Title: Targeted Literature Review to Describe Safety Outcomes in Immune Thrombocytopenia Patients Treated With Thrombopoietin-Receptor Agonists

Title	Targeted Literature Review to Describe Safety Outcomes in Immune Thrombocytopenia Patients Treated With Thrombopoietin-Receptor Agonists
Protocol version identifier	Version 1.0
Date of last version of the protocol	Not applicable
Therapeutic Area	Hematology / Oncology
Product Reference	Romiplostim
Research Objectives	Primary objectives: 1. To estimate the incidence of bone marrow fibrosis/reticulin formation in adults with immune thrombocytopenia (ITP) who have been treated with (a) romiplostim therapy, (b) other Thrombopoietin-Receptor Agonists (TPO-RAs), and (c) other ITP therapies. 2. To estimate the incidence of hematologic malignancy in adults with immune thrombocytopenia (ITP) who have been treated with (a) romiplostim therapy, (b) other Thrombopoietin-Receptor Agonists (TPO-RAs), and (c) other ITP therapies including corticosteroids, IVIG (intravenous immunoglobulin), anti-D (Rho[D] immune globulin intravenous), rituximab, splenectomy, cyclophosphamide, dapsone, danazol, cyclosporine A, azathioprine, mycophenolate mofetil, eltrombopag, and vinca alkaloids Secondary objectives: 1. To report details on data sources (eg, registries, cohort studies) of adult immune thrombocytopenia (ITP) patients in which outcomes of interest and availability of pre- and post-TPO bone marrow biopsy for patients treated with specific Thrombopoietin-Receptor Agonists (TPO-RAs) (eg, romiplostim, eltrombopag, lusutrombopag, avatrombopag) can be investigated. 2. To describe the event rate of thrombotic/thromboembolic events and the distribution of specific diagnoses of these events (eg, myocardial infarction,

	stroke, deep vein thrombosis, pulmonary embolism) in adult immune thrombocytopenia (ITP) patients who have been treated with (a) romiplostim therapy, (b) other Thrombopoietin Receptor Agonists (TPO-RAs), and (c) other ITP therapies. 3. To assess the event rate of pre-malignant states ([focused on acute myelogenous leukemia (AML) and myelodysplastic syndromes (MDS)] in adult immune thrombocytopenia (ITP) patients who have been treated with (a) romiplostim therapy, (b) other Thrombopoietin-Receptor Agonists (TPO-RAs), and (c) other ITP therapies 4. To describe the event rate of concurrent leukocytosis and anemia in adult immune cytopenia (ITP) patients who have been treated with (a) romiplostim therapy, (b) other Thrombopoietin-Receptor Agonists (TPO-RAs), and (c) other ITP therapies. 5. To describe the event rate of acute renal failure in adult immune thrombocytopenia (ITP) patients who have been treated with (a) romiplostim therapy, (b) other Thrombopoietin- Receptor Agonists (TPO-RAs), and (c) other ITP therapies.
Author	

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1. LIST OF ABBREVIATIONS

Abbreviation or Term	Definition/Explanation
AML	Acute myelogenous leukemia
EMA	European Medicines Agency
FDA	U.S. Food and Drug Administration
ITP	Immune thrombocytopenia
MDS	Myelodysplastic syndromes
NCPRR	Nordic Country Patient Registry for Romiplostim
PASS	Post Authorization Safety Study
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analysis
TPO-RA	Thrombopoietin-receptor agonists

2. ABSTRACT

- Title: Targeted Literature Review to Describe Safety Outcomes in Immune Thrombocytopenia Patients Treated with Thrombopoietin-Receptor Agonists
- Background and rationale: A Post Authorization Safety Study (PASS) is being conducted to investigate the association between romiplostim and selected safety outcomes including bone marrow fibrosis/reticulin formation and thrombosis/thromboembolism events in patients with immune thrombocytopenia (ITP). This study is being undertaken using the Nordic Country Patient Registry for Romiplostim (NCPRR), Amgen study 20070797. The purpose of this targeted literature review is to supplement the findings of the PASS by summarizing relevant research undertaken outside the NCPRR to further assess safety outcomes in adult ITP patients treated with romiplostim or other Thrombopoietin-Receptor Agonists (TPO-RAs) compared to those not treated with TPO-RAs.
- Objectives and research questions

