, HRQoL, symptoms (e.g., fatigue), treatment-free remission, need for rescue medication (e.g., IVIG, corticosteroids, platelet transfusions), reduction or discontinuation of corticosteroids, and mortality. Various other harms outcomes were considered important for clinical decision-making and were therefore included in the protocol. Any reasonable measurement tool or definition used by study authors for the outcomes presented, as well as any relevant follow-up time point, was considered and critically appraised when needed.

## Study Designs

Published phase III and phase IV RCTs were eligible for inclusion.

## Study Selection Process

Two reviewers independently screened titles and abstracts of all retrieved citations in duplicate (i.e., literature searches of academic databases, grey literature searches, and clinical trial database) against the eligibility criteria ([Table 2](#)). Exclusion by both reviewers was required for a record to be excluded at the title and abstract level. Full-text articles that were judged to be potentially relevant by at least 1 reviewer were retrieved for the second level of screening. The same 2 reviewers independently examined all full-text articles against the eligibility criteria, and consensus was required for inclusion in the review. Discrepancies between reviewers were resolved by discussion. Reasons for exclusion at the full-text level were documented. The list of final included studies was posted publicly on the CADTH website and feedback was solicited from stakeholders. Studies later identified via monthly database search alerts and semiannual grey literature search alerts meeting the selection criteria of the review were incorporated into the analysis.

## Quality Assessment

Risk of bias in the individual trials was assessed using the Cochrane risk of bias 2 (RoB 2) tool at the level of the reported result.<sup>24</sup> Risk of bias was appraised for the effect of assignment to the intervention (i.e., intent-to-treat [ITT]). Risk of bias assessments were completed by 2 reviewers independently in duplicate for each trial. The RoB 2 tool allowed for the assessment of 5 sources of bias or “domains”: bias arising from the randomization process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in measurement of the outcome, and bias in selection of the reported result. Each question within each domain was answered with a “yes,” “probably yes,” “probably no,” “no,” or “no information.” Afterward, a

judgment of “low risk of bias,” “high risk of bias,” or “some concerns” was assigned for each domain, with the rationale for each decision included in the comments box field.

For each unique RCT, we assessed the risk of bias of the original primary publication, with additional details sought from supporting literature (e.g., published protocol and ClinicalTrials.gov records). Disagreements were resolved by consensus. The risk of bias of each included study and how it affects the study findings was described narratively. Other critical appraisal points were noted by reviewers, such as assessment of the generalizability of the findings.

## Data Analyses and Synthesis

Data were extracted by 1 reviewer by the use of piloted and standardized data abstraction forms, and the extracted data were checked for accuracy and completeness by a second reviewer. Any disagreements were resolved by consensus. Modification to the extraction sheet was conducted after a pilot of 5 studies.

The original, primary publication for each included RCT was used for data extraction, with supplementary data obtained from companion reports and ClinicalTrials.gov records to address the research questions. In situations where multiple publications for a unique RCT were available (e.g., supplemental online appendices, companion publications of specific outcomes, or populations from the original study), the most recent data for each outcome were extracted, with preference given to published records.

The following relevant information was extracted, where available:

- Study level: description of publication (e.g., first author last name, title, publication year), study characteristics (e.g., clinical trial registry identification number, trial acronym, study design, year of study conduct, sample size, study setting, country of study conduct, randomization ratio, blinding status, superiority or noninferiority design, eligibility criteria, study duration)
- Patient level: number of patients, age, sex (as reported by study authors), clinical situation of the diagnosis, duration of disease
- Intervention and comparator level: type, dose, total duration of treatment, dosing frequency, route of administration, and concurrent and previous relevant therapies
- Outcome level: description of outcomes (e.g., method of measurement, unit of measurement, length of follow-up) and all data related to an eligible outcome domain
- Type of analysis: ITT or safety population; data from figures were extracted if explicit numerical data were reported on the figure.

After the conclusion of data extraction, a feasibility assessment was conducted for addressing the posed research questions, which included evaluating sources of methodological and clinical heterogeneity between the included studies. Study design, patients’ baseline characteristics, treatment characteristics, as well as outcome definitions were compared between studies. A qualitative assessment of feasibility was determined through close collaboration between the reviewers, methodologists, and clinical experts. Because the NMA was deemed infeasible, an alternate NMA was conducted with simplified assumptions. Ultimately, it was concluded that the NMA was not informative; therefore, a narrative summary was reported. Refer

to the prespecified statistical analysis plan for this report provided in [Appendix 2](#) for further details of the planned analysis.

## Results of Clinical Evaluation

### Selection of Primary Studies

A total of 1,421 citations were identified in the literature searches. Following screening of titles and abstracts, 124 studies were identified as potentially relevant and retrieved for full-text review. A total of 206 reports were retrieved from other sources (i.e., grey literature, handsearch, and search alerts). Of these 330 potentially eligible reports, 15 reports<sup>9-15,25-32</sup> presenting data from 10 unique studies met the inclusion criteria and were included for review. The report selection process is outlined in [Figure 1](#). A list of included and excluded reports, with details describing the rationale for those excluded, is presented in [Appendix 3](#) and [Appendix 4](#), respectively.

### Study and Patient Characteristics

A total of 15 publications met the inclusion criteria and were included in the systematic review, reporting results from 10 individual RCTs. Peer-reviewed publications were selected for inclusion if they met the prespecified review protocol criteria. Study characteristics are shown in [Appendix 6](#).

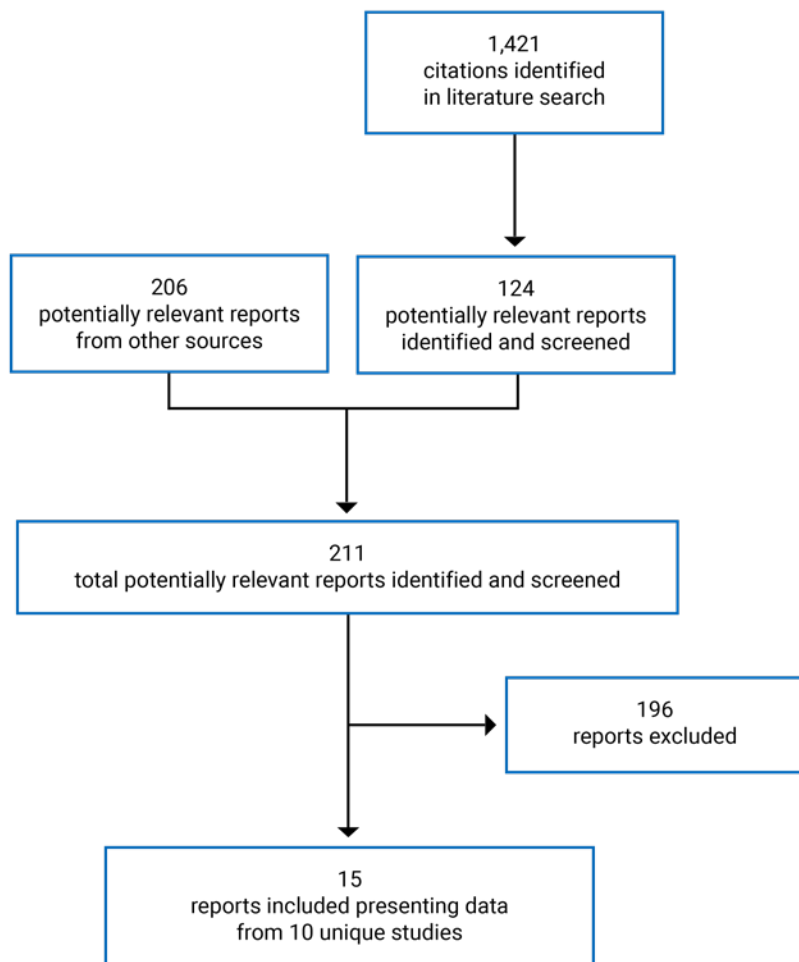
### Populations

One study was performed in patients who received corticosteroids without achieving a sustained response or who relapsed after discontinuation,<sup>32</sup> and 3 studies included patients who had insufficient response or relapse to any previous therapies for ITP.<sup>9,25,27</sup> While this was the main population of interest for the review, it limited the number of drug comparisons that could be evaluated and used to inform decision-making. Additional trials included patients who had experience with prior ITP therapies, without specifically requiring treatment failure, and these were included in the review as well.

### Interventions and Comparators

Four included studies were double-blind (DB), placebo-controlled RCTs comparing eltrombopag to placebo over 6 weeks<sup>9,25,27</sup> or 6 months<sup>10</sup>. One included study was a small DB RCT evaluating the use of avatrombopag compared with placebo over 26 weeks.<sup>12</sup> Three included RCTs compared romiplostim to either placebo in a DB setting<sup>11,13</sup> or standard of care in an open-label (OL) setting.<sup>14</sup> Two included studies evaluated interventions other than TPO-RA: 1 DB RCT evaluated the use of rituximab compared with placebo over 4 weeks<sup>32</sup> and 1 DB RCT compared fostamatinib to placebo over 24 weeks.<sup>15</sup> In addition to the interventions and comparators, the concomitant use of various ITP medications was allowed in all trials. These medications included, but were not limited to, corticosteroids, azathioprine, and danazol.

**Figure 1: Flow Chart of the Selection Process**



## Outcomes

All the studies included in the systematic review reported platelet count response as a primary or major outcome; however, the outcome measures used to assess platelet response varied substantially across the studies. The most frequently used was the proportions of patients achieving response. There were notable differences observed in thresholds and definitions for platelet count response across studies, including some that were not consistent with the international standardized definition<sup>1</sup> of a platelet count of  $30 \times 10^9/\text{L}$  or higher with at least a 2-fold increase in platelet count from baseline and an absence of bleeding, while a platelet count of  $100 \times 10^9/\text{L}$  or higher would typically be considered a complete response, as long as there is an absence of bleeding.<sup>1</sup> In addition, there were differences among all of the studies as to the conditions to be observed for patients to be considered responders, such as the time needed to be spent above the threshold value (ranging from at least once during the study to throughout the entire study follow-up), as well as criteria related to the use of rescue medication.

Nine studies reported bleeding as an outcome for either efficacy or harms assessment.<sup>9-12,14,15,25,27,32</sup>

Definitions of bleeding and reporting methods varied across the studies. Other frequently reported outcomes included the need for rescue medication (e.g., IVIG and corticosteroids), reduction or discontinuation of concomitant ITP medications, and various safety outcome measures. Three studies reported findings on HRQoL or ITP symptoms using various scales: the Functional Assessment of Chronic Illness Therapy (FACIT) – Fatigue subscale;<sup>10</sup> the Functional Assessment of Cancer Therapy – Thrombocytopenia 6-item questionnaire (FACT-Th6);<sup>10</sup> the Motivation and Energy Inventory – Short Form (MEI-SF);<sup>10</sup> the Short Form (36) Health Survey, Version 2 (SF-36v2);<sup>10</sup> EQ-5D;<sup>11</sup> and the Immune Thrombocytopenic Purpura Patient Assessment Questionnaire (ITP-PAQ).<sup>11,14</sup>

No data were reported for the outcomes of treatment-free remission, emergency department visits, or hospitalization.

### **Eltrombopag Versus Placebo**

In the 4 studies comparing eltrombopag to placebo, eltrombopag was administered at a dosage ranging from 12.5 mg to 75 mg orally once daily, with the dose to be adjusted based on platelet count response. The mean age of the patients ranged from 41 to 58 years across treatment groups at baseline. The median platelet count ranged from 9,500/ $\mu$ L to 21,000/ $\mu$ L; approximately half of the trials' populations had a platelet count of 15,000/ $\mu$ L or less. The proportions of patients using concomitant ITP medication at baseline was 82% in 1 trial,<sup>25</sup> and ranged from 42% to 55% in the other studies. All studies included a portion of patients who had a splenectomy; however, the proportions varied substantially from 1 trial to another.

### **Avatrombopag Versus Placebo**

One study evaluated the superiority of avatrombopag administered orally once daily, with the dose to be adjusted based on platelet count response and need for concomitant ITP medications, over placebo for 26 weeks. The mean age of the patients ranged from 41 to 46 years across treatment groups at baseline. Median platelet count at baseline was not reported; however, approximately half of the patient population had a platelet count of 15,000/ $\mu$ L or less, while the other half had a platelet count between 15,000/ $\mu$ L and 30,000/ $\mu$ L.<sup>12</sup> In this study, 45% of patients had concomitant ITP medication at baseline and 33% of patients had a prior splenectomy.<sup>12</sup>

### **Romiplostim Versus Placebo or Standard of Care**

In the 3 studies comparing romiplostim to placebo or standard of care, romiplostim was administered at a dosage ranging from 1 to 3 mcg/kg subcutaneously once weekly, with the dose to be adjusted up to a maximum between 10 and 15 mcg/kg based on platelet count response. In 1 study, the mean age of the patients at baseline was 59 years in the romiplostim treatment group and 48 years in the placebo treatment group;<sup>13</sup> in the 2 other romiplostim trials, the median age of the patients ranged from 52 to 58 years across treatment groups.<sup>11,14</sup> In 2 of the 3 studies, baseline mean or median platelet count was less than 20,000/ $\mu$ L;<sup>11,13</sup> however, 1 study included patients with a numerically higher median platelet count (33,000/ $\mu$ L in the romiplostim treatment arm and 27,000/ $\mu$ L in the placebo arm).<sup>14</sup> The proportions of patients using concomitant ITP medication at baseline varied substantially from 1 trial to another. Two studies reported the proportions of patients who had a splenectomy, ranging from 42% to 51% across treatment groups.<sup>11,13</sup>

Table 3: High-Level Study Characteristics

Criteria	Tomiyama et al. (2012) n = 23	Yang et al. (2017) n = 155	Bussel et al. (2009) n = 114	Cheng et al. (2011) n = 197	Jurczak et al. (2018) n = 49	Shirasugi et al. (2011) n = 34	Kuter et al. (2008) n = 125	Kuter et al. (2010) n = 234	Ghanima et al. (2015) n = 150	Bussel et al. 2018 n = 112
<b>Population</b>	Subsequent-line treatment in patients who have failed $\geq 1$ prior ITP therapies			Subsequent-line treatment in patients who have experience with prior ITP therapies						second-line after corticosteroid failure
<b>Interventions</b>	Eltrombopag adjusted based on platelet count				Avatrombopag adjusted based on platelet count	Romiplostim adjusted based on platelet count			Rituximab 375 mg/m <sup>2</sup> IV weekly	Fostamatinib 100 to 150 mg orally twice daily
<b>Comparators</b>	Matching placebo							Standard of care	Matching placebo	
<b>Primary outcome</b>	Platelet count response (various outcome measures)								Treatment failure	Platelet count response
<b>Other key outcomes</b>	<ul style="list-style-type: none"> <li>Bleeding</li> <li>Use of concurrent ITP drugs</li> <li>Use of rescue ITP treatment</li> </ul>	<ul style="list-style-type: none"> <li>Bleeding</li> <li>Use of concurrent ITP drugs</li> <li>Use of rescue ITP treatment</li> <li>Safety</li> </ul>	<ul style="list-style-type: none"> <li>Bleeding</li> <li>Safety</li> <li>HRQoL</li> </ul>	<ul style="list-style-type: none"> <li>Bleeding</li> <li>HRQoL</li> <li>Use of concurrent ITP drugs</li> <li>Use of rescue ITP treatment</li> </ul>	<ul style="list-style-type: none"> <li>Bleeding</li> <li>Use of concurrent ITP drugs</li> <li>Use of rescue ITP treatment</li> <li>Safety</li> </ul>	<ul style="list-style-type: none"> <li>Bleeding</li> <li>Use of rescue ITP treatment</li> <li>Safety</li> </ul>	<ul style="list-style-type: none"> <li>Use of concurrent ITP drugs</li> <li>Use of rescue ITP treatment</li> <li>Safety</li> <li>HRQoL</li> </ul>	HRQoL	<ul style="list-style-type: none"> <li>Bleeding</li> <li>Use of rescue ITP treatment</li> <li>Safety</li> </ul>	<ul style="list-style-type: none"> <li>Bleeding</li> </ul>

HRQoL = health-related quality of life; ITP = immune thrombocytopenia; IVIG = IV immunoglobulin.



**Table 4: Outcomes Assessing Platelet Count Response**

Intervention	Eltrombopag				Avatrombopag	Romiplostim			Rituximab	Fostamatinib
	Tomiyama et al. (2012)	Yang et al. (2017)	Bussel et al. (2009)	Cheng et al. (2011)	Jurczak et al. (2018)	Shirasugi et al. (2011)	Kuter et al. (2008)	Kuter et al. (2010)	Ghanima et al. (2015)	Bussel et al. (2018)
Primary platelet count response outcome	Proportion of responders				Cumulative number of weeks of platelet response	Number of weeks of platelet count response, median (IQR)	Proportion of patients with durable platelet count response rate	Incidence of treatment failure	Treatment failure	Proportion of patients with stable response
	60% vs. 0%; at week 6	58% vs. 6%; at week 6	59% vs. 16%; at week 6	79% vs. 28%; throughout 6 months	12.0 ± 8.75 weeks vs. 0.1 ± 0.49 week	IQR 9 to 12 vs. IQR 0 to 0; median 11 weeks	49% vs. 2%; last 8 weeks	11% vs. 30%; 52 weeks	NS	18% vs. 2%; 24 weeks
Secondary platelet count outcome	Proportion of responders				Proportion of responders	Proportions of patients with platelet count increase ≥ 20,000/μL, n	Proportions of patients with ≥ 4 weekly platelet count response	Platelet count / μL, median range	Complete response (platelet count ≥ 100,000/μL)	Overall response (platelet count ≥ 50,000/μL)
	33% vs. 0%; throughout 6 weeks	NR	NR	38% vs. 7%; ≥ 75% of assessments	66% vs. 0%; day 8	96% vs. 25%	83% vs. 7%; throughout 24 weeks	2.3 (95% CI 2.0 to 2.6); between week 2 and week 52	51% vs. 39%; at 78 weeks	43% vs. 14%; 24 weeks

CI = confidence interval; IQR = interquartile range; NR = not reported; NS = did not meet the a priori defined threshold for statistical significance; vs. = versus.

Table 5: Additional Outcomes

Intervention	Eltrombopag				Avatrombopag	Romiplostim			Rituximab	Fostamatinib
	Tomiyama et al. (2012)	Yang et al. (2017)	Bussel et al. (2009)	Cheng et al. (2011)	Jurczak et al. (2018)	Shirasugi et al. (2011)	Kuter et al. (2008)	Kuter et al. (2010)	Ghanima et al. (2015)	Bussel et al. (2018)
Bleeding events	Proportion of patients with any bleeding symptom	Any bleeding			Any bleeding	Incidence of bleeding symptoms	Incidence of significant bleeding events (severe, life-threatening, or fatal)	Proportions of patients with bleeding events throughout trial	Any bleeding symptoms	
	No change	16% vs. 34%	39% vs. 60%	79% vs. 93%	44% vs. 53%	36% vs. 83%; 12 weeks	7% vs. 12%	52% vs. 53%	38% vs. 50%	NR
Improvement in health-related quality of life	NR	NR	NR	FACT-Th questionnaire and SF-36v2 scales (physical role, vitality, and emotional role subscales; mental component summary score)	NR	NR	EQ-5D index score, EQ-5D index VAS score, the ITP-PAQ scales (symptoms, fatigue, bother, activity, psychological, fear, social quality of life, and women's reproductive health), and the EQ-5D index score	Improvement on ITP-PAQ scales (symptoms, bother, activity, psychological, fear, overall quality of life, and social quality of life)	NR	NR

Intervention	Eltrombopag				Avatrombopag	Romiplostim			Rituximab	Fostamatinib
	Tomiyama et al. (2012)	Yang et al. (2017)	Bussel et al. (2009)	Cheng et al. (2011)	Jurczak et al. (2018)	Shirasugi et al. (2011)	Kuter et al. (2008)	Kuter et al. (2010)	Ghanima et al. (2015)	Bussel et al. (2018)
Need for rescue medication	Proportion of patients with rescue treatment							Proportion of patients administered ITP treatment	Proportion of patients receiving rescue treatment	
	NR	9% vs. 34%	NR	18% vs. 40%	22% vs. 12%	9% vs. 17%	22% vs. 60%	44% vs. 79%	NR	30% vs. 45%
Reduction or discontinuation of concomitant ITP medication	NR	NR	NR	59% vs. 32%	33% vs. 0%	NR	52% vs. 19%	NR	NR	NR
Adverse events	73% vs. 25%	64% vs. 67%	59% vs. 37%	87% vs. 92%	97% vs. 59%	91% vs. 92%	100% vs. 95%	82% vs. 87%	NR	83% vs. 75%
Serious adverse events	7% vs. 0%	5% vs. 10%	NR	NR	28% vs. 6%	9% vs. 8%	2% vs. 0%	23% vs. 37%	NR	13% vs. 21%
Withdrawals due to adverse events	NR	3% vs. 2%	4% vs. 5%	10% vs. 7%	9% vs. 0%	0% vs. 0%	2% vs. 2%	NR	0% vs. 0%	10% vs. 8%
Mortality	NR	3% vs. 2%	4% vs. 5%	10% vs. 7%	0% vs. 0%	0% vs. 0%	1% vs. 5%	1% vs. 3%	0% vs. 2%	1% vs. 2%
Notable harm: infection	NR	NR	NR	NR	NR	NR	NR	NR	40% vs. 24%	NR

FACT-Th = Functional Assessment of Cancer Therapy – Thrombocytopenia questionnaire; ITP = immune thrombocytopenia; ITP-PAQ = Immune Thrombocytopenic Purpura – Patient Assessment Questionnaire; NR = not reported; SF-36v2 = Short Form (36) Health Survey, Version 2; VAS = visual analogue scale; vs. = versus.

This section highlights a summary of studies included for each treatment comparison. Additional study characteristics are shown in [Appendix 6](#).

### Interventions Other Than TPO-RA Versus Placebo

One study (Ghanima et al.;  $n = 112$ )<sup>32</sup> evaluated the superiority of rituximab over placebo. Rituximab was administered at a dosage of 375 mg/m<sup>2</sup> IV every week for 4 weeks and patients were followed for a total duration of 78 weeks. The median age of the patients was 46 years at baseline. The median platelet count ranged from 16,000/ $\mu$ L to 21,000/ $\mu$ L across treatment groups.

One trial evaluated the superiority of fostamatinib administered at a dosage of 100 mg orally twice daily over placebo for 24 weeks (Bussel et al.;  $n = 150$ ).<sup>15</sup> The median age of the patients was 54 years at baseline. The mean platelet count ranged from 16,052/ $\mu$ L to 19,818/ $\mu$ L across treatment groups.

### Summary of Critical Appraisal

The detailed risk of bias appraisal of all the included trials is available in [Appendix 7](#). The key limitations – that is, those having an impact on the interpretation of the findings – are summarized in this section for each treatment comparison.

### Eltrombopag Compared to Placebo

Eltrombopag was compared to placebo in 4 DB RCTs of a minimum of 6 weeks' duration. Of these, Yang et al. ( $n = 155$ )<sup>9</sup> and Cheng et al. ( $n = 197$ )<sup>10</sup> were both rated as having a low risk of bias and, therefore, were considered well conducted. Bussel et al. ( $n = 114$ )<sup>27</sup> was rated as having some concerns for overall risk of bias; the main issue with this study was that the differences in the incidence of adverse events (AEs) may have jeopardized blinding and have affected subjective outcome measurements.

Tomiyaama et al. ( $n = 23$ )<sup>25</sup> was rated as having some concerns for overall risk of bias. The small sample size of the study limits precision and affects confidence in the findings. Patients in the eltrombopag group had a higher baseline platelet count compared to placebo (mean platelet count of 21,000/ $\mu$ L versus 9,500/ $\mu$ L, and proportions of patients with platelet count of 15,000/ $\mu$ L or lower of 20% versus 75%, respectively). This is indicative of the failure of the randomization process, resulting in less severe ITP in patients randomized to eltrombopag, and may bias the results in favour of active treatment. Bleeding was not defined and, therefore, multiple and inconsistent definitions could have been used by assessors, again affecting precision and confidence in the findings.

Of note, 2 of the 4 trials<sup>9,25</sup> were performed exclusively in Asia; it is possible that standard of care is different in other countries, which would affect generalizability of the results to the Canadian population.

### Avatrombopag Compared to Placebo

Avatrombopag was compared to placebo in 1 DB RCT of 26 weeks' duration. Jurczak et al. ( $n = 49$ )<sup>12</sup> was rated as having an overall high risk of bias. The small sample size of the study limits precision and affects confidence in the findings. In addition, there were high discontinuation rates in both treatment arms, especially due to inadequate therapeutic response. Differences between groups in terms of reduction of

concomitant ITP medications from baseline and AEs may have jeopardized blinding and affected subjective outcome measurements.

### **Romiplostim Compared to Placebo**

Romiplostim was compared to placebo in 3 RCTs with substantial heterogeneity in methodology (e.g., DB versus OL setting) and follow-up duration. Of these, Kuter et al. (n = 125)<sup>11</sup> was a DB RCT of 24 weeks' duration rated as having a low risk of bias.

The other 2 studies were rated as having an overall high risk of bias. Shirasugi et al. (n = 34)<sup>13</sup> was a DB RCT of 12 weeks' duration and small sample size, limiting precision and affecting confidence in the findings. Kuter et al. (n = 234)<sup>14</sup> was an RCT of 52 weeks' duration with an OL design; considering that the definition of treatment failure, the primary outcome in the trial, included 1 subjective component (requirement for a change in therapy, which was based on clinical decision-making), it may be subject to bias in favour of active treatment due to the OL study design. In both studies, features suggestive of failure of the randomization process were observed, leading to imbalances between treatment groups in terms of disease severity. In Shirasugi et al.,<sup>13</sup> a higher proportion of patients in the placebo group had concomitant ITP medication at baseline compared to romiplostim (83% versus 59%, respectively), suggesting more severe ITP in patients randomized to placebo and biasing the results in favour of active treatment. In contrast, in Kuter et al.,<sup>14</sup> a higher proportion of patients in the romiplostim group had concomitant ITP medication at baseline compared to placebo (13% versus 6%, respectively), suggesting more severe ITP in patients in the romiplostim group, and may bias the results against active treatment. Shirasugi et al.<sup>13</sup> was also subject to blinding issues, as differences between groups in terms of AEs were observed, hence affecting subjective outcome measurements. The trial was performed exclusively in Japan; it is possible that standard of care is different in other countries, which would affect generalizability of the results to the Canadian population.

### **Rituximab Compared to Placebo**

Rituximab was compared to placebo in 1 DB RCT of 78 weeks' duration. Ghanima et al. (n = 112)<sup>32</sup> was rated as having some concerns for overall risk of bias. Not all hospital staff were blinded to treatment allocation, because it was communicated to local hospital pharmacies for infusion bag preparation; in addition, differences between groups in some AEs may also have jeopardized blinding, affecting subjective outcome measurements. The definition of treatment failure, the primary outcome in the trial, was a composite outcome that was amended during the study at a timing that was unclear to include being a candidate for splenectomy. Although this decision seemed to be based on clinical considerations, this may be perceived as an issue due to the lack of details surrounding it reported in the publication.

### **Fostamatinib Compared to Placebo**

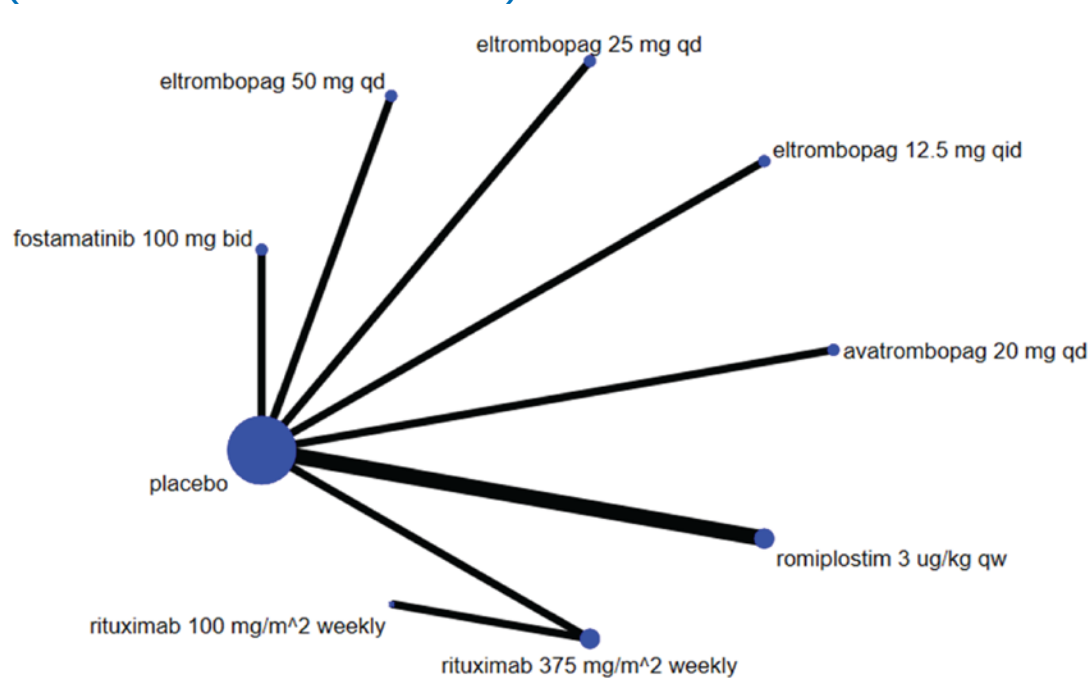
Fostamatinib was compared to placebo in 1 DB RCT of 24 weeks' duration. Bussel et al. (n = 150)<sup>15</sup> was rated as having an overall high risk of bias. Discontinuation rates were high, especially due to inadequate therapeutic response, in both fostamatinib and placebo groups. Differences between groups in some AEs may have jeopardized allocation concealment, but this would only affect the subjective outcome measurements.

## Data Analysis and Synthesis

### Findings of the NMA

Ten RCTs met the inclusion criteria. A network diagram is shown in [Figure 2](#) and additional details of the feasibility assessment are reported in [Appendix 5](#). Several issues were identified by the feasibility assessment both in terms of methodological and clinical heterogeneity of the network. As a result, the data in the network as described in the prespecified statistical analyses plan was considered infeasible for pooling and analyzing using NMA methodology. Alternative networks for analysis were also considered but had similar limitations for feasibility of conducting an NMA. For these reasons, a narrative synthesis of the evidence was conducted for the studies included in the network.

**Figure 2: Network for Platelet Count Response Using the Most Encompassing Threshold (20 Thousand or More Platelets)**



bid = twice daily; qd = once daily; qw = weekly.

### Narrative Synthesis

To mitigate the lack of informative results from the NMA, a narrative synthesis was conducted. The narrative review was conducted due to heterogeneity across the publications; as such, there were several differences in the way that outcomes were defined, measured, and reported. There was no additional restriction set other than the selection criteria for inclusion in the systematic review. The outcome measures that were considered by the review team to be the most relevant to decision-making were extracted from the peer-reviewed publications. This section lays out the body of evidence, as well as the results and findings, for each treatment comparisons that were available in the 10 studies included in the systematic review – that

is, a total of 5 placebo or standard of care comparisons of ITP drugs used as subsequent-line treatment in patients who have had experience with prior ITP therapies.

### **Results**

Detailed outcome results for studies included in the narrative review are presented in [Appendix 6](#) to [Appendix 9](#).

### **Splenectomy**

Among the studies identified for inclusion in the NMA, 8 studies reported the proportion of patients splenectomized at baseline. Only 1 study reported cohort-specific outcomes for splenectomized and nonsplenectomized groups.<sup>11</sup> Four studies reported splenectomy as an outcome on its own or within a composite outcome.<sup>9,32</sup> No studies were identified to draw conclusions on the place of splenectomy in second-line therapies.

## **Economic Analysis**

### **Economic Evaluation**

The intended economic evaluation was to address the following research questions:

1. What is the cost-effectiveness of therapies in adult patients with ITP who have failed first-line treatments?
2. What is the cost-effectiveness of splenectomy compared with second-line therapies (rituximab, fostamatinib, or TPO-RA [romiplostim, eltrombopag, avatrombopag]) in adult patients with ITP?

### **Primary Economic Analysis**

Given the findings from the CADTH clinical review, conclusions regarding the comparative clinical effects of treatments could not be drawn. As such, a primary economic evaluation could not be conducted due to both evidence gaps and limitations with the existing clinical evidence. Specifically, the disease trajectory of patients with ITP across different treatments could not be modelled due to limited and heterogeneous treatment-specific response data; heterogeneity across studies in the definition of treatment response thresholds, bleeding, and other adverse outcomes; and limited information on the time-dependent risk of bleeding events across treatments. Further, both baseline characteristics for patients with ITP and the measurement of outcomes of interest on standard or care treatment within a Canadian context were lacking.

Because CADTH conducted a scoping exercise for the economic evaluation, Appendix 11 provides a review of existing published decision-analytic models in this clinical area, an in-depth discussion of the limitations of the current evidence that precludes the conduct of an economic evaluation but can help inform areas for further research, and, a proposed structure for the “ideal” decision-analytic model that would be able to address the above research questions, highlighting the potential model inputs required and data gaps that would need to be resolved.

## Discussion

### Summary of Evidence

The aim of this HTA was 2-fold: to determine what treatment(s) should be used in adult patients with ITP who have failed first-line treatment, and to establish the place in second-line therapy of splenectomy in adult patients with ITP. The project scope and research protocol were informed by engaging with patient groups to better understand the challenges associated with ITP and current treatments. A total of 15 publications met the final inclusion criteria, reporting findings from 10 unique trials on the use of subsequent-line ITP treatments. No study with comparisons to splenectomy could be identified from the literature search.

Patients were eligible for inclusion in the studies if they were adults with a newly diagnosed, persistent, or chronic ITP, with a platelet count of less than  $30 \times 10^9/L$ . Four RCTs compared eltrombopag to placebo over a minimum of 6 weeks, 1 RCT compared avatrombopag to placebo over 26 weeks, and 3 RCTs compared romiplostim to placebo or standard of care. Two RCTs evaluated interventions other than TPO-RA, including 1 comparing rituximab to placebo over 4 weeks and 1 comparing fostamatinib to placebo over 26 weeks. Trials permitted concomitant use of other ITP medications including corticosteroids, azathioprine, and danazol. The primary efficacy outcome was platelet count response; however, there were several differences across the included trials in the way that platelet count response was defined, measured, and reported.

A feasibility assessment determined that an NMA of RCTs was not feasible due to clinical heterogeneity between studies and methodological constraints. An alternate NMA with simplified assumptions based on the limitations of the network was conducted and results were not deemed informative. For these reasons, conclusions from the NMA could not be drawn. Rather, a narrative synthesis of the evidence was conducted for the included studies.

The risk of bias across the 10 studies ranged from low<sup>9-11</sup> to high.<sup>12-15</sup> An overall limitation of the included trials was the small sample size, which limited the level of precision and affected the certainty in the findings. The study populations were generalizable to most ITP patients, bearing in mind that there were likely differences in local background standard of care treatments across the various countries where the studies were performed. Baseline characteristics between treatment groups were balanced in most cases, with few trials having baseline imbalances that could have introduced bias.<sup>13,25</sup> Study discontinuation rates were significant in some studies.<sup>12,15</sup> Finally, the concomitant use of other ITP medications, likely to be a significant confounding factor, was not always reported in publications, which could affect the interpretation of the findings.

### *Eltrombopag*

In patients with prior ITP treatment, 4 RCTs found that eltrombopag was superior to placebo at generating a long-lasting platelet count response (at least 6 weeks and up to 6 months), reducing bleeding events, and improving HRQoL. Eltrombopag was associated with a reduced need for rescue medication and concomitant ITP medications compared to placebo, including corticosteroids. Eltrombopag appeared to be well tolerated in the studies and no strong safety signal was identified.



### ***Romiplostim***

In patients who have experience with prior ITP therapies, 3 RCTs found that romiplostim induced a platelet count response compared to placebo or standard of care. Romiplostim also reduced the need for rescue medication and was associated with improvements in HRQoL compared with placebo and standard of care. Although romiplostim was generally well tolerated, there were inconsistencies in the harm profiles across studies.

### ***Avatrombopag***

In patients who have experience with prior ITP therapies, avatrombopag was assessed in a single, small, placebo-controlled study that had a high risk of bias, which contributed to a high level of uncertainty and limited the conclusions that could be drawn from this trial.

### ***Rituximab***

In patients with primary ITP who failed a short course of corticosteroid therapy, 1 RCT with a moderate risk of bias evaluated treatment failure (i.e., the absence of platelet response) in those receiving either rituximab or placebo. However, the a priori defined threshold for statistical significance for treatment failure was not met, limiting the conclusions that could be drawn from the trial.

### ***Fostamatinib***

In patients who have experience with prior ITP therapies, 1 RCT with a high risk of bias found that fostamatinib was associated with a higher proportion of patients with stable platelet response compared to placebo. However, the magnitude of the treatment response appeared low and discontinuation rates were high.

## **Interpretation of Clinical Results**

The systematic review was undertaken at the request of public drug plans to determine the efficacy and safety of therapies in adult patients with ITP who have failed first-line treatments. In consulting with patient groups, patients with ITP expressed a desire for more accessibility to additional therapies for ITP and a desire to avoid splenectomy.

A narrative synthesis of the trials identified in the systematic review found that eltrombopag and romiplostim increased platelet count response and demonstrated an improvement in symptoms and quality of life compared to placebo. Interpretation of the effectiveness of avatrombopag, rituximab, and fostamatinib were inconclusive due to the limited availability of evidence (i.e., 1 single trial for each intervention with varying risks of bias). Due to a scarcity of evidence, conclusions could not be drawn about the outcomes of time to platelet response, time to treatment failure, emergency department visits, hospitalization, and treatment-free remission.

No head-to-head study was identified, and the trials included in the systematic review were limited to comparisons to placebo or standard of care. In addition, methodological consideration prevented an NMA from being conducted. As such, direct comparisons of effectiveness between ITP treatments cannot be made. Similarly, there was insufficient evidence to inform the efficacy or sequence of subsequent-line

therapies in subgroups of adult patients with ITP or the role of splenectomy in the sequence of subsequent-line therapies.

A de novo economic model could not be conducted due to various clinical data gaps; therefore, the comparative cost-effectiveness of treatments for ITP remains unknown.

## **Strengths and Limitations of the Systematic Review**

### ***Strengths***

The systematic review was developed using robust methodology. The research protocol was developed a priori and registered with the PROSPERO database, and a detailed scoping plan was posted publicly for stakeholder input. Input from those with lived experience was used to inform the research protocol. The literature search was comprehensive and was also publicly posted for stakeholder feedback.

Evidence collection, data extraction, and evaluation of the quality of the studies were completed by a single reviewer, with verification by a second. Conflicts in data collection were adjudicated by a third reviewer. Heterogeneity across trials was assessed and the analytical approach for the NMA was aligned with ISPOR guidelines and employed a standard methodology.

### ***Limitations***

Following an NMA feasibility analysis, it was determined that an alternate and more simplified NMA be conducted. The number of trials that contributed to the NMA was limited and results reported were highly heterogeneous. Due to the limited size of the network, it was not possible to adequately account for the level of heterogeneity, and as a result, the variation around estimated effects were extremely wide and generally not informative. Thus, we were unable to use the findings of the NMA to draw conclusions for the report. The narrative review was based on limited availability of evidence, including single trials with low sample sizes for avatrombopag, rituximab, and fostamatinib.

## **Interpretation of Economic Evaluation**

Given that an economic model could not be conducted due to various clinical data gaps, the comparative cost-effectiveness of treatments for ITP is unknown.

## **Conclusions and Implications for Decision-Making or Policy-Making**

Public drug plans may consider revisiting reimbursement criteria for eltrombopag and romiplostim when used in ITP. CADTH suggests that interested jurisdictions request an implementation advice panel to suggest strategies (e.g., discontinuation criteria) to manage the clinical and economic uncertainty identified in the report. Outlining what specific discontinuation criteria should be considered is beyond the scope of this report.

Patients with ITP expressed a desire to avoid surgery (splenectomy) and the side effects associated with long-term steroid use. Patients also voiced a desire to see different types of therapies accessible to patients in Canada, including avatrombopag, fostamatinib, eltrombopag, romiplostim, and rituximab.

To determine what treatment(s) should be used in adult patients with ITP who have failed first-line treatments, a systematic review of the efficacy of treatments was undertaken at the request of public drug plans. A narrative review of 15 publications, reporting findings from 10 RCTs, found that eltrombopag and romiplostim increased platelet count response and improved ITP symptoms and HRQoL compared to placebo. Interpretation of the effectiveness of avatrombopag, rituximab, and fostamatinib was inconclusive due to limited evidence (i.e., 1 single trial for each intervention, with varying risks of bias). Of note, recently, CADTH recommended that fostamatinib not be reimbursed for the treatment of thrombocytopenia in adult patients with chronic ITP who have had an insufficient response to other treatments.<sup>33</sup> Avatrombopag for the treatment of thrombocytopenia in adult patients with chronic ITP who have had an insufficient response to a previous treatment is currently under CADTH Reimbursement Review.<sup>34</sup>

Due to the scarcity of evidence, conclusions could not be drawn about the outcomes of emergency department visits, hospitalizations, or treatment-free remission for any of the interventions. No direct treatment comparisons were identified, and methodological consideration prevented an NMA from being conducted; therefore, direct comparisons of effectiveness between ITP treatments could not be made. Similarly, there was insufficient evidence to inform the efficacy or sequence of subsequent-line therapies in specific subgroups of adult patients with ITP or the place in therapy of splenectomy. The comparative cost-effectiveness of treatments for ITP is unknown; further research is needed to compensate for clinical data gaps to inform an appropriate and relevant economic evaluation.

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## Appendix 1: Literature Search Strategy

Note that this appendix has not been copy-edited.

### Clinical Literature Search

#### Overview

Interface: Ovid

#### Databases:

- MEDLINE All (1946-present)
- Embase (1974-present)
- Cochrane Central Register of Controlled Trials (CCTR)
- Note: Subject headings and search fields have been customized for each database. Duplicates between databases were removed in Ovid.

Date of search: July 23, 2021

Alerts: Monthly search updates until July 26, 2022

**Search filters applied:** Systematic reviews; meta-analyses; network meta-analyses; health technology assessments; guidelines; overview of reviews; randomized controlled trials; and controlled clinical trials.

#### Limits:

- Humans
- Language limit: English- and French-language
- Conference abstracts: excluded

### Table 6: Syntax Guide

Syntax	Description
/	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
adj#	Requires terms to be adjacent to each other within # number of words (in any order)
.ti	Title
.ot	Original title
.ab	Abstract



Syntax	Description
.hw	Heading word; usually includes subject headings and controlled vocabulary
.kf	Keyword heading word
.kw	Author keyword (Embase); keyword (CDSR)
.dq	Candidate term word (Embase)
.pt	Publication type
.mp	Mapped term
.rn	Registry number
.nm	Name of substance word (MEDLINE)
.yr	Publication year
.jw	Journal title word (MEDLINE)
medall	Ovid database code: MEDLINE All, 1946 to present, updated daily
oomezd	Ovid database code; Embase, 1974 to present, updated daily
cctr	Ovid database code; Cochrane Central Register of Controlled Trials

### Multi-Database Strategy

1. (romiplostim\* or Nplate\* or Romiplate\* or amg531 or amg 531 or amgen megakaryopoiesis protein 531 or GN5XU2DXKV).ti,ab,kf,kw,ot,hw,nm,rn.
2. (eltrombopag\* or Revolade\* or Promacta\* or Elbonix\* or SB-497115 or SB497115 or SB-497-115 or SSS-20 or SSS20 or HSDB-8212 or HSDB8212 or S56D65XJ9G).ti,ab,kf,kw,ot,hw,nm,rn.
3. (avatrombopag\* or Doptelet\* or AKR 501 or AKR501 or E 5501 or E5501 or AS 1670542 or AS1670542 or YM 477 or YM477 or 3H8GSZ4SQL or GDW7M2P1IS).ti,ab,kf,kw,ot,hw,nm,rn.
4. (((thrombopoietin or TPO) adj2 (receptor agonist\* or RA or RAs)) or TPORA or TPORAS).ti,ab,kf,kw.
5. Rituximab/ or (rituximab\* or Rituxan\* or Truximab\* or MabThera\* or Mab Thera\* or Truxima\* or blitzima\* or reditux\* or ritemvia\* or rituxin\* or rituzena\* or rixathon\* or riximyo\* or truxella\* or HSDB 7455 or HSDB7455 or IDEC-102 or IDEC102 or IDEC-C2B8 or IDECC2B8 or PF-05280586 or PF05280586 or RO-452294 or RO452294 or RG-105 or RG105 or CT-P10 or CTP10 or 4F4X42SYQ6).ti,ab,kf,kw,ot,hw,nm,rn.
6. (fostamatinib\* or Tavalisse\* or Tavlesse\* or R935788 or R788 or R-788 or SQ8A3S5101 or 86EEZ49YVB or X9417132K8 or R 406 or R406 or R950091 or R 950091 or taminib fosdium).ti,ab,kf,kw,ot,hw,nm,rn.
7. Splenectomy/ or (splenectom\* or (spleen\* adj2 (removal or resection))).ti,ab,kf,kw.
8. ((secondary or tertiary or failure or failed) adj3 (therap\* or treatment\*)).ti,ab,kf,kw.
9. (second-line or secondline or third-line or thirdline).ti,ab,kf,kw.
10. or/1-9
11. Purpura, thrombocytopenic/ or idiopathic thrombocytopenic purpura/
12. ((autoimmune\* or immun\* or idiopathic\* or purpur\*) adj2 thrombocytopen\*).ti,ab,kf,kw.



13. (Werlhof disease\* or morbus werlhof\*).ti,ab,kf,kw.
14. ITP.ti,ab,kf,kw.
15. 11 or 12 or 13 or 14
16. 10 and 15
17. 16 use cctr
18. 16 use medall
19. \*romiplostim/ or (romiplostim\* or Nplate\* or Romiplate\* or amg531 or amg 531 or amgen megakaryopoiesis protein 531 or GN5XU2DXKV).ti,ab,kw,dq.
20. \*eltrombopag/ or (eltrombopag\* or Revolade\* or Promacta\* or Elbonix\* or SB-497115 or SB497115 or SB-497-115 or SSS-20 or SSS20 or HSDB-8212 or HSDB8212).ti,ab,kw,dq.
21. \*avatrombopag/ or (avatrombopag\* or Doptelet\* or AKR 501 or AKR501 or E 5501 or E5501 or AS 1670542 or AS1670542 or YM 477 or YM477 or 3H8GSZ4SQL or GDW7M2P1IS).ti,ab,kw,dq.
22. (((thrombopoietin or TPO) adj2 (receptor agonist\* or RA or RAs)) or TPORA or TPORAS).ti,ab,kw,dq.
23. \*rituximab/ or (rituximab\* or Rituxan\* or Truximab\* or MabThera\* or Mab Thera\* or Truxima\* or blitzima\* or reditux\* or ritemvia\* or rituxin\* or rituzena\* or rixathon\* or riximyo\* or truxella\* or HSDB 7455 or HSDB7455 or IDEC-102 or IDEC102 or IDEC-C2B8 or IDECC2B8 or PF-05280586 or PF05280586 or RO-452294 or RO452294 or RG-105 or RG105 or CT-P10 or CTP10 or 4F4X42SYQ6).ti,ab,kw,dq.
24. \*fostamatinib/ or (fostamatinib\* or Tavalisse\* or Tavlesse\* or R935788 or R788 or R-788 or SQ8A3S5101 or 86EEZ49YVB or X9417132K8 or R 406 or R406 or R950091 or R 950091 or tamatinib fosdium).ti,ab,kw,dq.
25. Splenectomy/ or (splenectom\* or (spleen\* adj2 (removal or resection))).ti,ab,kw,dq.
26. ((secondary or tertiary or failure or failed) adj3 (therap\* or treatment\*)).ti,ab,kw,dq.
27. (second-line or secondline or third-line or thirdline).ti,ab,kw,dq.
28. or/19-27
29. thrombocytopenic purpura/ or idiopathic thrombocytopenic purpura/
30. ((autoimmune\* or immun\* or idiopathic\* or purpur\*) adj2 thrombocytop\*).ti,ab,kw,dq.
31. (Werlhof disease\* or morbus werlhof\*).ti,ab,kw,dq.
32. ITP.ti,ab,kw,dq.
33. or/29-32
34. 28 and 33
35. 34 use oemezd
36. (conference abstract or conference review).pt.
37. 35 not 36

38. (Randomized Controlled Trial or Controlled Clinical Trial or Pragmatic Clinical Trial or Equivalence Trial or Clinical Trial, Phase III).pt.
39. Randomized Controlled Trial/
40. exp Randomized Controlled Trials as Topic/
41. "Randomized Controlled Trial (topic)"/
42. Controlled Clinical Trial/
43. exp Controlled Clinical Trials as Topic/
44. "Controlled Clinical Trial (topic)"/
45. Randomization/
46. Random Allocation/
47. Double-Blind Method/
48. Double Blind Procedure/
49. Double-Blind Studies/
50. Single-Blind Method/
51. Single Blind Procedure/
52. Single-Blind Studies/
53. Placebos/
54. Placebo/
55. Control Groups/
56. Control Group/
57. (random\* or sham or placebo\*).ti,ab,hw,kf,kw.
58. ((singl\* or doubl\*) adj (blind\* or dumm\* or mask\*)).ti,ab,hw,kf,kw.
59. ((tripl\* or trebl\*) adj (blind\* or dumm\* or mask\*)).ti,ab,hw,kf,kw.
60. (control\* adj3 (study or studies or trial\* or group\*)).ti,ab,kf,kw.
61. (Nonrandom\* or non random\* or non-random\* or quasi-random\* or quasirandom\*).ti,ab,hw,kf,kw.
62. allocated.ti,ab,hw.
63. ((open label or open-label) adj5 (study or studies or trial\*)).ti,ab,hw,kf,kw.
64. ((equivalence or superiority or non-inferiority or noninferiority) adj3 (study or studies or trial\*)).ti,ab,hw,kf,kw.
65. (pragmatic study or pragmatic studies).ti,ab,hw,kf,kw.
66. ((pragmatic or practical) adj3 trial\*).ti,ab,hw,kf,kw.
67. ((quasiexperimental or quasi-experimental) adj3 (study or studies or trial\*)).ti,ab,hw,kf,kw.
68. (phase adj3 (III or "3") adj3 (study or studies or trial\*)).ti,hw,kf,kw.
69. or/38-68

70. (systematic review or meta-analysis).pt.
71. meta-analysis/ or systematic review/ or systematic reviews as topic/ or meta-analysis as topic/ or "meta analysis (topic)"/ or "systematic review (topic)"/ or exp technology assessment, biomedical/ or network meta-analysis/
72. ((systematic\* adj3 (review\* or overview\*)) or (methodologic\* adj3 (review\* or overview\*))).ti,ab,kf,kw.
73. ((quantitative adj3 (review\* or overview\* or syntheses\*)) or (research adj3 (integrati\* or overview\*))).ti,ab,kf,kw.
74. ((integrative adj3 (review\* or overview\*)) or (collaborative adj3 (review\* or overview\*)) or (pool\* adj3 analy\*)).ti,ab,kf,kw.
75. (data syntheses\* or data extraction\* or data abstraction\*).ti,ab,kf,kw.
76. 76 (handsearch\* or hand search\*).ti,ab,kf,kw.
77. (mantel haenszel or peto or der simonian or dersimonian or fixed effect\* or latin square\*).ti,ab,kf,kw.
78. (met analy\* or metanaly\* or technology assessment\* or HTA or HTAs or technology overview\* or technology appraisal\*).ti,ab,kf,kw.
79. (meta regression\* or metaregression\*).ti,ab,kf,kw.
80. (meta-analy\* or metaanaly\* or systematic review\* or biomedical technology assessment\* or biomedical technology assessment\*).mp,hw.
81. (medline or cochrane or pubmed or medlars or embase or cinahl).ti,ab,hw.
82. (cochrane or (health adj2 technology assessment) or evidence report).jw.
83. (comparative adj3 (efficacy or effectiveness)).ti,ab,kf,kw.
84. (outcomes research or relative effectiveness).ti,ab,kf,kw.
85. (((indirect or indirect treatment or mixed-treatment or bayesian) adj3 comparison\*).ti,ab,kf,kw.
86. [(meta-analysis or systematic review).md.]
87. (multi\* adj3 treatment adj3 comparison\*).ti,ab,kf,kw.
88. (mixed adj3 treatment adj3 (meta-analy\* or metaanaly\*).ti,ab,kf,kw.
89. umbrella review\*.ti,ab,kf,kw.
90. (multi\* adj2 paramet\* adj2 evidence adj2 synthesis).ti,ab,kw,kf.
91. (multiparamet\* adj2 evidence adj2 synthesis).ti,ab,kw,kf.
92. (multi-paramet\* adj2 evidence adj2 synthesis).ti,ab,kw,kf.
93. or/70-92
94. 69 or 93
95. 18 and 94
96. 37 and 94
97. 17 or 95 or 96

98. limit 97 to (english or french)

99. remove duplicates from 98

### Clinical Trials Registries

#### *ClinicalTrials.gov*

Produced by the US National Library of Medicine. Targeted search used to capture registered clinical trials.