  Primary objectives:

  (1) To estimate the incidence of bone marrow fibrosis/reticulin formation in adults with ITP who have been treated with (a) romiplostim therapy, (b) other TPO-RAs, and (c) other ITP therapies including corticosteroids, IVIG (intravenous immunoglobulin), anti-D (Rho[D] immune globulin intravenous), rituximab, splenectomy, cyclophosphamide, dapsone, danazol, cyclosporine A, azathioprine, mycophenolate mofetil, and vinca alkaloids;

  (2) To estimate the incidence of hematologic malignancy in adults with ITP who have been treated with (a) romiplostim therapy, (b) other TPO-RAs, and (c) other ITP therapies.

  Secondary objectives:

  (1) To report details on data sources (eg, registries, cohort studies) of adult ITP patients in which outcomes of interest and availability of pre- and post- TPO-RA bone marrow biopsy for patients treated with specific TPO-RAs (eg, romiplostim, eltrombopag, lusutrombopag, avatrombopag) can be investigated;

  (2) To describe the event rate of thrombotic/thromboembolic events and the distribution of specific diagnoses of these events (eg, myocardial infarction, stroke, deep vein thrombosis, pulmonary embolism) in adult ITP patients who are treated with (a) romiplostim therapy, (b) other TPO-RAs, and (c) other ITP therapies;

  (3) To assess the event rate of pre-malignant states (acute myelogenous leukemia, AML and myelodysplastic syndromes, MDS) in adult ITP patients who are treated with (a) romiplostim therapy, (b) other TPO-RAs, and (c) other ITP therapies;

  (4) To describe the event rate of concurrent leukocytosis and anemia in adult ITP patients who are treated with (a) romiplostim therapy, (b) other TPO-RAs, and (c) other ITP therapies;

  (5) To describe the event rate of acute renal failure in adult ITP patients who are treated with (a) romiplostim therapy, (b) other TPO-RAs, and (c) other ITP therapies.

Primary research questions:

(1) What are the incidences of bone marrow fibrosis/reticulin formation in adults with ITP who have been treated with (a) romiplostim therapy, (b) other TPO-RAs, and (c) other ITP therapies?

(2) What are the incidences of hematologic malignancy in adults with ITP who have been treated with (a) romiplostim therapy, (b) other TPO-RAs, and (c) other ITP therapies?

Secondary research questions:

(1) What are the data sources of adult ITP patients with information on outcomes of interest and availability of pre- and post- TPO-RA bone marrow biopsy in ITP patients treated with specific TPO-RAs?

(2) What is the event rate of thrombotic/thromboembolic events and the distribution of specific diagnoses of these events (eg, myocardial infarction, stroke, deep vein thrombosis, pulmonary embolism) in adult ITP patients who are treated with (a) romiplostim therapy, (b) other TPO-RAs, and (c) other ITP therapies?

(3) What is the event rate of pre-malignant states (acute myelogenous leukemia, AML, and myelodysplastic syndromes, MDS) in adult ITP patients who are treated with (a) romiplostim therapy, (b) other TPO-RAs, and (c) other ITP therapies?

(4) What is the event rate of concurrent leukocytosis and anemia in adult ITP patients who are treated with (a) romiplostim therapy, (b) other TPO-RAs, and (c) other ITP therapies?

(5) What is the event rate of acute renal failure in adult ITP patients who are treated with (a) romiplostim therapy, (b) other TPO-RAs, and (c) other ITP therapies?