[Search -- Studies with results | ITP or immune thrombocytopenia]

#### *WHO ICTRP*

International Clinical Trials Registry Platform, produced by WHO. Targeted search used to capture registered clinical trials.

[Search terms -- ITP or immune thrombocytopenia]

#### *Health Canada's Clinical Trials Database*

Produced by Health Canada. Targeted search used to capture registered clinical trials.

[Search terms -- ITP or immune thrombocytopenia]

#### *EU Clinical Trials Register*

European Union Clinical Trials Register, produced by the European Union. Targeted search used to capture registered clinical trials.

[Search terms -- ITP or immune thrombocytopenia]

### Grey Literature

**Search dates:** August 9 to 15, 2021, July 26, 2021.

**Keywords:** ITP or immune thrombocytopenia

**Limits:** none

Relevant websites from the following sections of the CADTH grey literature checklist [Grey Matters: A Practical Tool for Searching Health-Related Grey Literature](#) were searched:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Advisories and Warnings

- Drug Class Reviews
- Clinical Trials Registries
- Databases (free)
- Health Statistics
- Internet Search
- Open Access Journals

The complete search archive of sites consulted for this report is available on request.

## Appendix 2: Statistical Analysis Plan

Note that this appendix has not been copy-edited.

### Objectives

The aim of this HTA to inform 2 policy questions:

1. What treatment(s) should be used in adult patients with immune thrombocytopenia who have failed first-line treatments?
2. What is the place in second-line therapy of splenectomy in adult patients with immune thrombocytopenia?

The objective is to review the available evidence on the use of therapies for ITP in adults with the objective of determining their comparative effectiveness.

The project will address the following research questions. Details on the specific interventions and outcomes are included in the selection criteria (See Protocol [Table 2](#): Selection criteria).

1. What is the efficacy and safety of therapies in adult patients with immune thrombocytopenia who have failed first-line treatments?
2. What is the efficacy and safety of splenectomy compared with second-line therapies (rituximab, fostamatinib, or TPO-RAs [romiplostim, eltrombopag, avatrombopag]) in adult patients with immune thrombocytopenia?

### Study Population

The study population are adult patients with ongoing active immune thrombocytopenia who have failed first-line treatments. Among the trials that meet the eligibility criteria (See Protocol [Table 2](#): Selection criteria), data will be grouped according to the following patient characteristics and used for subgroup analyses.

- Adult patients with chronic ITP (> 12 months)
- Adult patients with persistent ITP (between 3 to 12 months)
- Patients who have previously failed at least 1 second-line therapy.

For studies including more than 1 of these subpopulations, with no subgroup analysis reported, the study will be considered to belong to 1 of these subgroups if 80% of more of the enrolled patients belong to that subgroup.

### Interventions and Comparators

Intervention and comparators of interest will include all drugs specified here or belonging to the overall drug category specified here:

- Rituximab

- Eltrombopag
- Romiplostim
- Fostamatinib
- Avatrombopag
- Corticosteroids
- IVIG
- Immunosuppressants (e.g., azathioprine, cyclosporine, cyclophosphamide, mycophenolate mofetil, danazol, dapsone)
- Splenectomy
- Placebo/ standard of care

We will include studies reporting the standard doses of the treatment approved by Health Canada and doses considered of clinical relevance based on expert guidance or international clinical practice guidelines. All data on dosages and treatment duration for each included treatment will be reported.

In cases where there are variations in the dose or dosing schedule of 1 treatment across different studies, we will seek published literature to inform on the effect of such variations. In cases where no published literature is satisfactory, the clinical expert opinion on whether these differences are substantial enough to be a treatment effect modifier, in which case they will be analyzed as separate interventions. However, if dose and dosing schedule differences do not represent a substantial treatment difference in the opinion of the clinical expert, then they will be pooled together as a single intervention. In cases of a pooled treatment with variations in the dose or dosing schedule, a subsequent sensitivity analysis will be conducted to determine the effect of the pooling.

Any follow-up period without active intervention or open-label extension phase where all patients receive the same intervention will not be eligible for analysis.

## Outcomes

### Clinical Effectiveness Outcomes

#### *Platelet Count Response*

The proportion of patients with complete response, response, or no response as defined by the authors. We will also consider the mean difference in platelet count.

#### *Time to Platelet Response*

Time from starting treatment to time of achievement of complete response or response.

#### *Bleeding Events*

The proportion of patients with bleeding events.

### *Emergency Room Visits*

Number of emergency room visits for ITP-related clinical problem per patient.

### *Hospitalization*

Number of hospitalizations for ITP-related clinical problem per patient.

### *Health-Related Quality of Life*

The assessment of quality of life using any relevant metric will be eligible for analysis if an aggregate score is provided that represents the change from baseline to the end of treatment in the intervention groups. Domain-specific scores will not be eligible for analysis. Disease-specific measures will not be pooled with generic measures. Total scores will be converted to standardized mean differences and analyzed as a continuous outcome.

### *Symptoms (E.g., Fatigue)*

The proportion of patients with fatigue as reported by the authors or mean difference in fatigue scores.

### *Treatment-Free Remission*

The proportion of patients with treatment-free remission

### *Need for Rescue Medication:*

The proportion of patients who are given rescue medication, i.e., IVIG or corticosteroids.

### *Reduction or Discontinuation of Corticosteroids:*

The proportion of patients who reduce or discontinue their corticosteroid use.

## **Safety**

### *Adverse Events*

Proportion of patients reported to have any AEs.

### *Serious AEs*

Proportion of patients reported to have any serious AEs. Serious AEs as defined by the authors of the study or when a patient dies, has a life-threatening event, is hospitalized, or experiences disability or permanent damage.

### *Withdrawal Due to AEs*

Proportion of patients reported to have withdrawn from the study due to AEs.

### *Death*

Proportion of patients who die during the study.



## Check the Quality of Evidence

Risk of bias in the individual trials will be assessed using the Cochrane risk of bias 2 (RoB 2) tool.<sup>24</sup> Risk of bias assessments will be completed in duplicate for each trial. The RoB 2 tool can be used to assess bias arising from the randomization process, due to deviations from intended interventions, due to missing outcome data, measurement of the outcome, and bias in selection of the reported results. For each of these domains, a judgment of high risk of bias (the study is judged to be at high risk of bias in at least 1 domain or some concerns for multiple domains), some concerns (the study is judged to raise some concerns in at least 1 domain, but not at high risk of bias for any domain) or low risk of bias (the study is judged to be at low risk of bias from all domains) can be made. An assessment will be conducted separated for each outcome, and an overall risk of bias will be reached using the signalling questions algorithm included in the tool. We do not anticipate including any crossover or cluster RCTs. If we find any crossover or cluster trials, we will only use estimates that account for the correlation between participants in cluster trials and within participants in crossover trials. For each trial, the estimate regarding the effect of randomization i.e., ITT (as opposed to the effect of adhering to the intervention i.e., per protocol) will be considered. The results of these assessments will be displayed using the *robvis* tool for visualizing risk of bias. Overall risk of bias will be used as the basis for sensitivity analyses in which we will drop the studies at high risk of bias and examine how this affects the results.

In addition to searching for unpublished and ongoing studies, we will investigate small-study effects using Harbord's test for binary outcomes and Egger's test for continuous outcomes.<sup>35</sup> We will also inspect the network funnel plot for asymmetry.

## Construct Evidence Network

The evidence network for each outcome will be displayed graphically as a network plot. The lines will indicate direct comparisons and the thickness of the line will reflect the number of studies in each comparison. The vertices ("nodes") will represent individual interventions. Sizes of nodes will be directly proportional to the total sample size of participants contributing data to the node across all studies involving that intervention.

## Datasets

A standardized excel extraction sheet is piloted to abstract data from included studies. Modification to the extraction sheet will be conducted after a pilot of 5 studies. The data extraction will cover information pertaining to each study overall publication characteristics, study design, intervention, comparators, patients' characteristics, outcomes definitions, outcomes results, and AEs.

The primary publication for each unique study included will be used for data extraction, except where multiple publications for a single primary study are found. Multiple publications for a unique study (e.g., substudies, reports of additional outcomes or longer follow-up) will be used if they include data relevant to

our research question. The data will be entered as coming from the same study, but the related articles will be referenced as needed.

Where reported, patients' baseline characteristics and clinical efficacy outcomes will be abstracted from the ITT population in each study while AEs will be abstracted from the per-protocol i.e., safety population. The ITT approach implies the availability of a complete dataset i.e., no missing data. If an ITT analysis is not reported in the paper, we will use the per-protocol analysis. We will conduct sensitivity analyses to determine if the analytical strategy used in the trial affects the effect estimates. Trial definitions for intention to treat, modified intention to treat, and per-protocol data will be noted and compared for consistency.

For dichotomous outcomes, we use the number of patients with the event and the total number of patients in each arm. For continuous outcomes, we will extract the mean, standard deviation, and number of participants in each arm. For time to event outcomes, we will extract the mean/median time to event, standard deviation and the number of participants per-arm (arm-based approach). If only comparative effect estimates are reported, the NMA can be conducted with generic measures of effect such as the log of the odds ratio and hazard ratio and the corresponding standard errors (contrast-based approach).<sup>36</sup> For continuous outcomes, the standardized mean difference and its standard error can be used.

Screening, data extraction and risk of bias assessments will be conducted by 1 reviewer and verified by a second reviewer using a standardized data extraction form developed a priori, which will be piloted and modified as necessary.

## The Feasibility Assessment of an NMA

Prior to commencing the NMA, a qualitative feasibility assessment will be undertaken to assess clinical and methodological heterogeneity in the available data. Trials included in the same evidence network will be compared to identify any potential heterogeneity based on differences in participants, interventions, comparisons, outcomes, or study design. If substantial heterogeneity exists in certain comparisons or subsets of studies and the data are not meaningful to pool, narrative summaries of findings will be reported, including the report on the types of trials required to fill the knowledge gap. Quantitative analyses will not be conducted where there is insufficient data.

Where potential clinical or methods-related heterogeneity is identified and the degree of heterogeneity is considered large, and if we have data on potential effect modifiers, we will use meta-regression (if there are 10 or more studies) to adjust for these sources of heterogeneity.<sup>37</sup> If meta-regression is not possible, we will perform subgroup analyses or sensitivity analyses. Our process for assessing the feasibility of a NMA is outlined in [Appendix 5](#). If the feasibility assessment is positive, we can continue to the next steps in this analysis plan. If feasibility assessment is negative, then we may summarize why the network is not sufficient to support a valid NMA.

## Check Assumptions

Provided the NMA is deemed feasible, the identified network will be evaluated and tested for homogeneity.<sup>38</sup> For each study in the network, the patient population, definitions of interventions, definitions of outcomes, inclusion and exclusion criteria, and designs will be described and examined for similarity across the network. Patient baseline characteristics for potential effect modifiers identified by clinical experts will be examined for homogeneity across studies.

We will observe the logical structure of the graphs i.e., whether direct evidence is similar to indirect evidence, and evaluate the fitness of the statistical models. We will also measure the confidence intervals of the difference between the direct and indirect comparisons. We will use the node-splitting method, which will allow us to assess consistency locally within each closed loop of the network. We will also run an overall (global) test for inconsistency using the Wald test.<sup>39</sup>

We will use sensitivity analyses to determine the role of effect modifiers and meta regression to adjust for identified effect modifiers.

## Statistical Models

The NMAs will be conducted under a Frequentist framework using the multivariate meta-analysis approach.<sup>39,40</sup> Random-effects models will be used as the primary approach when feasible due to the anticipated clinical and methodological heterogeneity across studies. For sparse networks,<sup>41</sup> fixed effects models will be considered when the available network for a given outcome is insufficient for estimating a random-effects model, i.e., the confidence intervals are inaccurate. For each NMA we will use the design-by-treatment model (global test) to assess network coherence, and the side-splitting method to assess loop specific coherence,<sup>40</sup> computed as the difference between direct and indirect evidence. If there is large incoherence, we will use an inconsistency model to conduct the NMA.

The multivariate random-effects meta-analysis is estimated using restricted maximum likelihood that will be applied to arm-based or contrast-based data.<sup>36</sup> The results will be presented as network plots, contribution plots, and league tables.<sup>42</sup>

If an NMA is not feasible. We will conduct a pairwise random-effects meta-analysis, comparing all available treatments to placebo or to the most common (i.e., reported in most studies) available comparison or the most relevant standard of care. If this alternative approach is also not informative a narrative synthesis will be conducted.

For binary outcomes, odds ratios and 95% confidence intervals will be reported. In cases when events are rare, the Peto odds ratio will be used. For continuous outcomes measured on the same scale, mean differences and 95% confidence intervals will be reported. For continuous outcomes measured on different scales, standardized mean differences and 95% confidence intervals will be reported. If insufficient data are found for conducting meta-analyses, narrative descriptions will be provided.

For the network or pairwise meta-analysis, we will conduct subgroup analyses comparing outcomes in trials belonging to the following subgroups:

- Adult patients with chronic ITP (> 12 months)
- Adult patients with persistent ITP (between 3 to 12 months)
- Patients who have previously failed at least 1 second-line therapy

We will conduct additional sensitivity analysis by excluding studies with high risk of bias or studies with missing data to a relevant outcome. We will also explore the effect of outliers and influential trials by running models with and without them. All analyses will be conducted using Stata 16.0 (StataCorp, College Station, Texas, US). All comparisons will be 2 tailed using a threshold  $P \leq 0.05$ .

## Appendix 3: List of Included Studies

Note that this appendix has not been copy-edited.

- Tomiyama et al. 2012<sup>25</sup>
- Yang et al. 2017<sup>9</sup>
  - Liu et al. 2020<sup>26</sup>
- Bussel et al. 2009<sup>27</sup>
- Cheng et al. 2011<sup>10</sup>
- Jurczak et al. 2018<sup>12</sup>
- Shirasugi et al. 2011<sup>13</sup>
- Kuter et al. 2008<sup>11</sup>
- George et al. 2009<sup>28</sup>
  - Gernsheimer et al. 2010<sup>29</sup>
  - Sanz et al. 2011<sup>30</sup>
- Kuter et al. 2010<sup>14</sup>
  - Kuter et al. 2012<sup>31</sup>
- Ghanima et al. 2015<sup>32</sup>
- Bussel et al. 2018<sup>15</sup>

## Appendix 4: List of Excluded Studies During Data Extraction

Note that this appendix has not been copy-edited.

**Table 7: List of Excluded Studies During Data Extraction**

Author (year) NCT Number (If Available)	Reason for Exclusion
Abdallah et al. (2021) <a href="#">NCT03229746</a>	Intervention
Zhou et al. (2015) <a href="#">NCT01525836</a>	Intervention (rhTPO)
<a href="#">NCT00770562</a> Zaja et al. (2010) Hoffman-La Roche (2014) <a href="#">clinicaltrials.gov</a>	Patient population (treatment naive)
Cui et al. (2013)	Intervention (rhTPO)
Gudbrandsdottir et al. (2013) <a href="#">NCT00909077</a>	Patient population – includes treatment naive patients
Wang et al. (2012)	Intervention (rhTPO)
Li et al. (2011)	Patient population – includes treatment naive patients
Jamali et al. (2009)	Regulatory approval summary - unable to identify referenced studies
Newman et al. (2001)	Intervention
Lang et al. (1987)	Study design

## Appendix 5: Network Meta-Analysis

Note that this appendix has not been copy-edited.

Prior to conducting an NMA, we performed a qualitative feasibility assessment to determine if the data were sufficiently similar to pool from a clinical and a methodological perspective. Clinical heterogeneity is concerned with the homogeneity in participants, interventions, comparisons, and outcomes, while methodological heterogeneity is concerned with the design and analysis.

### Methodological Heterogeneity

While all the included studies were all phase III or IV two-arm parallel group randomized trials, we identified some design concerns. Three of the included studies were OL.<sup>14,15,43</sup> The study durations ranged from 6 to 78 weeks. These differences on their own would not have precluded an NMA.

We noted some differences in how data were analyzed across some outcomes. For example, in some studies the same outcome was reported as hazard ratio and in others only figures were reported. In some instances, percentages were reported without numerators or denominators, thus precluding the estimation of variances.

### Clinical Heterogeneity

*Participant* homogeneity was assured based on the inclusion criteria. All the studies met the inclusion criteria which included adult patients with ongoing active ITP who had failed first-line treatments.

*Intervention* and *comparator* homogeneity was ensured based on the inclusion criteria. All the included studies used either rituximab (100mg/m<sup>2</sup>/week, 375mg/m<sup>2</sup>/week), Eltrombopag (12.5mg once daily, 25mg once daily, 50mg once daily), Romiplostim (1mcg/kg qw, 3mcg/kg qw), Fostamatinib (100 mg bd) or Avatrombopag (20 mg once daily) compared to placebo or to each other. Placebo groups were uniform across studies.

There was considerable *outcome* heterogeneity. For example, platelet count response was defined at different thresholds ( $\geq 20,000$ ,  $\geq 30,000$ ,  $\geq 50,000$  and  $\geq 100,000$  platelets/ $\mu$ L). Some studies reported more than 1 threshold, but even when we had multiple studies with the same threshold, the definitions were different. These differences included the number of measurements and the timing of the measurements. Three examples are shown below:

“Platelet counts  $\geq 50 \times 10^9$  on at least 4 of the 6 clinic visits occurring every 2 weeks during weeks 14–24 inclusive”

“Proportion of patients with platelet counts  $\geq 50,000/\mu$ L and at least twice the baseline amount”

"At least 1 platelet count  $\geq 50 \times 10^9$  within first 12 weeks"

This heterogeneity was present for other outcomes such as bleeding, in which some studies used WHO-defined grades and others did not.

We attempted to pool all the studies with a threshold of  $\geq 20,000$  and  $\geq 30,000$  and found that the threshold impacted the relative effects of treatments (e.g., at higher thresholds, romiplostim was less likely to be better than placebo).

### Other Issues

In addition to the concerns with heterogeneity noted above, the data were sparse i.e., we had too few comparisons per study and any attempts to create smaller more homogenous groups further aggravated the issue, leading to very wide confidence intervals. These wide confidence intervals produced results (most active treatments were not statistically significantly better than placebo) that were contradictory to the findings from the individual studies.

Further, consistency could not be estimated since there was limited direct evidence for the same comparison (almost all comparisons were treatments versus placebo) i.e., there were no closed loops.

Based on this, we concluded that the available data were not meaningful to pool and have presented narrative summaries of the findings. This decision is in line with recommended guidance for addressing feasibility in NMA and our statistical analysis plan.



## Appendix 6: Summary Tables of Studies With Eltrombopag as Intervention

Note that this appendix has not been copy-edited.

**Table 8: Details of Included Studies — Eltrombopag as Intervention (N = 4 Studies)**

Criteria	Tomiyama et al. 2012	Yang et al. 2017	Bussel et al. 2009	Cheng et al. 2011
<b>Designs and Populations</b>				
<b>Study Design</b>	DB RCT	DB RCT	DB RCT	DB RCT
<b>Locations</b>	Multicenter: Japan	Multicenter: China	Multicenter: 23 countries	Multicenter: Canada, US, UK, New-Zealand, Peru, Europe, Asia
<b>Randomized</b>	n = 23	n = 155	n = 114	n = 197
<b>Place in Therapy</b>	Subsequent-line treatment in patients who have failed one or more prior ITP therapies	Subsequent-line treatment in patients who have failed one or more prior ITP therapies	Subsequent-line treatment in patients who have failed one or more prior ITP therapies	Subsequent-line treatment in patients who have experience with prior ITP therapies
<b>Inclusion Criteria</b>	<ul style="list-style-type: none"> <li>Adults (<math>\geq 20</math> years) diagnosed with ITP for <math>\geq 6</math> months</li> <li>Platelet count level <math>&lt; 30\,000/\mu\text{L}</math></li> <li>Received one or more prior ITP treatment and failed to achieve a platelet count <math>\geq 30\,000/\mu\text{L}</math> (refractory or relapse patients)</li> <li>Laboratory values within normal or close-to-normal range, with the exception of hemoglobin and neutrophil count</li> </ul>	<ul style="list-style-type: none"> <li>Adults (<math>\geq 18</math> years) diagnosed with ITP for <math>\geq 12</math> months</li> <li>Platelet count level <math>&lt; 30\,000/\mu\text{L}</math></li> <li>Received and failed one or more prior ITP treatment (refractory or relapse patients)</li> <li>Laboratory values within normal or close-to-normal range excepting neutrophil count and hemoglobin</li> <li>No preexisting cardiac disease within 3 months</li> <li>No other clotting disorder</li> </ul>	<ul style="list-style-type: none"> <li>Adults (<math>\geq 18</math> years) diagnosed with ITP for <math>\geq 6</math> months</li> <li>Platelet count level <math>&lt; 30\,000/\mu\text{L}</math></li> <li>Received <math>\geq 1</math> prior ITP treatment</li> <li>Normal creatinine and liver enzyme concentrations</li> </ul>	<ul style="list-style-type: none"> <li>Adults (<math>\geq 18</math> years) diagnosed with ITP for <math>\geq 6</math> months</li> <li>Platelet count level <math>&lt; 30\,000/\mu\text{L}</math></li> <li>Received <math>\geq 1</math> prior ITP therapies</li> <li>Initially responded to prior ITP therapy (platelet count <math>&gt; 100\,000/\mu\text{L}</math>)</li> <li>Laboratory values within normal or close-to-normal range, with the exception of platelets and hemoglobin</li> </ul>
<b>Exclusion Criteria</b>	<ul style="list-style-type: none"> <li>Severe medical condition other than ITP</li> <li>History of arterial or venous thrombosis within 1 year</li> </ul>	<ul style="list-style-type: none"> <li>Any relevant abnormality other than ITP</li> <li>Any history of arterial or venous thrombosis with</li> </ul>	<ul style="list-style-type: none"> <li>Congestive heart failure, arrhythmia, or thrombosis within 1 year</li> <li>MI within 3 months</li> </ul>	<ul style="list-style-type: none"> <li>Any relevant abnormality other than primary ITP</li> <li>History of arterial or venous thrombosis with <math>\geq 2</math> additional risk</li> </ul>

Criteria	Tomiyaama et al. 2012	Yang et al. 2017	Bussel et al. 2009	Cheng et al. 2011
	<ul style="list-style-type: none"> <li>Blood disorder other than ITP</li> <li>Platelet aggregation abnormality</li> <li>HIV, hepatitis B, or hepatitis C virus infection</li> <li>Malignancies</li> <li>Ongoing use of antiplatelet agents, anticoagulants, or NSAIDs</li> </ul>	<ul style="list-style-type: none"> <li>the presence of <math>\geq 2</math> additional risk factors for thrombosis</li> <li>History of platelet aggregation</li> <li>HIV, hepatitis B, or hepatitis C virus infection</li> <li>Ongoing use of antiplatelet agents, anticoagulants, or NSAIDs</li> </ul>	<ul style="list-style-type: none"> <li>HIV, hepatitis B, or hepatitis C virus infection</li> </ul>	<ul style="list-style-type: none"> <li>factors for thrombosis</li> <li>Cardiovascular disease</li> <li>History of platelet agglutination abnormality</li> <li>HIV, antiphospholipid antibody syndrome, hepatitis B, or hepatitis C virus infection</li> <li>Malignancies</li> <li>Use of anticoagulant, antiplatelet drug, or NSAID</li> </ul>
<b>Intervention</b>	Eltrombopag 12.5 to 50 mg orally once daily for 6 weeks Dose depending on the platelet count response + standard of care	Eltrombopag 25 mg orally once daily for 8 weeks (start dose) Dose to be adjusted based on platelet count + standard of care	Eltrombopag 50 mg orally once daily for 6 weeks Dose up to 75 mg based on platelet count + standard of care	Eltrombopag 50 mg orally once daily for 6 months (start dose) Dose to be adjusted based on platelet count + standard of care
<b>Comparator(s)</b>	DB PL orally once daily for 6 weeks + standard of care	DB PL orally once daily for 8 weeks + standard of care	DB PL orally once daily for 6 weeks + standard of care	DB PL orally once daily for 6 months + standard of care
<b>Concomitant Medications</b>	<ul style="list-style-type: none"> <li>Cyclosporine A, mycophenolate mofetil or danazol (stable dose for <math>\geq 3</math> months)</li> <li>Corticosteroids or azathioprine (stable dose for <math>\geq 4</math> weeks)</li> </ul>	Maintenance immunosuppressive therapy (stable dose for $\geq 1$ month)	Chronic maintenance steroid or ITP therapy – including azathioprine, danazol, cyclosporine A, and mycophenolate mofetil (stable dose for $\geq 1$ month)	<ul style="list-style-type: none"> <li>Cyclosporine A, mycophenolate mofetil or danazol (stable dose for <math>\geq 3</math> months)</li> <li>ITP medication (corticosteroids or azathioprine) stable dose for <math>\geq 4</math> weeks</li> </ul>
<b>Duration</b>				
DB Phase	6 weeks	8 weeks (primary end point evaluated at week 6)	6 weeks	6 months
OLE Phase	6 months	24 weeks	$\frac{3}{4}$	$\frac{3}{4}$
<b>Outcomes</b>				
<b>Primary Outcome</b>	Platelet count response Outcome measure: Number of responders at week 6 (defined as patients with platelet	Platelet count response Outcome measure: Number of responders during week 6	Platelet count response Outcome measure: Proportion of responders after 6 weeks (defined as	Platelet count response Outcome measure: Proportion of responders (platelet count between 50 000 and 400 000/ $\mu$ L)

Criteria	Tomiyama et al. 2012	Yang et al. 2017	Bussel et al. 2009	Cheng et al. 2011
	count $\geq 50\,000/\mu\text{L}$ and $\leq 400\,000/\mu\text{L}$ )	(defined as patients with platelet count $\geq 50\,000/\mu\text{L}$ )	patients with platelet count $\geq 50\,000/\mu\text{L}$ )	at each on-therapy day and 4 weeks after
<b>Secondary / Exploratory Outcomes</b>	<ul style="list-style-type: none"> <li>• Platelet count response – other outcome measurements</li> <li>• Bleeding episodes</li> <li>• Duration of response</li> <li>• Reduced dose or number of concomitant ITP medications</li> <li>• Rescue treatment for ITP</li> </ul>	<ul style="list-style-type: none"> <li>• Platelet count response – other outcome measurements</li> <li>• Bleeding (WHO Bleeding Scale grades 1 to 4)</li> <li>• Clinically significant bleeding (WHO Bleeding Scale grades 2 to 4)</li> <li>• Time to response</li> <li>• Duration of response</li> <li>• Reduced dose or number of concomitant ITP medications</li> <li>• Rescue treatment for ITP</li> <li>• AEs and SAEs</li> </ul>	<ul style="list-style-type: none"> <li>• Platelet count response – other outcome measurements</li> <li>• Bleeding (WHO Bleeding Scale)</li> <li>• Safety and tolerability</li> <li>• HRQoL (SF-36v2)</li> </ul>	<ul style="list-style-type: none"> <li>• Platelet count response – other outcome measurements</li> <li>• Bleeding (WHO Bleeding Scale)</li> <li>• HRQoL (SF-36v2, FACIT-F, FACT-Th, and MEI-SF)</li> <li>• Duration of response</li> <li>• Reduced dose or number of concomitant ITP medications</li> <li>• Rescue treatment for ITP</li> </ul>
<b>Notes</b>				
Publications	Tomiyama et al. 2012 <sup>25</sup>	Yang et al. 2017 <sup>9</sup> Liu et al. 2020 <sup>26</sup>	Bussel et al. 2019 <sup>27</sup>	Cheng et al. 2011 <sup>10</sup>

AEs = adverse events; DB = double-blind; FACIT-F = Functional Assessment of Chronic Illness Therapy – Fatigue questionnaire; FACT-Th = Functional Assessment of Cancer Therapy – Thrombocytopenia questionnaire; HRQoL = health-related quality of life; ITP = immune thrombocytopenia; MEI-SF = Motivation and Energy Inventory – Short Form questionnaire; MI = myocardial infarction; NSAIDs = nonsteroidal anti-inflammatory drugs; OLE = open-label extension; PL = placebo; RCT = randomized controlled trial; SAEs = serious adverse events; SF-36v2 = Short Form – 36v2 questionnaire.

**Table 9: Patient Characteristics – Eltrombopag as Intervention (N = 4 Studies)**

Patient Characteristic	Tomiyaama et al. 2012		Yang et al. 2017		Bussel et al. 2009		Cheng et al. 2011	
	Eltrombopag (N = 15)	Placebo (N = 8)	Eltrombopag (N = 104)	Placebo (N = 51)	Eltrombopag (N = 76)	Placebo (N = 38)	Eltrombopag (N = 135)	Placebo (N = 62)
Age, years								
Mean (SD)	53.7 (13.72)	58.4 (11.72)	44.7 (15.91)	41.3 (12.83)	51 (17)	48 (16)	46.5 (15.61)	51.0 (14.72)
Sex, n (%)								
Female	8 (53.3)	7 (87.5)	77 (74.0)	40 (78.4)	43 (57)	27 (71)	93 (69)	43 (69)
Male	7 (46.7)	1 (12.5)	27 (26.0)	11 (21.6)	33 (43)	11 (29)	42 (31)	19 (31)
Race / Ethnicity, n (%)								
Caucasian	0 (0)	0 (0)	0 (0)	0 (0)	58 (76)	26 (68)	101 (75)	44 (71)
Black	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)	0	nr	
Asian	15 (100.0)	8 (100.0)	104 (100.0)	51 (100.0)	nr		21 (16)	13 (21)
Other	0 (0)	0 (0)	0 (0)	0 (0)	17 (22)	12 (32)	13 (10)	5 (8)
Time since ITP diagnosis, years								
Mean (SD)	nr		nr		nr		nr	
Platelet count /μL								
Median (IQR)	21 000 (16 000 to 25 000)	9 500 (7 500 to 19 000)	14 000 (IQR nr)	13 500 (IQR nr)	nr		16 000 (8 000 to 22 000)	16 000 (9 000 to 24 000)
Platelet count, n (%)								
£ 15 000/μL	3 (20.0)	6 (75.0)	54 (51.9)	28 (54.9)	38 (50)	17 (45)	67 (50)	30 (49)
> 15 000 /μL	12 (80.0)	2 (25.0)	50 (48.1)	23 (45.1)	38 (50)	21 (55)	68 (50)	32 (51)
Concomitant ITP medication(s), n (%)								
Yes	12 (80)	7 (88)	53 (51.0)	28 (54.9)	32 (42)	17 (45)	63 (47)	31 (50)

Patient Characteristic	Tomiyaama et al. 2012		Yang et al. 2017		Bussel et al. 2009		Cheng et al. 2011	
	Eltrombopag (N = 15)	Placebo (N = 8)	Eltrombopag (N = 104)	Placebo (N = 51)	Eltrombopag (N = 76)	Placebo (N = 38)	Eltrombopag (N = 135)	Placebo (N = 62)
Splenectomy, n (%)								
Yes	11 (73)	5 (63)	18 (17.3)	7 (13.7)	31 (41)	14 (37)	50 (37)	21 (34)

ITP = immune thrombocytopenia; IQR = interquartile range; nr = not reported; SD = standard deviation.

**Table 10: Patient Disposition — Eltrombopag as Intervention (N = 4 Studies)**

Category, n	Tomiyaama et al. 2012		Yang et al. 2017		Bussel et al. 2009		Cheng et al. 2011	
	Eltrombopag	Placebo	Eltrombopag	Placebo	Eltrombopag	Placebo	Eltrombopag	Placebo
<b>Randomized</b>	<b>15</b>	<b>8</b>	<b>104</b>	<b>51</b>	<b>76</b>	<b>38</b>	<b>135</b>	<b>62</b>
Completed	14	8	100	49	52	30	112	55
<b>Discontinued</b>	<b>1</b>	<b>0</b>	<b>4</b>	<b>2</b>	<b>24</b>	<b>8</b>	<b>23</b>	<b>7</b>
AEs	1	0	2	1	3	2	13	4
Lack of efficacy	0	0	0	1	0	3	1	0
Patient decision	0	0	0	0	0	0	4	2
Lost to follow-up	0	0	0	0	0	0	3	0
Protocol violation	0	0	1	0	2	1	0	0
Platelet count > 200 000 / $\mu$ L	0	0	0	0	18	1	0	0
Other	0	0	1	0	1	1	2	1

AE = adverse events.

Four DB RCTs evaluated eltrombopag compared to placebo.<sup>9,10,25,27</sup> Detailed outcome results are presented in [Table 8](#).

## Outcomes Assessing Clinical Effectiveness

### Platelet Count Response

The use of eltrombopag was associated with higher proportions of responders compared with placebo at week 6 in 3 trials (60% versus 0% respectively, p value not reported;<sup>25</sup> 58% versus 6% respectively,  $P < 0.001$ ;<sup>9</sup> and 59% versus 16% respectively,  $P < 0.001$ ;<sup>27</sup>) as well as throughout 6 months in another trial (79% versus 28%, respectively;  $P < 0.0001$ ).<sup>10</sup> These were the primary outcome results in the studies, where response was mainly defined as a platelet count  $\geq 50\,000/\mu\text{L}$ , with slight variations across trials.

Other outcome measurements for platelet count response were included as secondary or exploratory outcomes with comparative data reported in 2 of these 4 studies.<sup>10,27</sup> The use of eltrombopag was associated with a higher proportion of responders compared with placebo, that is, at any time over the 6-week period in 1 trial,<sup>27</sup> and at  $\geq 75\%$  of the monthly assessments during the 6-month follow-up in the other trial.<sup>10</sup>

## Bleeding Events

Comparative data for any bleeding events were reported in 3 studies according to the WHO bleeding scale.<sup>9,10,27</sup> The use of eltrombopag was associated with fewer bleeding events compared with placebo in all 3 trials (OR 0.28; 95% CI 0.13 to 0.59;  $P < 0.001$ ;<sup>9</sup> 39% versus 60% respectively,  $P = 0.029$ ;<sup>27</sup> 79% versus 93% respectively,  $P < 0.001$ <sup>10</sup>).

## Health-Related Quality of Life

HRQoL was assessed in 1 study using various scales.<sup>10</sup> The use of eltrombopag was associated with greater improvements from baseline to week 26 compared to placebo in the FACT-Th questionnaire and in some of the SF-36v2 scales (physical role, vitality and emotional role subscales, as well as in the mental component summary score), supporting an improvement in HRQoL among patients treated with eltrombopag versus placebo. Greater improvements from baseline were also observed with eltrombopag compared with placebo in the SF-36v2 physical component summary, the MEI-FS and the FACIT-Fatigue questionnaires; however, statistical significance was not reached for these subscales. Detailed results are shown in [Appendix 6](#). Caution is advised however when interpreting nonsignificant findings to draw conclusions regarding difference between groups in HRQoL.

## Need for Rescue Medication

Two studies reported data pertaining to the use of rescue medications.<sup>9,10</sup> In both trials, eltrombopag was associated with a smaller proportion of patients necessitating rescue treatments compared with placebo (9% versus 34% respectively, OR = 0.13 with 95% CI 0.05 to 0.37,  $P < 0.001$ ;<sup>9</sup> 18% versus 40% respectively, OR = 0.33 with 95% CI 0.16 to 0.64;  $P = 0.001$ <sup>10</sup>). Rescue medications were defined similarly as either a new ITP medication, an increase in the dosage of a concomitant ITP medication, platelet transfusion, or splenectomy.<sup>9,10</sup>

## Reduction or Discontinuation of Concomitant ITP Medication

Two studies assessed the reduction or discontinuation of concomitant ITP medication;<sup>9,10</sup> however, comparative data were reported in only 1 of the 2 studies.<sup>10</sup> Eltrombopag was associated with a reduction in the proportions of patients with reduction or discontinuation of ITP baseline treatments compared with placebo (59% versus 32%, respectively; OR = 3.10 with 95% CI 1.24 to 7.75;  $P = 0.02$ ). The publication indicates that the drugs most frequently tapered or discontinued in both treatment groups were corticosteroids.

## Other Prespecified Effectiveness Outcomes

No data were reported to inform on the effectiveness of eltrombopag versus placebo for the outcomes of time to platelet response, emergency department visits, hospitalization, patient-reported specific symptoms of ITP and treatment-free remission.

## Outcomes Assessing Harms

### Adverse Events

There was inconsistency across the 4 studies in the proportions of patients with at least 1 AE, which ranged from 25% to 92% across treatment groups. In 2 studies, a numerically higher proportion of patients in the eltrombopag group experienced AEs compared to patients in the placebo group.<sup>25,27</sup> The proportions of patients experiencing AEs in the 2 other studies were relatively similar between treatment arms.<sup>9,10</sup>

### Serious AEs

Two studies reported the proportions of patients experiencing serious adverse events (SAEs),<sup>9,25</sup> which were less than 10% of patients per treatment arm. Only 1 trial reported the nature of the events; in this study, 1 patient receiving eltrombopag experienced a transient ischemic attack.<sup>25</sup>

### Withdrawals Due to AEs

Discontinuations of study treatment due to AEs were reported in 3 trials.<sup>9,10,27</sup> The proportions of patients who discontinued were less than 10% per treatment arm and differed between treatment arms only in 1 trial (9.6% with eltrombopag versus 6.6% with placebo).<sup>10</sup>

### Mortality

Mortality was assessed as a harm outcome in the studies and therefore, is reported as such in this report. Three studies reported mortality data;<sup>9,10,27</sup> overall, 2 patients in placebo groups died over the study period. The causes of death were undetermined or not individually reported.

### Notable Harm: Infection

No data were reported to specifically inform on the comparative effectiveness of eltrombopag versus placebo for the outcome of infection, except for patient-reported AEs of some types of infections.



**Table 11: Summary of Key Efficacy Outcomes – Eltrombopag as Intervention (N = 4 Studies)**

	Tomiyaama et al. 2012		Yang et al. 2017		Bussel et al. 2009		Cheng et al. 2011	
Outcome	Eltrombopag N = 15	Placebo N = 8	Eltrombopag N = 104	Placebo N = 50	Eltrombopag N = 74	Placebo N = 38	Eltrombopag N = 135	Placebo N = 62
Key Efficacy Outcomes								
Primary outcome in trial								
DB follow-up	6 weeks		6 weeks		6 weeks		6 months	
Platelet count response	Proportions of responders at week 6		Proportions of responders at week 6		Proportions of responders after week 6		Proportions of responders throughout 6 months	
n (%)	9 (60)	0 (0)	60 (58)	3 (6)	43 (59)	6 (16)	106 (79)	17 (28)
Between-group difference (95% CI) and p value	Absolute difference 0.6 (0.35 to 0.85) p nr		OR 26.08 (7.29 to 93.26) P < 0.001		OR 9.61 (3.31 to 27.86) P < 0.001		OR 8.2 (99% CI 3.59 to 18.73) P < 0.0001	
Secondary or exploratory outcomes in trial								
Platelet count response	Proportions of responders throughout the trial		nr		Proportions of responders at any time		Proportions of responders at <sup>3</sup> 75% of assessments	
n (%)	5 (33)	0 (0)			nr		51 (38)	4 (7)
Between-group difference (95% CI) and p value	nr				OR 8.79 (3.54 to 21.86) P < 0.001		OR 10.53 (3.48 to 31.91) P < 0.0001	
Time to platelet count response	nr		nr		Median platelet count /μL on Day 15		Median platelet count /μL - Range from Day 15 throughout treatment	
Median (IQR)	nr		nr		53 000 (IQR nr)	nr	Lowest: 53 000 (22 000 to 97 000)	Lowest: 17 500 (8 000 to 29 000)

Outcome	Tomiyaama et al. 2012		Yang et al. 2017		Bussel et al. 2009		Cheng et al. 2011	
	Eltrombopag N = 15	Placebo N = 8	Eltrombopag N = 104	Placebo N = 50	Eltrombopag N = 74	Placebo N = 38	Eltrombopag N = 135	Placebo N = 62
							Highest: 73 500 (32 000 – 131 000)	Highest: 23 000 (10 000 – 40 000)
Bleeding	Proportions of patients with any bleeding symptoms		Any bleeding (WHO bleeding scale) <sup>a</sup>		Any bleeding (WHO bleeding scale) <sup>a</sup>		Any bleeding (WHO bleeding scale) <sup>a</sup>	
Baseline, n (%)	5 (33)	No change reported	68 (65)	36 (72)	nr		47 (77)	98 (73)
End of trial, n (%)	2 (14)		17 (16)	17 (34)	20 (39)	18 (60)	106 (79)	56 (93)
Between-group difference (95% CI) and p value	nr		OR 0.28 (0.13 to 0.59) P < 0.001		OR at any time 0.49 (0.26 to 0.89) P = 0.021 OR after 6 weeks 0.27 (0.09 to 0.88) P = 0.029		OR 0.24 (0.16 to 0.38) P < 0.001	
Need for rescue medication	nr		Proportions of patients with rescue treatment		nr		Proportions of patients with rescue treatment	
n (%)			9 (9)	17 (34)			24 (18)	25 (40)
Between-group difference (95% CI) and p value			OR 0.13 (0.05 to 0.37) P < 0.001				OR 0.33 (0.16 to 0.64) P = 0.001	

Outcome	Tomiyaama et al. 2012		Yang et al. 2017		Bussel et al. 2009		Cheng et al. 2011	
	Eltrombopag N = 15	Placebo N = 8	Eltrombopag N = 104	Placebo N = 50	Eltrombopag N = 74	Placebo N = 38	Eltrombopag N = 135	Placebo N = 62
Concomitant ITP medication use	nr		nr		nr		Reduction or discontinuation of ITP baseline treatments	
N patients with baseline ITP medication							N = 63	N = 31
n (%)							37 (59)	10 (32)
Between-group difference (95% CI) and p value							OR 3.10 (1.24 to 7.75) P = 0.02	
HRQoL	nr		nr		nr		Improvement from baseline in HRQoL scores	
Instrument	nr		nr		nr		SF-36v2 * Physical component summary	
Mean change	nr		nr		nr		1.8	0.3
Difference (95% CI); p value	nr		nr		nr		1.3 (–0.2 to 2.9); P = 0.09	
Instrument	nr		nr		nr		SF-36v2 * Mental component summary	
Mean change	nr		nr		nr		1.7	–0.6
Difference (95% CI); p value	nr		nr		nr		2.1 (0.2 to 4.0); P = 0.03	
Instrument	nr		nr		nr		FACT-Th6	
Mean change	nr		nr		nr		2.1	0.7

Outcome	Tomiyaama et al. 2012		Yang et al. 2017		Bussel et al. 2009		Cheng et al. 2011	
	Eltrombopag N = 15	Placebo N = 8	Eltrombopag N = 104	Placebo N = 50	Eltrombopag N = 74	Placebo N = 38	Eltrombopag N = 135	Placebo N = 62
Difference (95% CI); p value	nr		nr		nr		1.5 (0.5 to 2.5); P = 0.004	
Instrument	nr		nr		nr		MEI-SF	
Mean change	nr		nr		nr		nr	
Difference (95% CI); p value	nr		nr		nr		3.3 (–0.6 to 7.3); P = 0.10	
Instrument	nr		nr		nr		FACIT-Fatigue	
Mean change	nr		nr		nr		nr	
Difference (95% CI); p value	nr		nr		nr		1.6 (–0.2 to 3.5); P = 0.08	

DB = double-blind; CI = confidence interval; FACIT-F = Functional Assessment of Chronic Illness Therapy – Fatigue questionnaire; FACT-Th = Functional Assessment of Cancer Therapy – Thrombocytopenia questionnaire; HRQoL = health-related quality of life; IQR = interquartile range; MEI-SF = Motivation and Energy Inventory – Short Form questionnaire; nr = not reported; OR = odds ratio; SF-36v2 = Short Form – 36v2 questionnaire.

Note: There were greater improvements from baseline for patients receiving eltrombopag than for patients receiving placebo in the following SF-36v2 scales: physical role, vitality and emotional role (statistical significance reached).

\*Bleeding symptoms included WHO bleeding scale grades 1 to 4

**Table 12: Summary of Key Harms Outcomes – Eltrombopag as Intervention (N = 4 Studies)**

Outcome	Tomiyama et al. 2012		Yang et al. 2017		Bussel et al. 2009		Cheng et al. 2011	
	Eltrombopag	Placebo	Eltrombopag	Placebo	Eltrombopag	Placebo	Eltrombopag	Placebo
<b>Key Harms Outcomes</b>								
Safety population	N = 15	N = 8	N = 104	N = 51	N = 76	N = 38	N = 135	N = 61
<b>Patients with ≥ 1 adverse events</b>								
n (%)	11 (73)	2 (25)	66 (64)	34 (67)	45 (59)	14 (37)	118 (87)	56 (92)
Most common events, n (%)	Any AEs		Treatment-emergent AEs		Any AEs		Any AEs (in > 5% of patients)	
Nasopharyngitis	4 (27)	0 (0)	nr		5 (7)	3 (8)	14 (10)	8 (13)
ALT increased	3 (20)	0 (0)	7 (6.7)	3 (5.9)	2 (3)	0	10 (7)	4 (7)
Headache	1 (7)	1 (13)	3 (2.9)	0 (0)	6 (8)	4 (11)	41 (30)	20 (33)
AST increased	1 (7)	0 (0)	6 (5.8)	3 (5.9)	2 (3)	0	7 (5)	2 (3)
Blood bilirubin increased	0 (0)	0 (0)	7 (6.7)	0 (0)	nr		nr	
Hypokalemia	0 (0)	0 (0)	4 (3.8)	1 (2.0)	nr		nr	
Hemoglobin increased	nr		3 (2.9)	0 (0)	nr		nr	
Neutrophil count increased	nr		3 (2.9)	0 (0)	nr		nr	
Rash	nr		3 (2.9)	1 (2.0)	nr		nr	
Nausea	1 (7)	0 (0)	nr		6 (8)	0 (0)	16 (12)	4 (7)
Diarrhea	nr		nr		4 (5)	1 (3)	17 (13)	6 (10)
Total protein increased	nr		nr		3 (4)	1 (3)	nr	

	Tomiyaama et al. 2012		Yang et al. 2017		Bussel et al. 2009		Cheng et al. 2011	
Outcome	Eltrombopag	Placebo	Eltrombopag	Placebo	Eltrombopag	Placebo	Eltrombopag	Placebo
Vomiting	nr		nr		4 (5)	0 (0)	10 (7)	1 (2)
Fatigue	1 (7)	0 (0)	nr		3 (4)	0 (0)	13 (10)	8 (13)
Myalgia	nr		nr		3 (4)	0 (0)	8 (6)	2 (3)
Upper respiratory tract infection	nr		nr		nr		14 (10)	7 (11)
Limb pain	nr		nr		nr		9 (7)	6 (10)
Urinary tract infection	nr		nr		nr		9 (7)	4 (7)
Arthralgia	0 (0)	0 (0)	nr		nr		9 (7)	3 (5)
Oropharyngeal pain	nr		nr		nr		9 (7)	3 (5)
Pharyngitis	nr		nr		nr		8 (6)	1 (2)
Patients with ≥ 1 serious adverse events								
n (%)	1 (7)	0 (0)	5 (4.8)	5 (9.8)	nr		nr	
Most common events, n (%)								
TIA	1 (7)	0 (0)	nr		nr		nr	
Patients who stopped treatment due to adverse events								
n (%)	nr		3 (2.9)	1 (2.0)	3 (4)	2 (5)	13 (9.6)	4 (6.6)
Events listing, n (%)								
Abnormal renal function	n/a		1	nr	0	0	0	1
Increased ALT	n/a		1	nr	0	0	4	0
Cerebral infarction	n/a		1	nr	0	0	0	0

Outcome	Tomiyaama et al. 2012		Yang et al. 2017		Bussel et al. 2009		Cheng et al. 2011	
	Eltrombopag	Placebo	Eltrombopag	Placebo	Eltrombopag	Placebo	Eltrombopag	Placebo
Abnormal hepatic function	n/a		0	nr	1	0	0	0
Hemorrhage	n/a		0	nr	2	1	1	1
Facial injury	n/a		0	nr	0	1		0
Thromboembolic event	n/a		0	nr	0	0	2	0
Cataract	n/a		0	nr	0	0	1	2
Rash / urticaria	n/a		0	nr	0	0	2	0
Tachycardia	n/a		0	nr	0	0	1	0
Headache	n/a		0	nr	0	0	1	0
Cancer	n/a		0	nr	0	0	1	0
<b>Mortality</b>								
n (%)	nr		0 (0)	1 (2.0)	0 (0)	0 (0)	0 (0)	1 (2)
<b>Causes of death, n (%)</b>								
Undetermined	n/a		0	1	n/a		nr	

AE = adverse event; ALT = alanine aminotransferase; AST = aspartate transaminase; n/a = not applicable; nr = not reported; TIA = transient ischemic attack.