- Study eligibility

  Studies of adult ITP patients from all countries/regions will be included. Other eligibility criteria include studies that examine use of romiplostim, other TPO-RAs (eg, eltrombopag, lusutrombopag, avatrombopag), or other treatments for adult ITP patients. Studies evaluating bone marrow fibrosis/reticulin formation among adult ITP patients treated with (a) romiplostim therapy, (b) other TPO-RAs, and (c) other ITP therapies including corticosteroids, IVIG (intravenous immunoglobulin), anti-D (Rho[D] immune globulin intravenous), rituximab, splenectomy, cyclophosphamide, dapsone, danazol, cyclosporine A, azathioprine, mycophenolate mofetil, and vinca alkaloids will be included. Studies evaluating hematologic malignancy among adult ITP patients treated with (a) romiplostim therapy, (b) other TPO-RAs, and (c) other ITP therapies will be included. Studies evaluating thrombotic/thromboembolic events among adult ITP patients treated with (a) romiplostim therapy, (b) other TPO-RAs, and (c) other ITP therapies will be included. Studies evaluating pre-malignant states (AML or MDS) among adult ITP patients treated with (a) romiplostim therapy, (b) other TPO-RAs, and (c) other ITP therapies will be included. Studies evaluating concurrent leukocytosis and anemia in adult ITP patients treated with (a) romiplostim therapy, (b) other TPO-RAs, and (c) other ITP therapies will be included. Studies evaluating acute renal failure among adult ITP patients treated with (a) romiplostim therapy, (b) other TPO-RAs, and (c) other ITP therapies will

be included. Articles published between 01 January 2005 and 31 August 2019 will be included. Studies published in English as either peer-reviewed journals or conference abstracts will be included. Though TPO-RAs are typically used in the second-line setting, the PASS study was not limited to second-line use of romiplostim. Thus, use of romiplostim regardless of treatment line will be included.

Exclusion criteria include non-human studies, intervention studies, and case reports. Studies evaluating only pediatric ITP patients will be excluded. NCPRR studies will be excluded. Studies without information on the use of romiplostim, eltrombopag, lusutrombopag, or avatrombopag or other ITP treatments including corticosteroids, IVIG (intravenous immunoglobulin), anti-D (Rho[D] immune globulin intravenous), rituximab, splenectomy, cyclophosphamide, dapsone, danazol, cyclosporine A, azathioprine, mycophenolate mofetil, and vinca alkaloids in adult ITP patients will be excluded. Outcomes other than those described will not be considered. Articles that are opinion pieces, without original data, and case series of less than 20 adult ITP patients will be excluded.

- Study identification

  Targeted literature searches will be conducted in the PubMed, Embase, and Web of Science databases using search terms including ITP, bone marrow fibrosis, hematologic neoplasm, thromboembolism, AML, MDS, leukocytosis, anemia, and acute kidney failure. The search strategy will include the search terms, planned date limits, and other suitable filters for each database searched, and will be designed such that outcomes of interest and possible stratification variables will be captured in the scope of the targeted literature review. Studies published between 01 January 2005 and 31 August 2019 will be considered for the targeted literature review. Market approval for romiplostim was granted in 2008. The start of the literature search (2005) was selected to include the evidence published relatively close to the launch date for romiplostim.

  Reference sections of relevant publications, meta-analyses and systematic reviews will be screened for additional publications.

  Review of the Grey literature will not be conducted for this targeted literature review.

- Study selection

  Articles identified in the literature searches will be uploaded into DistillerSR (https://www.evidencepartners.com/products/distillersr-systematic-review-software). DistillerSR is a specially designed software package for systematic literature reviews, to track and manage literature reviews, resulting in a fully transparent and auditable review process.

  Articles will be de-duplicated within DistillerSR based on title and author. Articles will be screened for relevance first at the level of title and abstract based on the inclusion/exclusion criteria. Ten percent of the abstracts will be reviewed for agreement by a second independent reviewer. All articles marked as relevant will be reviewed at the level of full-text with 100% review for agreement by an independent reviewer.

- Data abstraction

  A data abstraction form in DistillerSR will be used to abstract the data.