## Appendix 7: Summary Tables of Studies With Avatrombopag as Intervention

Note that this appendix has not been copy-edited.

**Table 13: Details of Included Studies – Avatrombopag as Intervention (N = 1 Study)**

Criteria	Jurczak et al. 2018
<b>Designs and Populations</b>	
<b>Study Design</b>	DB RCT, with OLE phase
<b>Locations</b>	Multicenter: Australia, New-Zealand, Singapore, South-Africa, Europe
<b>Randomized</b>	n = 49
<b>Place in Therapy</b>	Subsequent-line treatment in patients who have experience with prior ITP therapies
<b>Inclusion Criteria</b>	<ul style="list-style-type: none"> <li>Adults (<math>\geq 18</math> years) diagnosed with primary ITP for <math>\geq 12</math> months</li> <li>Received <math>\geq 1</math> prior ITP therapies</li> <li>Initially responded to prior ITP therapy (platelet count <math>&gt; 50\,000/\mu\text{L}</math>)</li> <li>Laboratory values within normal or close-to-normal range, with the exception of hemoglobin and neutrophil count</li> </ul>
<b>Exclusion Criteria</b>	<ul style="list-style-type: none"> <li>Significant medical condition other than ITP</li> <li>Secondary immune thrombocytopenia</li> <li><i>Helicobacter pylori</i> infection, HIV or hepatitis C virus infection, systemic lupus erythematosus</li> <li>History of myelodysplastic syndromes or pernicious anemia</li> <li>Any history of arterial or venous thrombosis with the presence of <math>\geq 2</math> additional risk factors for thrombosis</li> <li>History of significant cardiovascular disease</li> <li>History of cirrhosis, portal hypertension, or chronic active hepatitis</li> <li>Malignancies</li> </ul>
<b>Drugs</b>	
<b>Intervention</b>	Avatrombopag 20 mg orally once daily (start dose) for 26 weeks Dose to be titrated to maintain platelet count between $50\,000/\mu\text{L}$ and $150\,000/\mu\text{L}$ and reduce the dose or number of concomitant ITP medications + standard of care
<b>Comparator(s)</b>	DB PL orally once daily for 26 weeks + standard of care
<b>Concomitant Medications</b>	<ul style="list-style-type: none"> <li>Corticosteroids or azathioprine (stable dose for <math>\geq 4</math> weeks)</li> <li>Mycophenolate mofetil or danazol (stable dose for <math>\geq 12</math> weeks)</li> <li>Cyclosporine A only if deemed medically necessary (stable dose for <math>\geq 12</math> weeks)</li> <li>Acetyl salicylic acid, other salicylates, or adenosine diphosphate receptor antagonists allowed once platelet count has risen</li> </ul>



Criteria	Jurczak et al. 2018
<b>Duration</b>	
DB Phase	26 weeks
OLE Phase	76 weeks
<b>Outcomes</b>	
<b>Primary Outcome</b>	Platelet count response Outcome measure: Cumulative number of weeks of platelet response during the 6-month treatment period (defined as platelet count $\geq 50\,000/\mu\text{L}$ in the absence of rescue therapy)
<b>Secondary / Exploratory Outcomes</b>	<ul style="list-style-type: none"> <li>• Platelet count response – other outcome measurements</li> <li>• Reduced dose or number of concomitant ITP medications</li> <li>• Bleeding (WHO Bleeding Scale)</li> <li>• Rescue treatment for ITP</li> <li>• AEs and SAEs</li> </ul>
<b>Notes</b>	
<b>Publications</b>	Jurczak et al. 2018 <sup>12</sup>

AEs = adverse events; DB = double-blind; ITP = immune thrombocytopenia; OLE = open-label extension; PL = placebo; RCT = randomized controlled trial; SAEs = serious adverse events.

**Table 14: Patient Characteristics — Avatrombopag as Intervention (N = 1 Study)**

Patient Characteristic	Jurczak et al. 2018	
	Avatrombopag (N = 32)	Placebo (N = 17)
Age, years		
Mean (SD)	46.4 (14.2)	41.2 (14.7)
Sex, n (%)		
Female	23 (71.9)	8 (47.1)
Male	9 (28.1)	9 (52.9)
Race / Ethnicity, n (%)		
Caucasian	31 (96.9)	15 (88.2)
Black	0	1 (5.9)
Asian	1 (3.1)	1 (5.9)
Time since ITP diagnosis, years		
Mean (SD)	nr	
Platelet count / $\mu$ L		
Median (IQR)	nr	
Platelet count, n (%)		
$\leq 15\,000/\mu$ L	18 (56.3)	10 (58.8)
$> 15\,000\ /\mu$ L	14 (43.7)	7 (41.2)

Patient Characteristic	Jurczak et al. 2018	
	Avatrombopag (N = 32)	Placebo (N = 17)
<b>Concomitant ITP medication(s), n (%)</b>		
Yes	15 (46.9)	7 (41.2)
<b>Splenectomy, n (%)</b>		
Yes	11 (34.4)	5 (29.4)

ITP = immune thrombocytopenia; IQR = interquartile range; nr = not reported; SD = standard deviation.

**Table 15: Patient Disposition – Avatrombopag as Intervention (N = 1 Study)**

Category, n	Jurczak et al. 2018	
	Avatrombopag	Placebo
<b>Randomized</b>	<b>32</b>	<b>17</b>
Completed	22	1
<b>Discontinued</b>	<b>10</b>	<b>16</b>
AEs	3	0
Lack of efficacy	7	15
Sponsor decision	0	0
Withdrawal of consent	0	1

AE = adverse events.

One DB RCT evaluated avatrombopag compared to placebo.<sup>12</sup> Detailed outcome results are presented in [Table 13](#).

## Outcomes Assessing Clinical Effectiveness

### Platelet Count Response

The use of avatrombopag was associated with a higher cumulative mean number of weeks of platelet response compared with placebo at week 26 ( $12.0 \pm 8.75$  weeks in the avatrombopag group versus  $0.1 \pm 0.49$  week in the placebo group). The cumulative number of weeks of platelet response was the primary outcome in the trial, where response was defined as a platelet count  $\geq 50\,000/\mu\text{L}$  in the absence of rescue therapy. The use of avatrombopag was associated with a higher proportion of responders at day 8 compared to placebo (66% versus 0%, respectively; difference in response rate 65.63, 95% CI 49.17 to 82.08;  $P < 0.0001$ ).

### Bleeding Events

Comparative data for bleeding events were reported according to the WHO bleeding scale. The proportions of patients with any bleeding event were 44% with avatrombopag and 53% with placebo (p nonsignificant).

### **Need for Rescue Medication**

The proportions of patients who received rescue medication were 22% with avatrombopag and 12% with placebo (p nonsignificant).

### **Reduction or Discontinuation of Concomitant ITP Medication**

The proportions of patients who reduced or discontinued concomitant ITP medication were 33% with avatrombopag and 0% with placebo (difference in reduction rate of 33.33, 95% CI 9.48 to 57.19; p nonsignificant).

### **Other Prespecified Effectiveness Outcomes**

No data were reported to inform on the comparative effectiveness of avatrombopag versus placebo for the outcomes of time to platelet response, emergency department visits, hospitalization, HRQoL, patient-reported specific symptoms of ITP and treatment-free remission.

## **Outcomes Assessing Harms**

### **Adverse Events**

A numerically higher proportion of patients in the avatrombopag group experienced AEs compared to patients in the placebo group (97% versus 59%, respectively).

### **Serious AEs**

Nine patients in the avatrombopag group experienced SAEs. There was 1 SAE in the placebo group, the nature of which was not reported (28% versus 6%, respectively).

### **Withdrawals Due to AEs**

Three patients (9%) in the avatrombopag group discontinued study treatment due to AEs; the nature of the events was not reported. There was no withdrawal due to adverse event in the placebo group.

### **Mortality**

Mortality was assessed as a harm outcome in the study and therefore, is reported as such in this report. No patient died over the course of the study.

### **Notable Harm: Infection**

No data were reported to specifically inform on the comparative effectiveness of avatrombopag versus placebo for the outcome of infection, except for patient-reported AEs of some types of infections.

**Table 16: Summary of Key Efficacy Outcomes — Avatrombopag as Intervention (N = 1 Study)**

Outcome	Jurczak et al. 2018	
	Avatrombopag (N = 32)	Placebo (N = 17)
Key Efficacy Outcomes		
Primary outcome in trial		
DB follow-up	6 months (26 weeks) Note: Mean duration of exposure was 22.8 weeks for avatrombopag patients and 8.9 weeks for placebo patients.	
Platelet count response	Cumulative number of weeks of platelet response	
Mean (SD)	12.0 (8.75)	0.1 (0.49)
Between-group p value	P < 0.0001	
Secondary or exploratory outcomes in trial		
Platelet count response	Proportions of responders at Day 8	
n (%)	21 (65.6)	0 (0)
Between-group difference (95% CI); p value	Difference in response rate 65.63 (49.17 to 82.08); P < 0.0001	
Bleeding	Any bleeding (WHO bleeding scale) <sup>a</sup>	
n (%)	14 (43.8)	9 (52.9)
Between-group p value	P = 0.5394	
Need for rescue medication	Proportions of patients with rescue treatment	
n (%)	7 (21.9)	2 (11.8)
Between-group p value	P = 0.4668	
Concomitant ITP medication use	Reduction in use of ITP baseline treatments	
N patients with baseline ITP medication	N = 15	N = 7
n (%)	5 (33.3)	0 (0)
Between-group difference (95% CI); p value	Difference in reduction rate 33.33 (9.48 to 57.19); P = 0.1348	

DB = double-blind; CI = confidence interval; nr = not reported.

<sup>a</sup>Bleeding symptoms included WHO bleeding scale grades 1 to 3

**Table 17: Summary of Key Harms Outcomes – Avatrombopag as Intervention (N = 1 Study)**

Outcome	Jurczak et al. 2018	
	Avatrombopag	Placebo
Key Harms Outcomes		
Safety population	N = 32	N = 17
Patients with ≥ 1 adverse events		
n (%)	31 (96.9)	10 (58.8)
Most common events, n (%)	Treatment-emergent AEs (in > 10% of patients)	
Headache	12 (37.5)	2 (11.8)
Contusion	10 (31.3)	4 (23.5)
Upper respiratory tract infection	6 (18.8)	1 (5.9)
Arthralgia	4 (12.5)	0 (0)
Epistaxis	4 (12.5)	3 (17.6)
Fatigue	4 (12.5)	1 (5.9)
Gingival bleeding	4 (12.5)	0 (0)
Petechiae	4 (12.5)	1 (5.9)
Diarrhea	nr	
Nausea	nr	
Nasopharyngitis	3 (9.4)	0 (0)
Musculoskeletal pain	nr	
Dizziness	nr	
Insomnia	nr	
Patients with ≥ 1 serious adverse events		
n (%)	9 (28.1)	1 (5.9)
Headache	2 (6.3)	0 (0)
Vomiting	2 (6.3)	0 (0)
Platelet count decreased	1 (3.1)	0 (0)
Idiopathic thrombocytopenic purpura	0 (0)	1 (5.9)
Thrombocytopenia	1 (3.1)	0 (0)
Food poisoning	1 (3.1)	0 (0)
Mouth hemorrhage	1 (3.1)	0 (0)
Nausea	1 (3.1)	0 (0)
Polyserositis	1 (3.1)	0 (0)
Urinary tract infection	1 (3.1)	0 (0)

Outcome	Jurczak et al. 2018	
	Avatrombopag	Placebo
Cerebrovascular accident	1 (3.1)	0 (0)
Uterine hemorrhage	1 (3.1)	0 (0)
Epistaxis	1 (3.1)	0 (0)
Petechiae	1 (3.1)	0 (0)
Deep vein thrombosis	1 (3.1)	0 (0)
Patients who stopped treatment due to adverse events		
n (%)	3 (9.4)	0 (0)
Events listing, n (%)	nr	
Mortality		
n (%)	0 (0)	0 (0)

AE = adverse event; nr = not reported.

## Appendix 8: Summary Tables of Studies With Romiplostim as Intervention

Note that this appendix has not been copy-edited.

**Table 18: Details of Included Studies — Romiplostim as Intervention (N = 3 studies)**

Criteria	Shirasugi et al. 2011	Kuter et al. 2008	Kuter et al. 2010
<b>Designs and Populations</b>			
<b>Study Design</b>	DB RCT	DB RCTs (parallel trials), with OLE phase	OL RCT
<b>Locations</b>	Multicenter: Japan	Multicenter: US, Europe	Multicenter: North America, Europe, Australia
<b>Randomized</b>	n = 34	n = 125 in two parallel trials: n = 62 nonsplenectomized patients n = 63 splenectomized patients	n = 234
<b>Place in Therapy</b>	Subsequent-line treatment in patients who have experience with prior ITP therapies	Subsequent-line treatment in patients who have experience with prior ITP therapies	Subsequent-line treatment in patients who have experience with prior ITP therapies
<b>Inclusion Criteria</b>	<ul style="list-style-type: none"> <li>Adults (<math>\geq 20</math> years) diagnosed with ITP for <math>\geq 6</math> months</li> <li>Platelet count level <math>&lt; 30\,000/\mu\text{L}</math></li> <li>ECOG performance status 0 to 2</li> <li>Received <math>\geq 1</math> prior ITP therapies</li> <li>Laboratory values within normal or close-to-normal range</li> </ul>	<ul style="list-style-type: none"> <li>Adults (<math>\geq 18</math> years) diagnosed with ITP for <math>\geq 6</math> months</li> <li>Received <math>\geq 1</math> prior ITP therapies or splenectomy</li> <li>Platelet count level <math>&lt; 30\,000/\mu\text{L}</math> (if not receiving any ITP therapy)</li> <li>Platelet count level <math>&lt; 50\,000/\mu\text{L}</math> (if receiving corticosteroids, azathioprine, or danazol)</li> <li>Laboratory values within normal or close-to-normal range</li> </ul>	<ul style="list-style-type: none"> <li>Adults (<math>\geq 18</math> years) diagnosed with ITP (no specified duration)</li> <li>Received <math>\geq 1</math> prior ITP therapies</li> <li>Platelet count level <math>&lt; 50\,000/\mu\text{L}</math></li> </ul>
<b>Exclusion Criteria</b>	<ul style="list-style-type: none"> <li>History of bone marrow stem cell disorder or abnormal findings other than ITP</li> <li>Active malignancy</li> <li>Documented diagnosis of arterial thrombosis or antiphospholipid antibody syndrome</li> <li>History of venous thrombosis and receiving anticoagulants</li> </ul>	<ul style="list-style-type: none"> <li>History of bone marrow stem cell disorder</li> <li>Active malignancy</li> <li>Venous thrombosis or recent arterial thrombosis</li> <li>Significant uncontrolled medical condition other than ITP</li> <li><math>\geq 3</math> risk factors for thromboembolic events</li> </ul>	<ul style="list-style-type: none"> <li>Splenectomy</li> <li>Active malignancy or recent history of cancer</li> <li>History of bone marrow stem cell disorder</li> <li>Previous exposure to a thrombopoietin mimetic</li> </ul>

Criteria	Shirasugi et al. 2011	Kuter et al. 2008	Kuter et al. 2010
		<ul style="list-style-type: none"> <li>HIV or hepatitis C virus infection</li> </ul>	
<b>Drugs</b>			
<b>Intervention</b>	Romiplostim 3 mcg/kg SC (start dose) once weekly for 12 weeks Dose to be titrated to maintain platelet count between 50 000/ $\mu$ L and 200 000/ $\mu$ L (max dose 10 mcg/kg)	Romiplostim 1 mcg/kg SC (start dose) once weekly for 24 weeks Dose to be titrated to maintain platelet count between 50 000/ $\mu$ L and 200 000/ $\mu$ L (max dose 15 mcg/kg)	Romiplostim 3 mcg/kg SC (start dose) once weekly for 52 weeks Dose to be titrated to maintain platelet count between 50 000/ $\mu$ L and 200 000/ $\mu$ L (max dose 10 mcg/kg)
<b>Comparator(s)</b>	DB PL SC once weekly for 12 weeks	DB PL SC once weekly for 24 weeks	OL standard of care for 52 weeks
<b>Concomitant Medications</b>	Oral corticosteroids, azathioprine, or danazol (stable dose for $\geq 4$ weeks)	Oral corticosteroids, azathioprine, or danazol (stable dose and schedule)	ITP therapies including short-term rescue therapies (e.g., IV immunoglobulin) but excluding other thrombopoietin mimetics
<b>Duration</b>			
DB Phase	12 weeks	24 weeks	52 weeks
OLE Phase	$\frac{3}{4}$	285 weeks	$\frac{3}{4}$
<b>Outcomes</b>			
<b>Primary Outcome</b>	Platelet count response Outcome measure: Number of weeks with weekly platelet response	Platelet count response Outcome measure: Durable platelet response, defined as $\geq 6$ of the last 8 weeks of treatment with weekly platelet counts $\geq 50\,000/\mu\text{L}$ and no rescue medication	Platelet count response Coprimary outcome measures: <ul style="list-style-type: none"> <li>Incidence of treatment failure (recurrent platelet count <math>\leq 20\,000/\mu\text{L}</math> despite optimal dosage, major bleeding, or WDAE)</li> <li>Incidence of splenectomy</li> </ul>
<b>Secondary / Exploratory Outcomes</b>	<ul style="list-style-type: none"> <li>Platelet count response – other outcome measurements</li> <li>Rescue treatment for ITP</li> <li>Bleeding symptoms</li> <li>AEs</li> </ul>	<ul style="list-style-type: none"> <li>Platelet count response – other outcome measurements</li> <li>Reduced dose or number of concomitant ITP medications</li> <li>Rescue treatment for ITP</li> <li>HRQoL (ITP-PAQ, EQ-5D)</li> <li>AEs</li> </ul>	<ul style="list-style-type: none"> <li>Platelet count response – other outcome measurements</li> <li>Time to splenectomy</li> <li>HRQoL (ITP-PAQ)</li> </ul>
<b>Notes</b>			
<b>Publications</b>	Shirasugi et al. 2011 <sup>13</sup>	Kuter et al. 2008 <sup>11</sup> George et al. 2009 <sup>28</sup> Gernsheimer et al. 2010 <sup>29</sup> Sanz et al. 2011 <sup>30</sup>	Kuter et al. 2010 <sup>14</sup> Kuter et al. 2012 <sup>31</sup>

AEs = adverse events; DB = double-blind; ECOG = Eastern Cooperative Oncology Group; OL = open label; HRQoL = health-related quality of life; ITP = immune thrombocytopenia; ITP-PAQ = Immune Thrombocytopenic Purpura – Patient Assessment Questionnaire; OLE = open-label extension; PL = placebo; RCT = randomized controlled trial; SC = subcutaneously; WDAE = withdrawal from therapy due to adverse event.



**Table 19: Patient Characteristics — Romiplostim as Intervention (N = 3 studies)**

Patient Characteristic	Shirasugi et al. 2011		Kuter et al. 2008		Kuter et al. 2010	
	Romiplostim (N = 22)	Placebo (N = 12)	Romiplostim (N = 83)	Placebo (N = 42)	Romiplostim (N = 157)	Standard of care (N = 77)
Age, years						
Mean (SD)	58.5 (12.6)	47.6 (13.4)	nr		nr	
Median (range)	nr		52 (21 to 88)	52 (23 to 88)	58 (18 to 90)	57 (18 to 86)
Sex, n (%)						
Female	14 (63.6)	10 (83.3)	54 (65)	27 (64)	85 (54)	46 (60)
Male	8 (36.4)	2 (16.7)	29 (35)	15 (36)	72 (46)	31 (40)
Race / Ethnicity, n (%)						
Caucasian	0	0	65 (78)	37 (88)	137 (87)	69 (90)
Black	0	0	6 (7)	3 (7)	6 (4)	0
Asian	22 (100.0)	22 (100.0)	nr		nr	
Other	0	0	12 (14)	2 (5)	14 (9)	8 (10)
Time since ITP diagnosis, years						
Mean (SD)	9.7 (10.4)	7.6 (5.9)	nr		nr	
Median (range)	nr		nr		2.1 (0 to 44.2)	2.3 (0 to 33.2)
Platelet count / $\mu$ L						
Mean (SD)	18 400 (8 300)	15 800 (600)	nr		nr	
Median (range)	nr		16 000 (2 000 to 29 000)	18 000 (2 000 to 31 000)	33 000 (1 000 to 123 000)	27 000 (2 000 to 62 000)
Concomitant ITP medication(s), n (%)						
Yes	13 (59.1)	10 (83.3)	23 (28)	16 (38)	21 (13)	5 (6)
Splenectomy, n (%)						
Yes	10 (45.5)	5 (41.7)	42 (51)	21 (50)	n/a	

ITP = immune thrombocytopenia; n/a = not applicable; nr = not reported; SD = standard deviation.

**Table 20: Patient Disposition — Romiplostim as Intervention (N = 3 studies)**

Category, n	Shirasugi et al. 2011		Kuter et al. 2008		Kuter et al. 2010	
	Romiplostim	Placebo	Romiplostim	Placebo	Romiplostim	Standard of care
<b>Randomized</b>	<b>22</b>	<b>12</b>	<b>83</b>	<b>42</b>	<b>157</b>	<b>77</b>
Completed	22	12	79	36	145	62
<b>Discontinued</b>	<b>0</b>	<b>0</b>	<b>4</b>	<b>6</b>	<b>12</b>	<b>15</b>
AEs	0	0	3	1	nr	
Withdrawn consent	0	0	1	2	5	4

Category, n	Shirasugi et al. 2011		Kuter et al. 2008		Kuter et al. 2010	
	Romiplostim	Placebo	Romiplostim	Placebo	Romiplostim	Standard of care
Other	0	0	0	3	7	11

AE = adverse events.

Three RCTs evaluated romiplostim compared to placebo.<sup>11,13,14</sup> Detailed outcome results are presented in [Table 18](#).

## Outcomes Assessing Clinical Effectiveness

### Platelet Count Response

The 3 romiplostim trials used different outcome measurements as primary end point for platelet count response (number of weeks in response, response rates and incidence of treatment failure), as well as different definitions and thresholds for platelet response.

In 1 12-week DB RCT, the use of romiplostim was associated with a higher number of weeks of platelet count response compared with placebo (median 11 weeks, IQR 9 to 12; versus 0, IQR 0 to 0, respectively;  $P < 0.0001$ ).<sup>13</sup> Platelet count response was defined as  $\geq 50\,000/\mu\text{L}$  in the publication. The use of romiplostim was also associated with a higher proportion of patients with platelet count increase  $\geq 20\,000/\mu\text{L}$  compared with placebo (96% versus 25%, respectively;  $P < 0.001$ ).<sup>13</sup>

One 24-week DB RCT evaluated the platelet count response rate during at least 8 weeks, which was higher with romiplostim compared with placebo (49% versus 2%, respectively;  $P < 0.01$ ).<sup>11</sup> In this study, platelet count response was defined as  $\geq 6$  of the last 8 weeks of treatment with weekly platelet counts  $\geq 50\,000/\mu\text{L}$  and no rescue medication. The use of romiplostim was also associated with a higher proportion of patients with  $\geq 4$  weekly platelet count response at any time compared with placebo (83% versus 7%, respectively;  $P < 0.0001$ ).<sup>11</sup>

The third study was a 52-week OL RCT with incidence of treatment failure (i.e., patients who did not have a platelet response) as primary outcome, which was lower in patients receiving romiplostim compared with standard of care (11% versus 30%, respectively; between-group difference of 0.31; 95% CI 0.15 to 0.61;  $P < 0.001$ ).<sup>14</sup> Treatment failure was defined in the study as a recurrent platelet count  $\leq 20\,000/\mu\text{L}$  despite optimal dosage, a major bleeding or withdrawal due to adverse event. The use of romiplostim was also associated with a higher median platelet count between week 2 and end of trial compared with standard of care (between-group difference of 2.3 (95% CI 2.0 to 2.6);  $P < 0.001$ ).<sup>14</sup>

### Bleeding Events

The 3 studies reported some data for bleeding events; however, definitions for bleeding as well as comparative data were not consistently provided. The proportions of patients with any bleeding event were 36% after 12 weeks with romiplostim versus 83% with placebo (no statistical analysis was performed) in 1 trial;<sup>13</sup> 57% with romiplostim versus 61% with placebo in the second trial (p nonsignificant);<sup>11</sup> and 52% with romiplostim versus 53% with OL standard of care in the third trial (no statistical analysis was performed).<sup>14</sup>

## Health-Related Quality of Life

HRQoL was assessed in 2 studies using the ITP-PAQ questionnaire<sup>11,14</sup> and in 1 study using the EQ-5D.<sup>11</sup> The use of romiplostim was associated with greater improvements from baseline to week 24 compared to placebo in the some of the ITP-PAQ scales (symptoms, bother, activity, psychological, fear, social quality of life, and women's reproductive health – menstrual symptoms) as well as in the EQ-5D index score.<sup>11</sup> At week 52, romiplostim was associated with greater improvements from baseline compared to OL standard of care in the following ITP-PAQ scales: symptoms, bother, activity, fear, overall quality of life, and social quality of life.<sup>14</sup> Standard of care treatments were at the discretion of the investigators and based on local practices or therapeutic guidelines.<sup>14</sup>

Greater improvements from baseline were also observed with romiplostim compared with placebo at 24 weeks in the EQ-5D VAS score and in the ITP-PAQ fatigue and overall quality of life scales,<sup>11</sup> as well as at 52 weeks in the ITP-PAQ fatigue scale,<sup>14</sup> however, statistical significance was not reached.

## Need for Rescue Medication

The studies<sup>11,13,14</sup> reported some data pertaining to the use of rescue medications. All results are presented in [Appendix 6](#). One trial performed a between-group comparison with sufficient power to show a difference between treatments. In a 24-week DB RCT, romiplostim was associated with a reduction in the proportions of patients necessitating rescue treatments compared with placebo (22% versus 60%, respectively;  $P < 0.0001$ ).<sup>11</sup> Rescue medications were defined in the trial as an increase in the dosage of a concomitant ITP medication or the use of any new drug to increase platelet count.

## Reduction or Discontinuation of Concomitant ITP Medication

One study assessed the reduction or discontinuation of concomitant ITP medication.<sup>11</sup> More patients in the romiplostim treatment group were able to discontinue a concomitant ITP medication or reduce the dose of at least 1 medication by more than 25% compared with placebo; however, no analysis between treatment groups was reported.

## Other Prespecified Effectiveness Outcomes

No data were reported to inform on the comparative effectiveness of romiplostim versus placebo or standard of care for the outcomes of time to platelet response, emergency department visits, hospitalization, patient-reported specific symptoms of ITP and treatment-free remission.

## Outcomes Assessing Harms

### Adverse Events

AEs were reported in 2 studies.<sup>11,13</sup> Almost all patients in these 2 trials experienced at least 1 AE. The most common AEs reported across all studies included headache, nasopharyngitis, fatigue, contusion, epistaxis, arthralgia, and petechiae.

### **Serious AEs**

There was inconsistency across the 3 studies in the proportions of patients with SAEs. In 2 studies, the proportions of patients experiencing SAEs were similar between treatment groups and were less than 10% of patients per treatment arm.<sup>11,13</sup> In the OL 52-week trial, the proportions of patients with SAEs were much higher, being 23% of patients under romiplostim and 37% of patients receiving standard of care.<sup>14</sup> In this study, the most common SAEs reported included thrombocytopenia, pneumonia, peripheral edema, and pulmonary embolism.

### **Withdrawals Due to AEs**

Discontinuations due to AEs were reported in 1 study and the proportions of patients who discontinued were similar between groups and less than 10% per treatment arm.<sup>11</sup>

### **Mortality**

Mortality was assessed as a harms outcome in the studies and therefore, is reported as such in this report. The 3 studies reported mortality data; however, no death was observed in 1 trial.<sup>13</sup> One patient randomized to romiplostim died in each of the 2 other trials, as well as 2 patients in the placebo or standard of care groups over each study period.<sup>11,14</sup> The causes of death included cerebral or intracranial hemorrhage, pulmonary embolism, pneumonia, and hepatic failure.

### **Notable Harm: Infection**

No data were reported to specifically inform on the comparative effectiveness of romiplostim versus placebo for the outcome of infection, except for patient-reported AEs of some types of infections.

**Table 21: Summary of Key Efficacy Outcomes — Romiplostim as Intervention (N = 3 Studies)**

Outcome	Shirasugi et al. 2011		Kuter et al. 2008		Kuter et al. 2010	
	Romiplostim N = 22	Placebo N = 12	Romiplostim N = 83	Placebo N = 42	Romiplostim N = 157	Standard of care N = 77
Key Efficacy Outcomes						
Primary outcome in trial						
DB follow-up	12 weeks		24 weeks		52 weeks	
Platelet count response	Number of weeks of platelet count response, median (IQR)		Durable platelet count response rate during last 8 weeks, n (%)		Incidence of treatment failure	
Response per group	11 (9 to 12)	0 (0 to 0)	41 (49)	1 (2)	18 (11)	23 (30)
Between-group difference (95% CI) and/or p value	P < 0.0001		Splenectomized patients: 38% (23.4% to 52.8%); P = 0.0013 Nonsplenectomized patients: 56% (38.7% to 73.7%); P < 0.0001		0.31 (0.15 to 0.61); P < 0.001	
Secondary or exploratory outcomes in trial						
Platelet count response	Proportions of patients with platelet count increase ≥ 20 000 /μL, n (%)		Proportions of patients with ≥ 4 weekly platelet count response at any time during the study, n (%)		Platelet count /μL between Week 2 and Week 52, median range	
Response per group	21 (96)	3 (25)	69 (83.1)	3 (7.1)	108 000 – 176 000	35 000 – 52 000
Between-group difference (95% CI) and/or p value	P < 0.0001		P < 0.0001		2.3 (2.0 to 2.6); P < 0.001	
Bleeding	Incidence of bleeding symptoms		Incidence of significant bleeding events (severe, life-threatening, or fatal)		Proportions of patients with bleeding events <sup>a</sup>	
Baseline, n (%)	14 (63.6)	10 (83.3)	nr		nr	
After 4 weeks, n (%)	7 (31.8)	10 (83.3)				
After 8 weeks, n (%)	7 (31.8)	12 (100.0)				
After 12 weeks, n (%)	8 (36.4)	10 (83.3)				

Outcome	Shirasugi et al. 2011		Kuter et al. 2008		Kuter et al. 2010	
	Romiplostim N = 22	Placebo N = 12	Romiplostim N = 83	Placebo N = 42	Romiplostim N = 157	Standard of care N = 77
Throughout the trial, n (%)	16 (72.7)	12 (100.0)	6 (7)	5 (12)	80 (52)	40 (53)
Need for rescue medication	Proportions of patients with rescue treatment		Proportions of patients with rescue treatment		Proportions of patients administered ITP treatment	
n (%)	2 (9)	2 (17)	26 (21.7)	25 (59.5)	67 (44)	59 (79)
Between-group p value	P = 0.6015		P < 0.0001		nr	
Concomitant ITP medication use	nr		Concomitant ITP medication use		nr	
N patients with baseline ITP medication			N = 23	N = 16		
Discontinued, n (%)			12 (52)	3 (19)		
Reduced at least 1 drug by more than 25%, n (%)			8 (35)	3 (19)		
HRQoL	nr		Improvement in HRQoL scores			
Instrument or scale	nr		EQ-5D index score		nr	
N patients with data	nr		N = 76	N = 41	nr	
Mean change from baseline to end of treatment (SE)	nr		0.05 (0.02)	-0.03 (0.02)	nr	
Between-group p value	nr		P = 0.015		nr	
Instrument or scale	nr		EQ-5D index score VAS score		nr	
N patients with data	nr		N = 73	N = 41	nr	
Mean change from baseline to end of treatment (SE)	nr		6.42 (2.08)	0.48 (2.59)	nr	
Between-group p value	nr		P = 0.066		nr	
Instrument or scale	nr		ITP-PAQ Symptoms Scale			

Outcome	Shirasugi et al. 2011		Kuter et al. 2008		Kuter et al. 2010	
	Romiplostim N = 22	Placebo N = 12	Romiplostim N = 83	Placebo N = 42	Romiplostim N = 157	Standard of care N = 77
Mean change from baseline to end of treatment (SE)	nr		nr	nr	16.0 (1.9)	12.5 (2.1)
LSM estimate (SE)	nr		7.48 (2.08)		nr	
Between-group p value	nr		P = 0.0005		P = 0.0133	
Instrument or scale	nr		ITP-PAQ Fatigue Scale			
Mean change from baseline to end of treatment (SE)	nr		nr	nr	11.2 (3.1)	9.5 (3.2)
LSM estimate (SE)	nr		1.78 (2.83)		nr	
Between-group p value	nr		P = 0.53		P = 0.3434	
Instrument or scale	nr		ITP-PAQ Bother Scale			
Mean change from baseline to end of treatment (SE)	nr		nr	nr	16.8 (2.5)	13.0 (2.7)
LSM estimate (SE)	nr		8.94 (2.76)		nr	
Between-group p value	nr		P = 0.002		P = 0.0076	
Instrument or scale	nr		ITP-PAQ Activity Scale			
Mean change from baseline to end of treatment (SE)	nr		nr	nr	17.1 (3.5)	8.2 (3.7)
LSM estimate (SE)	nr		8.52 (3.47)		nr	
Between-group p value	nr		P = 0.016		P = 0.0246	
Instrument or scale	nr		ITP-PAQ Psychological Scale			
Mean change from baseline to end of treatment (SE)	nr		nr	nr	18.9 (2.7)	15.7 (2.8)
LSM estimate (SE)	nr		5.71 (2.77)		nr	
Between-group p value	nr		P = 0.042		P = 0.0490	

Outcome	Shirasugi et al. 2011		Kuter et al. 2008		Kuter et al. 2010	
	Romiplostim N = 22	Placebo N = 12	Romiplostim N = 83	Placebo N = 42	Romiplostim N = 157	Standard of care N = 77
Instrument or scale	nr		ITP-PAQ Fear Scale			
Mean change from baseline to end of treatment (SE)	nr		nr	nr	13.9 (1.7)	8.7 (1.7)
LSM estimate (SE)	nr		7.13 (1.99)		nr	
Between-group p value	nr		P = 0.0005		P = 0.0001	
Instrument or scale	nr		ITP-PAQ Overall quality of life Scale			
Mean change from baseline to end of treatment (SE)	nr		nr	nr	16.1 (3.6)	15.0 (3.7)
LSM estimate (SE)	nr		4.14 (3.07)		nr	
Between-group p value	nr		P = 0.18		P = 0.0246	
Instrument or scale	nr		ITP-PAQ Social quality of life Scale			
Mean change from baseline to end of treatment (SE)	nr		nr	nr	9.7 (2.4)	5.5 (2.5)
LSM estimate (SE)	nr		9.66 (3.12)		nr	
Between-group p value	nr		P = 0.0025		P = 0.0020	
Instrument or scale	nr		ITP-PAQ Women's reproductive health – menstrual symptoms		nr	
LSM estimate (SE)	nr		24.23 (5.86)		nr	
Between-group p value	nr		P = 0.0001		nr	

HRQoL = health-related quality of life; IQR = interquartile range; ITP = immune thrombocytopenia; ITP-PAQ = Immune Thrombocytopenic Purpura Patient Assessment Questionnaire; LSM = least square means; nr = not reported; SD = standard deviation; SE = standard error; VAS = visual analogue scale.

<sup>a</sup>Including grade 2 bleeding events (moderate severity)



**Table 22: Summary of Key Harms Outcomes — Romiplostim as Intervention (N = 3 Studies)**

Outcome	Shirasugi et al. 2011		Kuter et al. 2008		Kuter et al. 2010	
	Romiplostim	Placebo	Romiplostim	Placebo	Romiplostim	Standard of care
<b>Key Harms Outcomes</b>						
Safety population	N = 22	N = 12	N = 83	N = 41	N = 154	N = 75
<b>Patients with ≥ 1 adverse events</b>						
n (%)	20 (90.9)	11 (91.7)	83 (100)	39 (95)	136 (82)	60 (87)
Most common events, n (%)	Any AEs (in > 10% of patients)		Any AEs (in > 10% of patients)		Any AEs (in > 10% of patients)	
Nasopharyngitis	9 (41)	2 (17)	7 (8)	7 (17)	36 (23)	14 (19)
Headache	7 (32)	2 (17)	29 (35)	13 (32)	54 (35)	14 (19)
Peripheral edema	4 (18)	0 (0)	NR	NR	15 (10)	3 (4)
Back pain	3 (14)	0 (0)	11 (13)	4 (10)	16 (10)	4 (5)
Pain in extremity	3 (14)	0 (0)	11 (13)	2 (5)	20 (13)	6 (8)
Malaise	1 (5)	2 (17)	NR	NR	NR	NR
Contusion	0 (0)	2 (17)	21 (25)	10 (24)	22 (14)	13 (18)
Fatigue	nr		28 (33)	12 (29)	43 (28)	16 (22)
Epistaxis	nr		27 (32)	10 (24)	29 (19)	17 (23)
Arthralgia	nr		22 (26)	8 (20)	23 (15)	4 (5)
Petechiae	nr		14 (17)	9 (22)	25 (16)	13 (18)
Diarrhea	nr		14 (17)	6 (15)	21 (13)	4 (5)
Upper respiratory tract infection	nr		14 (17)	5 (12)	18 (12)	6 (8)
Dizziness	nr		14 (17)	0 (0)	21 (13)	6 (8)
Insomnia	nr		13 (16)	3 (7)	14 (9)	9 (12)
Myalgia	nr		12 (14)	1 (2)	17 (11)	1 (1)
Nausea	nr		11 (13)	4 (10)	24 (16)	6 (8)

Outcome	Shirasugi et al. 2011		Kuter et al. 2008		Kuter et al. 2010	
	Romiplostim	Placebo	Romiplostim	Placebo	Romiplostim	Standard of care
Cough	nr		10 (12)	7 (17)	25 (16)	4 (5)
Anxiety	nr		9 (11)	5 (12)	NR	NR
Gingival bleeding	nr		9 (11)	5 (12)	NR	NR
Abdominal pain	nr		9 (11)	0 (0)	NR	NR
Ecchymosis	nr		6 (7)	6 (15)	NR	NR
Pyrexia	nr		NR	NR	15 (10)	8 (11)
Haematoma	nr		NR	NR	12 (8)	9 (12)
Pruritus	nr		NR	NR	16 (10)	5 (7)
Urinary tract infection	nr		NR	NR	18 (12)	7 (10)
Constipation	—		—	—	16 (10)	6 (8)
Patients with ≥ 1 serious adverse events						
n (%)	2 (9.1)	1 (8.3)	2 (2.4)	0 (0)	35 (23)	28 (37)
Most common events, n (%)						
Increased bone marrow reticulin	nr		1 (1.2)	0 (0)	nr	
Popliteal artery thrombosis	nr		1 (1.2)	0 (0)	nr	
Thrombocytopenia	nr		0 (0)	0 (0)	5 (3)	9 (12)
Pneumonia	nr		0 (0)	0 (0)	4 (3)	2 (3)
Edema, peripheral	nr		0 (0)	0 (0)	3 (2)	0 (0)
Pulmonary embolism	nr		0 (0)	0 (0)	3 (2)	0 (0)
Patients who stopped treatment due to adverse events						
n (%)	0 (0)	0 (0)	2 (2.4)	1 (2.4)	nr	
Event listing, n (%)	n/a		nr			

Outcome	Shirasugi et al. 2011		Kuter et al. 2008		Kuter et al. 2010	
	Romiplostim	Placebo	Romiplostim	Placebo	Romiplostim	Standard of care
<b>Mortality</b>						
n (%)	0 (0)	0 (0)	1 (1.2)	2 (4.9)	1 (0.6)	2 (2.6)
Causes of death, n (%)						
Cerebral hemorrhage	0 (0)	0 (0)	0 (0)	1 (2.4)	0 (0)	0 (0)
Pulmonary embolism	0 (0)	0 (0)	0 (0)	1 (2.4)	0 (0)	0 (0)
Intracranial hemorrhage	0 (0)	0 (0)	1 (1.2)	0 (0)	0 (0)	0 (0)
Pneumonia	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)
Hepatic failure	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1.3)
Cardiorespiratory arrest	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1.3)

AE = adverse event; n/a = not applicable; nr = not reported.

## Appendix 9: Summary Tables of Studies With Interventions Other Than TPO-RA

Note that this appendix has not been copy-edited.

**Table 23: Details of Included Studies — Interventions other than TPO-RA (N = 2 Studies)**

Criteria	Ghanima et al. 2015	Bussel et al. 2018
<b>Designs and Populations</b>		
<b>Study Design</b>	DB RCT	DB RCTs (parallel trials), with OLE phase
<b>Locations</b>	Multicenter: Norway, Tunisia, France	Multicenter: North America, Australia, Europe
<b>Randomized</b>	n = 112	n = 150 in two parallel trials: n = 76 (FIT1) n = 74 (FIT2)
<b>Place in Therapy</b>	Second-line treatment in patients with primary ITP who failed a short course of corticosteroid therapy	Subsequent-line treatment in patients who have experience with prior ITP therapies
<b>Inclusion Criteria</b>	<ul style="list-style-type: none"> <li>Adults (<math>\geq 18</math> years) diagnosed with primary ITP (no specified duration)</li> <li>Platelet count level <math>&lt; 30\,000/\mu\text{L}</math> after a 2-week prednisone treatment or during tapering period; or</li> <li>Platelet count level <math>&lt; 50\,000/\mu\text{L}</math> if considered necessary due to bleeding predisposition</li> </ul>	<ul style="list-style-type: none"> <li>Adults (<math>\geq 18</math> years) diagnosed with primary persistent or chronic ITP for <math>\geq 3</math> months</li> <li>Platelet count level <math>&lt; 30\,000/\mu\text{L}</math></li> <li>Received <math>\geq 1</math> prior ITP therapies</li> <li>Karnofsky score <math>\geq 70</math></li> </ul>
<b>Exclusion Criteria</b>	<ul style="list-style-type: none"> <li>Previous administration of any second-line treatment for ITP</li> <li>Splenectomy</li> <li>Active or recent malignancy or chemotherapy</li> <li>Immunosuppressive therapy other than corticosteroids or danazol</li> <li>HIV, hepatitis B, or hepatitis C virus infection</li> <li>Systemic lupus erythematosus</li> <li>Active/recent evolutive infection</li> <li>Any underlying pathology predisposing to serious infections</li> </ul>	<ul style="list-style-type: none"> <li>Secondary ITP</li> <li>Recent major cardiovascular event or any history of coagulopathy</li> <li>ITP Bleeding Scale – Grade 2</li> <li>Significant uncontrolled medical condition other than ITP</li> </ul>
<b>Drugs</b>		
<b>Intervention</b>	Rituximab 375 mg/m <sup>2</sup> IV once weekly for 4 weeks	Fostamatinib 100 mg orally twice daily for 24 weeks
<b>Comparator(s)</b>	DB PL IV once weekly for 4 weeks	DB PL orally once daily for 24 weeks

Criteria	Ghanima et al. 2015	Bussel et al. 2018
<b>Concomitant Medications</b>	Corticosteroids	<ul style="list-style-type: none"> <li>Only one of the following (stable dose for <math>\geq 2</math> weeks): <ul style="list-style-type: none"> <li>Corticosteroids</li> <li>Azathioprine</li> <li>Danazol</li> </ul> </li> <li>Rescue therapies</li> </ul>
<b>Duration</b>		
DB Phase	78 weeks	24 weeks
OLE Phase	$\frac{3}{4}$	6 months
<b>Outcomes</b>		
<b>Primary Outcome</b>	Treatment failure, defined as: <ul style="list-style-type: none"> <li>splenectomy; or</li> <li>platelet count <math>&lt; 20\ 000/\mu\text{L}</math>; or</li> <li>need for prednisone increments at doses <math>&gt; 7.5</math> mg/day</li> </ul>	Platelet count response Outcome measure: Number of patients with stable platelet response by week 24 (defined as patients with platelet count $\geq 50\ 000/\mu\text{L}$ on at least 4 of the last 6 scheduled visits)
<b>Secondary / Exploratory Outcomes</b>	<ul style="list-style-type: none"> <li>Platelet count response</li> <li>Bleeding (WHO Bleeding Scale)</li> <li>Other harms events (including infections and thrombosis)</li> <li>Corticosteroid consumption</li> </ul>	<ul style="list-style-type: none"> <li>Platelet count response – other outcome measurements</li> <li>Bleeding (WHO Bleeding Scale and ITP Bleeding Score)</li> </ul>
<b>Notes</b>		
<b>Publications</b>	Ghanima et al. 2015 <sup>32</sup>	Bussel et al. 2018 <sup>15</sup>

DB = double-blind; ITP = immune thrombocytopenia; OLE = open-label extension; PL = placebo; RCT = randomized controlled trial; TPO-RA = thrombopoietin receptor agonists.

**Table 24: Patient Characteristics – Interventions Other Than TPO-RA (N = 2 Studies)**

Patient Characteristic	Ghanima et al. 2015		Bussel et al. 2018	
	Rituximab (N = 55)	Placebo (N = 54)	Fostamatinib (N = 101)	Placebo (N = 49)
<b>Age, years</b>				
Mean (SD)	nr		nr	
Median (range)	46 (27 to 61)	46 (28 to 60)	54 (20 to 88)	53 (20 to 78)
<b>Sex, n (%)</b>				
Female	40 (73)	39 (72)	61 (60)	30 (61)
Male	15 (27)	15 (28)	40 (40)	19 (39)
<b>Race / Ethnicity, n (%)</b>				
Caucasian	nr		94 (93)	45 (92)
Black	nr		2 (2)	2 (4)
Asian	nr		3 (3)	2 (4)

Patient Characteristic	Ghanima et al. 2015		Bussel et al. 2018	
	Rituximab (N = 55)	Placebo (N = 54)	Fostamatinib (N = 101)	Placebo (N = 49)
Other	nr		2 (2)	0
Time since ITP diagnosis				
Mean (SD), years	nr		nr	
Median (range), years	nr		8.7 (0.3 to 53)	7.8 (0.4 to 45)
Median (IQR), weeks	37 (8 to 288)	50 (14 to 211)	nr	
Platelet count / $\mu$ L				
Median (IQR)	16 000 (6 000 to 27 000)	21 000 (9 000 to 29 000)	nr	
Mean (SD)	nr		nr	
Mean (range)	nr		16 052 (1 000 to 51 000)	19 818 (1 000 to 156 000)
Platelet count, n (%)				
$\leq 15\,000/\mu$ L	nr		54 (53.5)	28 (57.1)
$> 15\,000/\mu$ L			47 (46.5)	21 (42.9)
Concomitant ITP medication(s), n (%)				
Yes	nr		nr	
Splenectomy, n (%)				
Yes	nr		34 (34)	19 (39)

ITP = immune thrombocytopenia; IQR = interquartile range; nr = not reported; SD = standard deviation.

**Table 25: Patient Disposition – Interventions Other Than TPO-RA (N = 2 Studies)**

Category, n	Ghanima et al. 2015		Bussel et al. 2018	
	Rituximab	Placebo	Fostamatinib	Placebo
<b>Randomized</b>	<b>58</b>	<b>54</b>	<b>101</b>	<b>49</b>
Completed	55	52	25	3
<b>Discontinued</b>	<b>3</b>	<b>2</b>	<b>76</b>	<b>46</b>
AEs	0	0	9	4
Lack of efficacy	0	0	61	41
Patient decision	0	1	2	1
Lost to follow-up	0	1	1	0
Investigator decision	0	0	3	0
Refused treatment	3	0	0	0

AE = adverse events.

One DB RCT evaluated rituximab compared to placebo.<sup>32</sup> Detailed outcome results are presented in [Table 23](#). It should be noted that the primary outcome for this study, which was treatment failure, did not meet the a priori defined threshold for statistical significance and therefore, formal testing was halted for all secondary outcomes. As a result, any conclusion drawn from this study must consider the increased risk of type I error due to the failed primary end point.

## Outcomes Assessing Clinical Effectiveness

### Platelet Count Response

The proportions of patients with overall response in the trial (platelet count  $\geq 30\,000$  / $\mu$ L) were 73% with rituximab versus 67% with placebo (p nonsignificant); for complete response (platelet count  $\geq 100\,000$  / $\mu$ L), the proportions were 51% with rituximab versus 39% with placebo (p nonsignificant).

### Bleeding Events

The proportions of patients with any bleeding symptoms were 38% with rituximab versus 50% with placebo (p nonsignificant).

### Other Prespecified Effectiveness Outcomes

No data were reported to inform on the comparative effectiveness of rituximab versus placebo for the outcomes of time to platelet response, emergency department visits, hospitalization, HRQoL, reduction, or discontinuation of concomitant ITP medication, patient-reported specific symptoms of ITP, need for rescue medication, and treatment-free remission.

## Outcomes Assessing Harms

### Adverse Events

A higher proportion of patients in the rituximab group experienced AEs compared to patients in the placebo group (40% versus 24%, respectively). The most common AEs included infections, influenza, throat irritation, headache, bronchitis, and pyrexia.

### Serious AEs

No data were reported to inform on the comparative effectiveness of rituximab versus placebo for the outcome of SAEs.

### Withdrawals Due to AEs

No patient experienced withdrawal due to adverse event throughout the study duration.

### Mortality

Mortality was assessed as a harms outcome in the studies and therefore, is reported as such in this report. One patient in the placebo group died over the study period. The cause of death was gastrointestinal bleeding.