  Information to be collected (shell data extraction sheets and tables) include study characteristics, population characteristics, details of previous and/or current therapy received (including splenectomy), and incidence of safety outcomes.

- Assessment of methodological quality

  A systematic approach for abstracting data from the selected publications to maximize reliability will be implemented. DistillerSR will be used for data abstraction.

  Critical data elements that are abstracted such as author name, citation ID, incidence proportion, and incidence rate will be 100% reviewed for quality control by an independent reviewer. 20% of the non-critical variables will be reviewed for agreement by a second independent reviewer.

  The Newcastle Ottawa Scale will be used to evaluate study quality and assess risk of bias in individual studies.

- Data synthesis (descriptive only): A narrative synthesis of the studies included in the targeted literature review will be presented that will describe the overall strength of the collective evidence to address the research questions on safety outcomes in adult ITP patients treated with (a) romiplostim therapy, (b) other TPO-RAs, and (c) other ITP therapies.

3. AMENDMENTS AND UPDATES

No amendments and updates have been made.

4. BACKGROUND AND RATIONALE

4.1 Disease or Therapeutic Area

Primary immune thrombocytopenia (formerly known as idiopathic thrombocytopenic purpura) is an autoimmune disorder with clinical manifestations ranging from minor bruising to severe hemorrhaging (Neylon et al. 2003; Nomura et al. 2016; Provan 2009). Bleeding is due to unusually low levels of platelets. In children, acute ITP (lasting < 6 months) may occur from a viral infection, but complete recovery is possible without treatment (NHLBI, accessed 2019). Chronic ITP can last 6 months or more and usually affects adults (NHLBI, accessed 2019). The primary goal of treatment for a ITP patient is to achieve a safe platelet count (above which he/she does not experience bleeding episodes). Common first-line therapies include corticosteroids, intravenous immunoglobulin, and anti-D (Rho[D] immune globulin intravenous) (Cooper 2009; Kitchens et al. 1986; Newland et al. 1983). Relapse or failure to respond to the first-line therapies may necessitate second-line treatments including splenectomy or other medical therapies, many of which have not been approved by regulatory authorities for the treatment of ITP but are being used because of efficacy demonstrated in other

immune diseases or as immune suppressants (Provan et al. 2015). Romiplostim and other TPO-RAs are usually given in second-line treatment (Bylsma et al. 2019).

Thrombopoietin-receptor agonists (TPO-RAs) such as romiplostim have received market authorization by the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for adult patients with ITP. However, at the time of market authorization, specific safety concerns were raised, and they included bone marrow changes, higher risk for blood clots, possible worsening of blood cancers, and worsening low blood platelet count after stopping the drug (FDA, 2011). Currently, a Post Authorization Safety Study (PASS) is being conducted using the Nordic Country Patient Registry for Romiplostim (NCPRR), Amgen study 20070797. The purpose of this targeted literature review is to supplement the findings of the PASS by summarizing relevant research undertaken outside NCPRR. This targeted literature review will assess safety outcomes in adult ITP patients treated with TPO-Ras and other ITP therapies. While TPO-RAs are typically used in the second-line setting, the PASS study did not restrict to romiplostim use in the second-line setting. Thus, all use of TPO-RAs, regardless of treatment line, will be included in the current review.

4.2 Scope for Analysis

The targeted review will include peer-reviewed research articles published between 01 January 2005 and 31 August 2019 that describe the incidence of bone marrow fibrosis/reticulin formation or incidence of hematologic malignancy in adults with ITP who have been treated with (a) romiplostim therapy, (b) other TPO-RAs, and (c) other ITP therapies including corticosteroids, IVIG (intravenous immunoglobulin), anti-D (Rho[D] immune globulin intravenous), rituximab, splenectomy, cyclophosphamide, dapsone, danazol, cyclosporine A, azathioprine, mycophenolate mofetil, and vinca alkaloids, as reported in population-based observational research. Studies evaluating use of other TPO-RAs (eg, eltrombopag, lusutrombopag, avatrombopag) and other ITP treatments in adult ITP patients will also be considered. Clinical trials, prospective or retrospective observational cohort studies, case-control studies, and case series will be considered. Case series will be limited to those studies with 20 or more cases. Individual articles from previously published systematic reviews will also be evaluated for inclusion. Opinion pieces, editorials, articles without original data (except systematic reviews), case reports with less than 20 cases, and qualitative studies will be excluded. Studies that have not undergone peer-review, regardless of type, will be also excluded. Information on bone marrow fibrosis/reticulin formation or hematologic malignancy in