### Notable Harm: Infection

A total of 40% of patients (n = 20) in the rituximab group and 24% of patients in the placebo group (n = 13) reported an AE of infection.

One DB RCT evaluated fostamatinib compared to placebo.<sup>15</sup> Detailed outcome results are presented in [Table 23](#).

## Outcomes Assessing Clinical Effectiveness

### Platelet Count Response

The use of fostamatinib was associated with higher proportions of patients with what was labelled as stable platelet response by week 24 compared with placebo (18% versus 2%, respectively; P = 0.0003).<sup>15</sup> This was the primary outcome in the trial and was defined as a platelet count  $\geq 50\,000/\mu\text{L}$  on at least 4 of the last 6 scheduled visits during weeks 14 to 24. Despite being statistically significant, the proportions of patients with platelet response appeared low in the study. It should be noted however that the median time since ITP diagnosis in the study was approximately 8 years. There was also an improvement with fostamatinib in the proportions of patients with overall response (platelet count  $\geq 50\,000/\mu\text{L}$ ) at any time compared with placebo (43% versus 14%, respectively; P = 0.0006).

### Need for Rescue Medication

Greater improvements from baseline were observed with fostamatinib compared with placebo in the proportions of patients receiving rescue medication (30% versus 45%, respectively; p nonsignificant).

### Other Prespecified Effectiveness Outcomes

No data were reported to inform on the comparative effectiveness of fostamatinib versus placebo for the outcomes of time to platelet count response, bleeding, emergency department visits, hospitalization, HRQoL, patient-reported specific symptoms of ITP, reduction or discontinuation of concomitant ITP medication and treatment-free remission.

## Outcomes Assessing Harms

### Adverse Events

A higher proportion of patients in fostamatinib group experienced AEs compared to patients in the placebo group (83% versus 75%, respectively). The most common AEs included diarrhea, hypertension, nausea, dizziness respiratory infections, and ALT increase.

### Serious AEs

A total of 13% of patients in the fostamatinib group experienced SAEs, which is numerically lower than the proportion of patients experiencing SAEs in the placebo group (21%). The most common AEs included thrombocytopenia, epistaxis, and menorrhagia.



## Withdrawals Due to AEs

The proportions of patients who discontinued due to AEs were 10% in the fostamatinib group and 8% in the placebo group.

## Mortality

Mortality was assessed as a harm outcome in the studies and therefore, is reported as such in this report. One patient in each group died over the study period. The causes of death were myeloma and sepsis.

## Notable Harm: Infection

No data were reported to specifically inform on the comparative effectiveness of fostamatinib versus placebo for the outcome of infection, except for patient-reported AEs of some types of infections.

**Table 26: Summary of Key Efficacy Outcomes – Interventions Other Than TPO-RA (N = 2 Studies)**

Outcome	Ghanima et al. 2015		Bussel et al. 2018	
	Rituximab N = 55	Placebo N = 54	Fostamatinib N = 101	Placebo N = 49
Key Efficacy Outcomes				
Primary outcome in trial				
DB follow-up	4 weeks of treatment 78 weeks of follow-up		24 weeks	
Platelet count response	Treatment failure		Proportions of patients with stable response	
n (%)	32 (58)	37 (68)	18 (18)	1 (2)
Kaplan-Meier estimate of cumulative incidence	46%	52%	nr	
Between-group difference (95% CI) and / or p value	HR 0.89 (0.55 to 1.45); P = 0.65		P = 0.0003	
Secondary or exploratory outcomes in trial				
Platelet count response	Complete response at 78 weeks (platelet count ≥ 100 000/μL)		Overall response (platelet count ≥ 50 000/μL)	
n (%)	28 (51)	21 (39)	43 (43)	7 (14)
Kaplan-Meier estimate of cumulative incidence	58%	50%	nr	
Between-group p value	P = 0.12		P = 0.0006	
Platelet count response	Overall response at 78 weeks (platelet count ≥ 30 000/μL)		nr	
n (%)	40 (73)	36 (67)		
Kaplan-Meier estimate of cumulative incidence	81%	73%		
Between-group p value	P = 0.15			

Outcome	Ghanima et al. 2015		Bussel et al. 2018	
	Rituximab N = 55	Placebo N = 54	Fostamatinib N = 101	Placebo N = 49
Bleeding	Any bleeding symptoms		nr	
n (%)	21 (38)	27 (50)		
Between-group p value	P = 0.08			
Need for rescue medication	Probability of receiving rescue treatment		Proportions of patients receiving rescue medication	
n (%)	nr		30 (30)	22 (45)
Between-group p value	P = 0.09		P = 0.07	

HR = hazard ratio; ITP = immune thrombocytopenia; nr = not reported; SD = standard deviation.

**Table 27: Summary of Key Harms Outcomes — Interventions Other Than TPO-RA (N = 2 Studies)**

Outcome	Ghanima et al. 2015		Bussel et al. 2018	
	Rituximab	Placebo	Fostamatinib	Placebo
<b>Key Harms Outcomes</b>				
Safety population	N = 55	N = 54	N = 102	N = 48
<b>Patients with ≥ 1 adverse events</b>				
n (%)	nr		85 (83)	36 (75)
Most common events, n (%)	Any AEs (Grade 2 to 3)		Treatment-emergent AEs	
Infections	20 (40)	13 (24)	nr	
Influenza	8 (15)	4 (7)	nr	
Throat irritation	8 (5)	1 (2)	nr	
Headache	5 (9)	2 (4)	nr	
Bronchitis	4 (7)	2 (4)	nr	
Pyrexia	4 (7)	2 (4)	nr	
Upper respiratory tract infection	3 (5)	2 (4)	nr	
Rash	3 (5)	2 (4)	9 (9)	1 (2)
Diarrhea	nr		32 (31)	7 (15)
Hypertension	nr		29 (28)	6 (13)
Nausea	nr		19 (19)	4 (8)
Dizziness	nr		11 (11)	4 (8)
ALT increase	nr		11 (11)	0 (0)
Respiratory infection	nr		11 (11)	3 (6)
AST increase	nr		9 (9)	0 (0)
Fatigue	nr		6 (6)	1 (2)

Outcome	Ghanima et al. 2015		Bussel et al. 2018	
	Rituximab	Placebo	Fostamatinib	Placebo
Chest pain	nr		6 (6)	1 (2)
Neutropenia	nr		6 (6)	0 (0)
Patients with ≥ 1 serious adverse events				
n (%)	nr		13 (13)	10 (21)
Epistaxis	nr		1 (1)	1 (2)
Thrombocytopenia			1 (1)	2 (4)
Menorrhagia			0 (0)	2 (4)
Patients who stopped treatment due to adverse events				
n (%)	0 (0)	0 (0)	10 (10)	4 (8)
Chest pain / syncope	n/a		1 (1)	nr
Pneumonia			1 (1)	nr
Thrombocytopenia			1 (1)	nr
Mortality				
n (%)	(0)	1 (2)	1 (1)	1 (2)
Gastrointestinal bleeding	0 (0)	1 (2)	0 (0)	0 (0)
Sepsis	0 (0)	0 (0)	0 (0)	1 (2)
Myeloma	0 (0)	0 (0)	1 (1)	0 (0)

AE = adverse event; ALT = alanine aminotransferase; AST = aspartate transaminase; n/a = not applicable; nr = not reported.

## Appendix 10: Critical Appraisal

Note that this appendix has not been copy-edited.

**Table 28: Critical Appraisal of Included Studies**

First Author, Publication Year	Strengths and Limitations
Jurczak et al. (2018) was rated as an overall high risk of bias.	There were differences in baseline characteristics between treatment arms at baseline, the proportion of females was 72% for AVA and 47% for PBO. All other baseline characteristics reported were balanced. Investigators, investigational site personnel and sponsor staff were blinded to treatment codes but not dose levels. Differences in reduction in use of concomitant ITP meds from baseline and differences in treatment-related TEAEs (63% AVA vs. 18% PBO) and other safety data may have made patients aware of the treatment received. The most frequent reason for discontinuation from the core study was lack of treatment effect (avatrombopag, N = 7; placebo, N = 15). The full analysis set included all randomized patients. The FAS was used, but there was a high discontinuation rate (> 50%). The timing of discontinuation and availability of data at later time points is unknown. High discontinuation rates due to inadequate therapeutic response: 70% (7/10) of discontinuations from AVA and 94% (15/16) of discontinuations from PBO. "cumulative number of weeks with $\geq 50 \times 10^9/L$ during the core study in the absence of rescue therapy," the clinical expert indicated that a threshold of 30 would be more appropriate - this would miss clinically relevant responders. Down-titration of concomitant ITP medication was implemented at the discretion of the investigator and could only be considered if the patient's platelet count remained $> 150 \times 10^9/L$ . Patients with a platelet count $> 150 \times 10^9/L$ to $\leq 250 \times 10^9/L$ could have their concomitant ITP medication down titrated by $\leq 25\%$ of the original dose for 14 days, whereas the dose was reduced by $\leq 50\%$ in patients with a platelet count $> 250 \times 10^9/L$ for 14 days. If a patient was receiving $\geq 2$ concomitant ITP medications, only one medication was down titrated at a time. Decision to reduce concomitant meds was at the discretion of the investigator, which could introduce bias.
Yang et al. (2017) was rated as low overall risk of bias.	All patients randomized into this study were assigned a unique randomization code, with randomization stratified by splenectomy status (Yes/No), use of maintenance concomitant ITP therapy at baseline (Yes/No), and baseline platelet counts ( $\leq 15 \times 10^9/L$ or $> 15 \times 10^9/L$ ). No information about allocation concealment, although it was likely concealed given the randomization strategy. Patients, caregivers, investigators, and outcomes assessors were blinded to treatment assignment. The analysis of the primary efficacy end point was performed for both the ITT and PP populations. 149/154 of the patients included in the ITT population completed stage I. 135 patients were included in the PP population. Proportion of patients with a platelet count $\geq 50 \times 10^9/L$ after day 42 in the absence of rescue therapy. Very unlikely. The primary efficacy end point was the proportion of patients who had a platelet count $\geq 50 \times 10^9/L$ after day 42 (week 6) during stage I without use of rescue treatment. Defined as either a new ITP medication, an increase in dose of concomitant ITP medication from baseline, platelet transfusion, or splenectomy. The decision to use rescue treatment is a clinical decision and therefore may vary slightly between the evaluators. The odds of bleeding and clinically significant bleeding in the eltrombopag-treated group relative to placebo, based on information at each stage I assessment, were compared using a generalized linear mixed model with a Logit canonical link function for repeated binary data, which allowed for baseline dichotomized WHO bleeding grade, use of ITP medication at baseline, splenectomy, baseline platelet count, and treatment arm as fixed effects. In addition, the patient was treated as a random effect and assumed to follow a normal distribution [ $\sim N(0, r2)$ ].

First Author, Publication Year	Strengths and Limitations
Ghanima et al. (2015) was rated as some concerns for overall risk of bias.	<p>Patients were randomized using precoded concealed envelopes, permuted block randomization with stratification by centre with a block size of 4. Patients, investigators, and reviewers were masked to allocation. Treatment allocation was communicated to local hospital pharmacies by fax. Infusion bags were concealed in opaque plastic bags that were sealed to mask the solution from the patient and health care providers. Pharmacists were not masked to treatment allocation. Treatment group imbalances (R vs. PBO): median bleeding score (2 vs. 4), treatment with corticosteroids (58% vs. 44%), Duration of ITP in weeks (newly diagnosed: 33% vs. 22%, persistent: 24% vs. 30%, chronic: 44% vs. 48%). Double-blind study. Infections were higher with rituximab (40% vs. 24%) and bleeding was higher with placebo (38% vs. 50%). Outcomes were assessed using the full analysis set (ITT). Low discontinuation rate. Platelet count <math>\geq 30 \times 10^9/L</math> (overall response) after week 4; and platelet count needed to be at least double that at baseline without administration of any platelet increasing therapy (except stable/decreasing prednisone or prednisolone) in the past 4 weeks. Efficacy outcomes were adjudicated by 2 reviewers who were masked to treatment allocation. Treatment failure was defined as a composite of splenectomy or meeting criteria for splenectomy after week 12 if splenectomy was not done, assessed in all patients who received at least one dose of study treatment. The primary end point was amended from splenectomy within 78 weeks to the rate of treatment failure, defined as a splenectomy or meeting the criteria for a splenectomy after week 12, if a splenectomy was not done because of contraindications or patients' refusal. At which point in the study the end point was amended is unclear.</p>
Shirasugi et al. (2011) was rated at overall high risk of bias.	<p>The randomization procedure was conducted centrally by Transcosmos Inc. (Tokyo, Japan) using a preprepared randomization list and communication via fax. No information about allocation concealment. Treatment group imbalances (ROM vs. PBO): female (64% vs. 83%), age (mean of 58.5 vs. 47.6), ECOG scores (0 = 77% vs. 92%, 1 = 23% vs. 8%), concomitant ITP therapy (59% vs. 83%). Double-blind study design. Frequency of AEs were much higher with romiplostim than placebo, which may have resulted in knowledge of treatment assignment. Full analysis set used. Rescue medication was defined as any medication administered for the intended purpose of raising platelet counts; permitted were IVIG, platelet transfusions, corticosteroids, and an increase in dose or frequency of a concomitant oral corticosteroid, azathioprine, and/or danazol. The decision to use rescue medication may vary between assessors. Throughout the study, rescue medication was permitted for severe bleeding or if the investigator believed that the patient was at immediate risk of bleeding.</p>
Kuter et al. (2010) was rated as a high overall risk of bias.	<p>Randomized in a 2:1 ratio, stratified by geographic region. Open-label study design. In general, the treatment groups were fairly balanced. Treatment group imbalances were present for the following (ROM vs. SOC): previous treatment with IVIg (57% vs. 64%), previous treatment with rituximab (20% vs. 31%), more than 2 previous treatments (70% vs. 78%), medications for ITP at baseline (13% vs. 6%). No information about protocol deviations; but discontinuations from study were 8% vs. 19% for ROM vs. SOC and the most common reason was withdrawal of consent. Primary and secondary efficacy end points were analyzed using the ITT set. Discontinuations from study were 8% vs. 19% for ROM vs. SOC. Patients who received study treatment and discontinued from study were counted as having had both treatment failure and splenectomy. A platelet count of <math>20 \times 10^9/L</math> or lower for 4 consecutive weeks at the highest recommended dose, a major bleeding event, or requirement for a change in therapy (including splenectomy) because of an adverse event or bleeding symptoms. The outcome is based on mostly objective components, with the exception of "requirement for a change in therapy," which is based on clinical decision-making and may be subject to bias due to open-label study design. The definition of major bleeding was not defined; however, it is unlikely that this outcome would not be assessed appropriately given the level of severity. Definition of major bleed is unclear. The definition of treatment failure was a composite outcome. Further, "Given the length of the treatment</p>

First Author, Publication Year	Strengths and Limitations
	period, it was anticipated that some patients might discontinue the study early; therefore, in the primary end point analyses, a patient who had received any study treatment and had then discontinued the study was counted as having had both treatment failure and splenectomy”.
Bussel et al. (2018) was rated as an overall high risk of bias.	Diarrhea, hypertension, nausea, and dizziness were reported more frequently in the fostamatinib treatment group, which may have allowed patients and assessors to deduce the assigned intervention. ITT analysis set. Very high discontinuation rates in both studies. High discontinuation rates due to lack of response the majority of nonresponders on fostamatinib and most patients on placebo discontinued study treatment at week 12 to enter the open-label, long-term extension study: 88% of patients in FIT1 and 79% in FIT2 on placebo vs. 55% in FIT1 and 66% in FIT2 on fostamatinib. The outcome was defined a priori but details of the analysis are unclear. Further, it is unclear why the denominator is less than the ITT set.
Eisai Inc. (2019) was rated as some concerns for overall risk of bias.	Not enough information to assess. Only baseline characteristics available were age and sex. Study was double-blind, but SAE were only reported in the avatrombopag group. The study was terminated early due to significant enrolment challenges.
Cheng et al. (2011) was rated as an overall low risk of bias.	Patients were randomly allocated in a 2:1 ratio to receive treatment with local standard of care plus either 50 mg eltrombopag or matching placebo. All randomizations were done with RAMOS, an automated interactive voice recognition telephone randomization and drug ordering system. Patients, investigators, and those assessing the data were masked to allocation. Well balanced groups, but higher baseline bleeding symptoms and clinically significant bleeding symptoms among the placebo group. ITT population was used. All randomized patients were included in the efficacy analysis, but 23/135 discontinued from eltrombopag; 7/62 discontinued from placebo. Response to treatment (platelet count 50,000 to 400,000 per uL) during the 6-month treatment period; a period of rescue treatment was recorded as a nonresponse. Unlikely, but decisions regarding concomitant ITP medication use may differ between clinicians/investigators.
Tomiyama, et al. (2012) was rated as some concerns for overall risk of bias.	Patients were randomly allocated to either eltrombopag or placebo, and randomization was performed centrally. Treatment assignment was unblinded at week 7 (before entry into the open-label phase) on an individual patient basis. Treatment group imbalances by (PBO vs. E): sex % female (88% vs. 53%), median platelet count (9500 vs. 21,000), splenectomy (64% vs. 73%), platelet count < 15 000 uL (75% vs. 20%). Double-blind during the 6-week evaluation; AEs were more frequent with eltrombopag vs. placebo. Minimal information about the analyses conducted. All patients in the 6-week double-blind period were enrolled in the OLE. Assume that data were available for all patients. Patient disposition was not reported, but the results appear to include data for all patients. A responder was defined as a patient achieving a platelet count $\geq 50 \times 10^9/L$ and $\leq 400 \times 10^9/L$ . This was predefined as the primary end point. The primary end point for 6-week evaluation was the proportion of responders at week 6 in the eltrombopag group vs. the placebo group. The definition of bleeding was not defined. It is possible that assessors recorded incidence of bleeding differently, although it is unlikely. Bleeding was not defined; therefore multiple definitions could have been used.
Kuter et al. (2008) was rated as an overall low risk of bias.	Patients were randomly assigned 2:1 to receive romiplostim or placebo. Random allocation sequence was generated by Amgen Inc. (Thousand Oaks, CA, US) with the blocked randomization method. Clinphone was used to randomly assign patients into the study with the interactive voice response system. Difference in the proportion of patients receiving concurrent ITP therapy (38% placebo, 28% romiplostim). Double-blind study and no major differences between AEs. Analysis was per protocol. Discontinuations were balanced between groups and limited so this was unlikely to cause attrition bias. Weekly platelet responses during 6 or more weeks of the last 8 weeks of treatment in the absence of rescue therapy. The decision of the treating physician to use rescue treatment may vary, although there is no reason to expect this to differ systematically between treatment groups.

First Author, Publication Year	Strengths and Limitations
Bussel et al. (2009) was rated with some concerns for overall risk of bias.	Patients were randomly assigned 2:1 to receive standard of care and either eltrombopag or placebo. Patients were randomly assigned by an in-house validated randomization system (RANDALL). Some treatment group imbalances to note (E vs. PBO): % women (57% vs. 71%), race, white (76% vs. 68%), baseline platelet counts = < 15,000 per uL (50% vs. 45%), at least 2 previous ITP therapies (74% vs. 68%). Differences in AEs may have lead to patients inferring treatment received. Nausea, vomiting, fatigue, and myalgia were only reported in the eltrombopag group. Bleeding was more common in the placebo group. ITT population was reported. Proportion of responders, defined as patients who had an increase in platelet counts to $\geq 50\ 000/\mu\text{L}$ at day 43 (i.e., 6 weeks after the start of treatment); patients who withdrew prematurely because of a platelet count greater than $200\ 000/\mu\text{L}$ were considered responders.

**Figure 3: Risk of Bias Assessments Per Outcome Within Each Study (Jurczak, Arnold, Yang, Ghanima, Shirasugi)**

Study ID	Experimental	Comparator	Outcome	Weight	D1	D2	D3	D4	D5	Overall		
Jurczak	avatrombopag	placebo	Duration of platelet count response	1	!	+	+	+	+	+	+	Low risk
Jurczak	avatrombopag	placebo	platelet count response - duration of response	1		+	+	!	+	+	!	Some concerns
Jurczak	avatrombopag	placebo	platelet count response - durable response	1	!	+	+	+	+	+	+	High risk
Jurczak	avatrombopag	placebo	Platelet count response - % pts	1	!	+	+	+	+	+	+	
Jurczak	avatrombopag	placebo	Reduction in use of concomitant ITP medications	1	!	+	+	+	+	+	+	D1 Randomisation process
Jurczak	avatrombopag	placebo	bleeding (incidence, all grades)	1	!	+	+	+	+	+	+	D2 Deviations from the intended interventions
Jurczak	avatrombopag	placebo	rescue treatment	1	!	+	+	+	+	+	+	D3 Missing outcome data
Jurczak	avatrombopag	placebo	WHO Grade 1 bleeding	1	!	+	+	+	+	+	+	D4 Measurement of the outcome
Jurczak	avatrombopag	placebo	WHO Grade 2 bleeding	1	!	+	+	+	+	+	+	D5 Selection of the reported result
Jurczak	avatrombopag	placebo	WHO Grade 3 bleeding	1	!	+	+	+	+	+	+	
Jurczak	avatrombopag	placebo	Complete platelet response	1	!	+	+	+	!	+	+	
Jurczak	avatrombopag	placebo	Platelet response	1	!	+	+	+	!	+	+	
Arnold	eltrombopag	IVIg	perioperative platelet count	1	!	+	+	+	+	!	!	
Arnold	eltrombopag	IVIg	bleeding - severe (grade 2 and above) bleeding events	1	!	+	+	+	+	!	!	
Arnold	eltrombopag	IVIg	bleeding - grade 1 bleeding events	1	!	+	+	+	+	!	!	
Arnold	eltrombopag	IVIg	rescue treatment	1	!	+	+	!	+	!	!	
Arnold	eltrombopag	IVIg	splenectomy	1	!	+	+	+	+	!	!	
Arnold	eltrombopag	IVIg	postoperative blood transfusion	1	!	+	+	+	+	!	!	
Arnold	eltrombopag	IVIg	time to reach platelet count target (median)	1	!	+	+	+	+	!	!	
Yang	eltrombopag	placebo	Platelet count response - % pts	1	!	+	+	+	+	+	+	
Yang	eltrombopag	placebo	platelet count response - composite outcome	1	+	+	+	+	+	+	+	
Yang	eltrombopag	placebo	Platelet count response - duration of response (mean)	1	!	+	+	+	+	+	+	
Yang	eltrombopag	placebo	platelet count response - max time with continuous response (mean)	1	!	+	+	+	+	+	+	
Yang	eltrombopag	placebo	rescue treatment	1	!	+	+	+	+	!	!	
Yang	eltrombopag	placebo	bleeding - gr 1 to 4	1	+	+	+	+	+	+	+	
Yang	eltrombopag	placebo	bleeding - gr 2 to 4	1	+	+	+	+	+	+	+	
Yang	eltrombopag	placebo	time to response	1	+	+	+	+	+	+	+	
Ghanima	rituximab	placebo	platelet count response - overall	1	!	+	+	+	+	!	!	
Ghanima	rituximab	placebo	platelet count response - complete	1	!	+	+	+	+	!	!	
Ghanima	rituximab	placebo	Platelet count response - duration of response (overall)	1	!	+	+	+	+	!	!	
Ghanima	rituximab	placebo	Platelet count response - duration of response (complete)	1	!	+	+	+	+	!	!	
Ghanima	rituximab	placebo	bleeding (patients with ≥1 bleeding episodes as per WHO criteria for treatment failure [or splenectomy])	1	!	+	+	+	+	!	!	
Ghanima	rituximab	placebo	splenectomy	1	!	+	+	+	!	!	!	
Shirasugi	romiplostim	placebo	Platelet count response - duration of response (median)	1	+	!	+	+	+	+	+	
Shirasugi	romiplostim	placebo	rescue treatment	1	+	+	+	+	+	+	+	
Shirasugi	romiplostim	placebo	platelet count response - % patients	1	+	+	+	+	+	!	!	
Shirasugi	romiplostim	placebo	platelet count (x 10 <sup>9</sup> ) - change from baseline (mean)	1	+	+	+	+	+	+	+	
Shirasugi	romiplostim	placebo	platelet response - target range	1	+	+	+	+	+	+	+	
Shirasugi	romiplostim	placebo	platelet count (mean weekly count)	1	+	+	+	+	+	+	+	



**Figure 4: Risk of Bias Assessments Per Outcome Within Each Study (Kuter 2010, Bussel 2018, Eisai, Cheng)**

Study ID	Experimental	Comparator	Outcome	Weight	D1	D2	D3	D4	D5	Overall	
Kuter 2010	romiplostim	placebo (SOC)	treatment failure (composite outcome)	1	⊖	⊕	⊕	⊕	⊖	⊖	⊕ Low risk
Kuter 2010	romiplostim	placebo (SOC)	treatment failure (component) - major bleeding	1	⊖	⊕	⊕	⊕	⊕	⊖	⊕ Some concerns
Kuter 2010	romiplostim	placebo (SOC)	treatment failure (component) - lack of efficacy	1	⊖	⊕	⊕	⊖	⊕	⊖	⊖ High risk
Kuter 2010	romiplostim	placebo (SOC)	treatment failure (component) - severe side effect or bleeding	1	⊖	⊕	⊕	⊕	⊕	⊖	
Kuter 2010	romiplostim	placebo (SOC)	splenectomy	1	⊖	⊕	⊕	⊕	⊕	⊖	D1 Randomisation process
Kuter 2010	romiplostim	placebo (SOC)	platelet count	1	⊖	⊕	⊕	⊕	⊕	⊖	D2 Deviations from the intended interventions
Kuter 2010	romiplostim	placebo (SOC)	platelet response	1	⊖	⊕	⊕	⊕	⊕	⊖	D3 Missing outcome data
Kuter 2010	romiplostim	placebo	quality of life, change from baseline (mean (SD))	1	⊖	⊕	⊕	⊖	⊕	⊖	D4 Measurement of the outcome
Kuter 2010	romiplostim	placebo (SOC)	bleeding events (safety, all)	1	⊖	⊕	⊕	⊕	⊕	⊖	D5 Selection of the reported result
Kuter 2010	romiplostim	placebo (SOC)	bleeding (safety outcome, at least grade 2)	1	⊖	⊕	⊕	⊕	⊕	⊖	
Kuter 2010	romiplostim	placebo (SOC)	bleeding (safety outcome, at least grade 3)	1	⊖	⊕	⊕	⊕	⊕	⊖	
Bussel 2018	fostamatinib	placebo	platelet count response - stable	1	⊕	⊕	⊖	⊕	⊕	⊖	
Bussel 2018	fostamatinib	placebo	platelet count response - overall	1	⊕	⊕	⊖	⊕	⊕	⊖	
Bussel 2018	fostamatinib	placebo	platelet count response - achievement ≥ 30	1	⊕	⊕	⊖	⊕	⊕	⊖	
Bussel 2018	fostamatinib	placebo	time to platelet count response	1	⊕	⊕	⊖	⊕	⊕	⊖	
Bussel 2018	fostamatinib	placebo	bleeding events (SAE)	1	⊕	⊕	⊖	⊕	⊕	⊖	
Bussel 2018	fostamatinib	placebo	bleeding events (mod or sev bleeding-related AE)	1	⊕	⊕	⊖	⊕	⊕	⊖	
Bussel 2018	fostamatinib	placebo	platelet count over time	1	⊕	⊕	⊖	⊕	⊕	⊖	
Eisai	avatrombopag	eltrombopag	change in platelet count	1	⊕	⊕	⊕	⊕	⊕	⊕	
Cheng	eltrombopag	placebo	platelet count response	1	⊕	⊕	⊕	⊕	⊕	⊕	
Cheng	eltrombopag	placebo	platelet count response- 75% assessments - % patients	1	⊕	⊕	⊕	⊕	⊕	⊕	
Cheng	eltrombopag	placebo	platelet count response - duration of response (mean, weeks)	1	⊕	⊕	⊕	⊕	⊕	⊖	
Cheng	eltrombopag	placebo	platelet count response - cumulative duration of response (mean, weeks)	1	⊕	⊕	⊕	⊕	⊕	⊖	
Cheng	eltrombopag	placebo	bleeding (WHO gr 1-4)	1	⊕	⊕	⊕	⊕	⊕	⊕	
Cheng	eltrombopag	placebo	bleeding (WHO gr 2-4)	1	⊕	⊕	⊕	⊕	⊕	⊕	
Cheng	eltrombopag	placebo	Reduction in use of concomitant ITP medications	1	⊕	⊕	⊕	⊕	⊕	⊕	
Cheng	eltrombopag	placebo	rescue treatment	1	⊕	⊕	⊕	⊕	⊕	⊕	
Cheng	eltrombopag	placebo	HRQoL - SF-36v2 (PCS)	1	⊕	⊕	⊕	⊕	⊕	⊖	
Cheng	eltrombopag	placebo	HRQoL - SF-36v2 (MCS)	1	⊕	⊕	⊕	⊕	⊕	⊖	
Cheng	eltrombopag	placebo	fatigue	1	⊕	⊕	⊕	⊕	⊕	⊕	
Cheng	eltrombopag	placebo	MEI-SF	1	⊕	⊕	⊕	⊕	⊕	⊕	
Cheng	eltrombopag	placebo	FACT-Th6	1	⊕	⊕	⊕	⊕	⊕	⊕	
Cheng	eltrombopag	placebo	POST-HOC platelet count response - durable response	1	⊕	⊕	⊕	⊕	⊕	⊕	

**Figure 5: Risk of Bias Assessments Per Outcome Within Each Study (Tomiyaama, Kuter 2008, Kuter 2009, Kuter 2010, Kuter 2011, Bussel 2009)**

Study ID	Experimental	Comparator	Outcome	Weight	D1	D2	D3	D4	D5	Overall		
Tomiyaama	eltrombopag	placebo	platelet count response - % patients	1	!	!	+	+	+	!	+	Low risk
Tomiyaama	eltrombopag	placebo	platelet count, median	1	!	!	+	+	!	!	!	Some concerns
Tomiyaama	eltrombopag	placebo	platelet count response - % patients by week (proportion of responders at week	1	!	!	+	+	+	!	!	High risk
Tomiyaama	eltrombopag	placebo	platelet count response - % patients by week (proportion of responders at week	1	!	!	+	+	+	!		
Tomiyaama	eltrombopag	placebo	platelet count response - % patients by week (proportion of responders at week	1	!	!	+	+	+	!	D1	Randomisation process
Tomiyaama	eltrombopag	placebo	platelet count response - % patients at least 4 assessments	1	!	!	+	+	+	!	D2	Deviations from the intended interventions
Tomiyaama	eltrombopag	placebo	bleeding (incidence of bleeding episodes (defined as abnormal bleeding))	1	!	!	+	!	!	!	D3	Missing outcome data
Kuter 2008	romiplostim	placebo	durable platelet response	1	+	+	+	+	+	+	D4	Measurement of the outcome
Kuter 2008	romiplostim	placebo	durable platelet response, despite rescue treatment	1	+	+	+	+	+	+	D5	Selection of the reported result
Kuter 2009	romiplostim	placebo	overall platelet response	1	+	+	+	+	+	+		
Kuter 2010	romiplostim	placebo	rescue treatment	1	+	+	+	+	+	+		
Kuter 2011	romiplostim	placebo	reduction in concurrent therapy	1	+	+	+	+	+	+		
Bussel 2009	eltrombopag	placebo	platelet count response - % patients	1	!	+	+	+	+	!		
Bussel 2009	eltrombopag	placebo	platelet count, median	1	!	+	+	+	+	!		
Bussel 2009	eltrombopag	placebo	odds of responding during weeks 2-6	1	!	+	+	+	+	!		
Bussel 2009	eltrombopag	placebo	bleeding	1	!	+	+	+	+	!		
Bussel 2009	eltrombopag	placebo	platelet count response - % patients	1	!	+	+	+	+	!		

## Appendix 11: Economic Evaluation

Note that this appendix has not been copy-edited.

### Literature Review

As part of the development of the economic evaluation for chronic ITP, a literature review of existing decision-analytic models in chronic ITP was conducted. With the goal to determine whether any of the published economic evaluations could directly address the research questions; and, if not, whether details on the model structure could assist the development of a model. This was not a systematic review and hence likely to be nonexhaustive. Conference abstracts and manuscripts published in a different language than English were excluded.

[Table 29](#) below summarizes the main characteristics of the identified studies. None of the identified studies were directly applicable to the economic analysis research questions. Given that the rationale for conducting this review was to further inform the development of a decision-analytic model, less emphasis was placed on the results of the analysis. Instead, the review focused on the model structure.

**Table 29: Summary of ITP Decision–Analytic Models**

Source	Model type	Target population	Intervention/ Comparators	Health states	Time horizon	Cycle length	Perspective
Allen 2016 <sup>44</sup>	Markov	UK patients with chronic ITP	Eltrombopag Romiplostim	1. NR w1 to 4 2. NR w5 to 8 3. NR w9 to 12 4. NR w13 to 16 5. Responder 6. Long-term NR	Lifetime	4 weeks	Public health care (UK)
Lee 2013 <sup>45</sup>	Markov / decision tree combination	Irish adults with chronic ITP	Romiplostim + SoC Eltrombopag + SoC SoC, including rituximab	1. Sufficient platelets 2. Low platelets 3. Death	Lifetime	4 weeks	Public health care (Irish)
Tremblay 2020 <sup>46</sup>	Markov	American patients with chronic ITP	Eltrombopag Romiplostim	1. On treatment 2. Treatment failure/ discontinuation 3. Mortality	Lifetime	28 days	US payer perspective
Xie 2009 <sup>47</sup>	Markov	Canadian adults with chronic ITP	IVIG Prednisone	1. Remission 2. No response 3. Refractory 4. Post splenectomy remission 5. Death	Lifetime	1 year	Public health care (Canada)

ITP = immune thrombocytopenia; NR = no response; SoC = standard of care.

Four studies were identified that had developed a decision-analytic model to support either a cost-effectiveness or a cost-utility analysis. All analyses were models and adopted the same national public health care perspective (except for Tremblay 2020 in which the US payer perspective was used). All studies used a cohort state-transition (Markov) model with discrete time cycles. The cycle lengths varied but all models used a lifetime time horizon. Disease progression, modelled by health states, varied across the published models but could be broadly categorized as response, nonresponse, and death.

## Ideal Model Structure

As part of the scoping process, existing published models were reviewed, and clinical experts were consulted to determine the most appropriate characterization of ITP. The conceptual structure below was the outcome of the exercise, which clinical experts considered an appropriate representation of the natural history of chronic ITP. Of note, the proposed structure below was developed without taking data availability into consideration.

As the model's target population is adults with ongoing, active ITP after failure of first-line therapy, the baseline characteristics of the target population ideally would be defined in such a way that resemble the characteristics of ITP patients diagnosed across Canadian jurisdictions. Real world administrative data would be a source to inform this set of model parameters, assuming that the population can be adequately identified through administrative data.

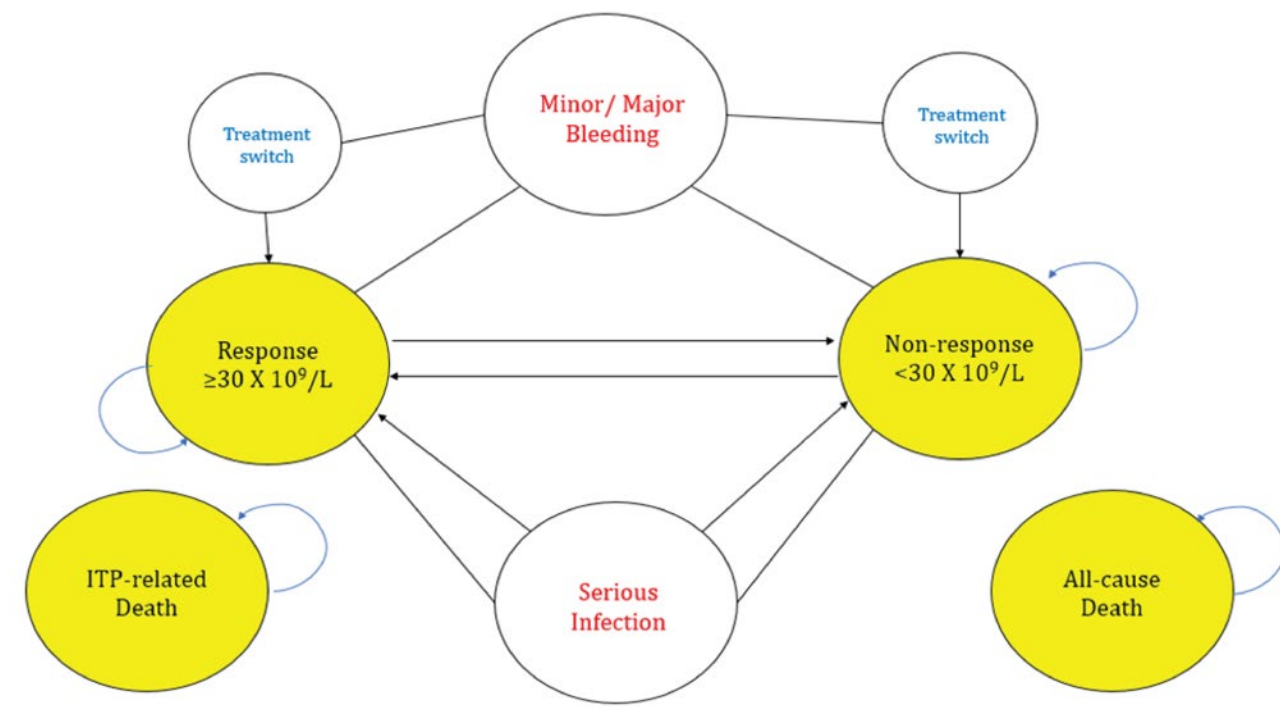
The base-case analysis would be conducted from the perspective of the Canadian publicly funded health care system. The model time horizon would be life-long with weekly cycle lengths. As per CADTH guideline, the discount rates for costs and utilities would be 1.5% annually. We assumed that a weekly cycle length would be a sufficient minimum duration to capture recurrent events (e.g., bleeding) or transitions between health states. A lifetime horizon would be appropriate since some of the modelled events (e.g., severe bleeding/intracranial hemorrhage) can be life altering with an increased risk of mortality.

The model would be an individual-level state-transition model, also known as a microsimulation model, with discrete time cycles. A microsimulation approach was proposed so that time dependency (e.g., differential response and bleeding events over time), the effect of past events, and individual heterogeneity is adequately considered in the model. Treatment choice after nonresponse to therapy is dependent on past treatment exposure, hence, treatment history may be considered a past event that needs to be recorded within the model. An example of individual heterogeneity relevant to consider within this decision problem, as per input from clinical experts consulted by CADTH, was the increased risk of bleeding for individuals who already experienced a bleeding episode. Hence, history of bleeding events should be taken into consideration as this would impact an individual's risk of bleeding and have associated utility and cost impacts.

Using input from the clinical team, the model should capture the following 6 treatments: rituximab, eltrombopag, romiplostim, fostamatinib, avatrombopag, and splenectomy. It remains unclear presently whether IVIG, immunosuppressants (azathioprine, cyclosporine, cyclophosphamide, mycophenolate mofetil, danazol, dapsone) and corticosteroids constitute real world treatment alternatives.

The proposed model structure would have 4 states: nonresponse, response, and ITP-related death and death from all-cause mortality. The model diagram is presented below (Figure 6). As patients transition between states, they can experience bleeding (major and minor), experience a serious infection, switch treatment, or require rescue medication. Only some of these events are included in the model diagram for simplicity. All states lead to both ITP-related death (through bleeding or infection) and non-ITP-related death (death from other causes). These transition arrows are omitted from the model diagram for simplicity. Transitions may be modelled with time and state residence dependencies, where appropriate, to factor time dependencies, the effect of past events, and individual heterogeneity. The relationships among these events are also modelled, as noted in the transition arrows within the Figure 6.

**Figure 6: Diagram of the Ideal Model**



## Model Inputs

The following outcomes would be needed to meaningfully inform the proposed economic model:

- Clinical effectiveness outcomes would include time to platelet count response; time and treatment-dependent risk of (severe) bleeding and (severe) infections; time to treatment discontinuation; need for rescue medication (e.g., IVIG, corticosteroids, platelet transfusions), and mortality.
- Severity and location of bleeding would be a function of treatment (e.g., intracranial hemorrhage vs. other bleeding) and the risk of bleeding would depend on response status.
- Treatment adherence would be dependent on time and treatment history.

- Safety outcomes should include AEs, serious AEs, discontinuation due to AEs, and adverse event-related death. Preference based HRQoL estimates would be required to assign utility values in occupying a given health state or experiencing an event such as severe bleeding or infection. Treatment effectiveness, AEs, treatment adherence, and costs would ideally be conditional on treatment dosage.

[Table 30](#) and [Table 31](#) provide a subset of the probability, utility, and cost input parameters currently available that could be used to develop a chronic ITP decision-analytic model. Of note, provided utility estimates were by platelet count and not categorized by response (where ideally a model could simulate platelet count movement).

**Table 30: Model Input Parameters That Were Successfully Identified and Sourced**

Input parameter		Value				Source
Proportion with ITP-related minor bleed		1.4% [0.9%, 2.1%]				Neunert 2015 <sup>48</sup>
Proportion with ITP-related major bleed		9.6% [4.1%, 17.1%]				Neunert 2015 <sup>48</sup>
Major bleed mortality (1-year)		0.454				Fernando 2021 <sup>49</sup>
5-year MRR after severe bleeding		10.6 [4.2, 26.6]				Norgaard 2011 <sup>50</sup>
Adjusted 1-year relative risk of infection		4.5 [3.3, 6.1]				Norgaard 2011 <sup>50</sup>
Mortality rate ratio after infection (5-year)		4.2 [2.4, 7.2]				Norgaard 2011 <sup>50</sup>
Utility estimates	≤ 10k (n = 25)	11 to 29k (n = 75)	30 to 49k (n = 109)	50 to 99k (n = 210)	100 to 149k (n = 139)	≥ 150k (n = 444)
EQ-5D Index Score	0.75	0.83	0.82	0.82	0.79	0.82

**Table 31: Treatment Costs That Were Successfully Identified and Sourced**

Treatment	Strength / concentration	Form	Price (\$)	Recommended dosage	Daily cost (\$)	Course or annual cost (\$)
Fostamatinib (Tavalisse)	100 mg 150 mg	Tablet	80.8700 121.3050	Initially 100 mg twice daily. After 4 weeks, increase to 150 mg twice daily if platelet count has not reached at least 50 × 10 <sup>9</sup> /L	161.74 to 242.61	59,035 to 88,553
TPO-RAs						
Eltrombopag (Revolade)	25 mg 50 mg	Tablet	65.0000 130.0000	Initially 50 mg once daily (25 mg in Asian patients). After 2 weeks, increase dose by 25 mg if platelet count < 50 × 10 <sup>9</sup> /L, up to a maximum of 75 mg daily. Reduce dose when platelet count is above 200 × 10 <sup>9</sup> /L	65.00 to 195.00	23,725 to 71,175 <sup>c</sup>
Romiplostim (Nplate)	250 mcg/0.5 mL 500 mcg/1 mL	Vial of lyophilized powder for solution	1,021.7900 2,043.6000	1 mcg/kg SC weekly, adjusting by increments of 1 mcg/kg until platelet count ≥ 50 × 10 <sup>9</sup> /L. Do not exceed 10 mcg/kg	145.97 initially, up to 437.91	53,279 initially, up to 159,837
CD20 Inhibitor (off-label)						
Rituximab (Rituxan, Truxima, Riximyo, Ruxince)	10 mg/mL	10 mL 50 mL Single use vials	297.0000 1,485.0000	375 mg/m <sup>2</sup> IV once per week for 4 weeks	NA	Cost per 4-week course: 8,316
				100 mg IV once per week for 4 weeks	NA	Cost per 4-week course: 1,188
Immunosuppressants (off-label)						
Azathioprine (generic)	50 mg	Tablet	0.2405	1 to 2 mg/kg daily, maximum 150 mg/day	0.48 to 0.72	176 to 263



Treatment	Strength / concentration	Form	Price (\$)	Recommended dosage	Daily cost (\$)	Course or annual cost (\$)
Cyclosporin A (Neoral, generic)	10 mg 25 mg 50 mg 100 mg	Tablet	0.6700 0.9952 1.9400 3.8815	5 mg/kg/day for 6 days, then 2.5 to 3 mg/kg/day	Initial: 15.53 Then: 7.76 to 9.70	2,881 to 3,577
	100 mg/mL	Oral solution	5.4030		Initial: 21.61 Then: 10.81 to 12.97	4,009 to 4,785
Cyclophosphamide (Procytox)	25 mg 50 mg	Tablet	0.3545 0.4773	1 to 2 mg/kg daily for at least 16 weeks <sup>d</sup>	0.83 to 1.43	304 to 523
	200 mg 500 mg 1000 mg 2000 mg	Vial for injection 20mg/mL	74.23 93.14 168.8300 310.6000	0.3 to 1 g/m <sup>2</sup> IV every 2 to 4 weeks for one to 3 doses	NA	Per course: 167 to 932
Danazol (Cyclomen)	50 mg 100 mg 200 mg	Capsule	1.0212 1.5156 2.4220	200 mg 2 to 4 times daily	4.84 to 9.69	1,768 to 3,536
Dapsone (generic)	100 mg	Tablet	0.7031	100 mg per day	0.70	257
Mycophenolate mofetil (generic)	250 mg 500 mg	Capsule	0.3712 0.7423	1.5 to 2 g/day for at least 12 weeks	2.23 to 2.97	813 to 1,084
Vincristine (generic)	1 mg/mL	Solution for injection	30.6000	6 mg total at 1 to 2 mg per weekly infusion	NA	Per course: 184
Vinblastine (generic)	10 mg/ 10 mL	Solution for injection	185.6300	30 mg total at 10 mg per weekly infusion	NA	Per course: 557
<b>IV Immunoglobulins (Human), 10%</b>						
Gamunex <sup>b</sup>	5g/50mL 10 g/100mL 20 g/100mL	Injectable solution	27.2743	0.1 and 0.6 g/kg every 3 or 4 weeks	7.32 to 56.49	2,673 to 20,619

Treatment	Strength / concentration	Form	Price (\$)	Recommended dosage	Daily cost (\$)	Course or annual cost (\$)
IGIVnex <sup>c</sup>	10% solution	Injectable solution	27.2743	0.1 and 0.6 g/kg every 3 or 4 weeks	7.32 to 56.49	2,673 to 20,619
Gammagard Liquid <sup>b</sup>	1 g/10 mL 2.5 g/25 mL 5 g/50 mL 10 g/100 mL 20 g/200 mL 30 g/300mL	Solution for infusion	26.9247	Starting dose: 0.4 to 0.8 g/kg Thereafter: 0.2 to 0.8 g/kg	Initial: 28.92 to 74.36 Subsequent: 14.46 to 111.53	Initial: 10,554 to 27,140 Subsequent: 5,277 to 40,710
Gammagard S/D <sup>d</sup>	5 g 10 g	Vial	40.8342	At least 0.1 mg/kg, monthly recommended. (Initially, patients may receive 0.2 to 0.4 g/kg)	9.40	3,430
Octagam <sup>b,e</sup>	5 g/50 mL 10 g/100 mL 20 g/100 mL 50 mg/mL	Solution for infusion	24.4666	Replacement therapy in PID: Monthly doses of at least 0.1 g/kg recommended. Replacement therapy in SIDs: 0.2 to 0.4 g/kg body weight every 3 to 4 weeks	16.89 to 26.28	6,166 to 9,591
Panzyga	100 mg/mL	Solution for infusion	59.5375	0.2 to 0.8 g/kg, every 3 to 4 weeks	31.97 to 164.42	11,669 to 60,013
Privigen <sup>b</sup>	5 g/50 mL 10 g/ 100 mL 20 g/200 mL 40 g/ 400 mL	Solution for infusion and IV	41.9715	0.2 to 0.8 g/kg, every 3 to 4 weeks	22.54 to 115.91	8,226 to 42,307
Weighted IVIG cost from public sources			\$47.39 per gram	<a href="http://www.cdha.nshealth.ca/nova-scotia-provincial-blood-coordinating-program-9">http://www.cdha.nshealth.ca/nova-scotia-provincial-blood-coordinating-program-9</a> See Figure 8 of 2019/20		

## Discussion

The existing published decision-analytic models informed the fundamental structure of the proposed economic model. A Markov model was considered to be a less effective approach to incorporate the complexities of the course of treatment and disease trajectories, as well as the interrelationships between treatment, AEs, and other clinical outcomes. As such, a microsimulation was felt to allow the flexibility to capture these effects and could represent the ideal modelling approach. The data collected, described in the Model inputs section of this Appendix, provide several core input parameters to this model. However, these data would not be sufficient by themselves to support the development of the model described in the model section of this Appendix.

Given the lack of data at this time, simplifications to the ideal model may be required to what could be feasible, however this should be revisited as data in this space evolves. A simplified model would have the same structure and components as the ideal model except that treatment effects would be time-independent, while bleeding and infection risks would not be treatment or time-specific (given the current lack of information). To overcome these limitations, several data points and input parameter estimates, which we could not successfully source, are required. Time-dependent treatment effects and time-dependent transition probabilities between health states need to come from a robust NMA; where the heterogeneity around the definition of treatment response, both across the studies identified in the NMA, but also in real world clinical practice complicate the comparison of the alternative identified treatment strategies in a common framework. Estimates of population baseline risk of infection, estimates of treatment-specific bleeding, and infection risks are needed, and would ideally be sourced from data reflective of the population of interest (chronic ITP patients in Canada who have failed first-line treatment). More recent and more accurate estimates of health utility associated with treatment response and bleeding or infection outcomes would also be required.

Once data that are reflective of the need of such model are generated and/or collected, we can then inform core components of the economic model, such as the risk of treatment switching or treatment-specific rates of bleeding events. If Canadian patient databases exist, this would ideally be able to be used to inform the baseline characteristics of the model population. If patient data are sufficiently granularly reported (e.g., age, splenectomy at baseline), subgroup analyses of interest, such as splenectomy status, could further be supported in the economic analysis. Another possibility that comes with these data are the ability to model treatment effectiveness more explicitly, by modelling the waning of treatment efficacy and adherence with differential waning across treatments (e.g., Rituximab vs. Fostamatinib). Thus, the effects of treatment switching on treatment effectiveness can also be more explicitly estimated and modelled.