adults with ITP that is available from other sources that have not been peer-reviewed or published, such as online databases, will not be included.

A search of PubMed using the terms [(immune thrombocytopenia) AND (romiplostim) AND ((bone marrow fibrosis) OR (hematologic malignancy)] and limited to reviews of adults did not return any prior relevant systematic literature reviews that have been published on incidence of these outcomes. One systematic literature review provided summaries on the efficacy and effectiveness of therapies used to treat adult immune thrombocytopenia in the second-line setting (Bylsma et al. 2019). Hence, this targeted literature review will build upon the findings of Bylsma et al. (2019) and provide valuable and useful information to the scientific community.

5. OBJECTIVES

Primary objectives:

1. To estimate the incidence of bone marrow fibrosis/reticulin formation in adults with ITP who have been treated with (a) romiplostim therapy, (b) other TPO-RAs, and (c) other ITP therapies including corticosteroids, IVIG (intravenous immunoglobulin), anti-D (Rho[D] immune globulin intravenous), rituximab, splenectomy, cyclophosphamide, dapsone, danazol, cyclosporine A, azathioprine, mycophenolate mofetil, and vinca alkaloids;
2. To estimate the incidence of hematologic malignancy in adults with ITP who have been treated with (a) romiplostim therapy, (b) other TPO-RAs, and (c) other ITP therapies.

Secondary objectives:

1. To report details on data sources (eg, registries, cohort studies) of adult ITP patients in which outcomes of interest and availability of pre- and post- TPO-RA bone marrow biopsy for patients treated with specific TPO-RAs (eg, romiplostim, eltrombopag, lusutrombopag, avatrombopag) can be investigated;
2. To describe the event rate of thrombotic/thromboembolic events and the distribution of specific diagnoses of these events (eg, myocardial infarction, stroke, deep vein thrombosis, pulmonary embolism) in adult ITP patients who are treated with (a) romiplostim therapy, (b) other TPO-RAs, and (c) other ITP therapies;
3. To describe the event rate of pre-malignant states (AML and MDS) in adult ITP patients who are treated with (a) romiplostim therapy, (b) other TPO-RAs, and (c) other ITP therapies;
4. To describe the event rate of concurrent leukocytosis and anemia in adult ITP patients who are treated with (a) romiplostim therapy, (b) other TPO-RAs, and (c) other ITP therapies;
5. To describe the event rate of acute renal failure in adult ITP patients who are treated with (a) romiplostim therapy, (b) other TPO-RAs, and (c) other ITP therapies.

6. RESEARCH QUESTIONS

Primary research questions:

1. What are the incidences of bone marrow fibrosis/reticulin formation in adults with ITP who have been treated with (a) romiplostim therapy, (b) other TPO-RAs, and (c) other ITP therapies?
2. What are the incidences of hematologic malignancy in adults with ITP who have been treated with (a) romiplostim therapy, (b) other TPO-RAs, and (c) other ITP therapies?

Secondary research questions:

1. What are the data sources of adult ITP patients with information on outcomes of interest and availability of pre- and post- TPO-RA bone marrow biopsy for patients treated with specific TPO-RAs (eg, romiplostim, eltrombopag, lusutrombopag, avatrombopag)?
2. What is the event rate of thrombotic/thromboembolic events and the distribution of specific diagnoses of these events (eg, myocardial infarction, stroke, deep vein thrombosis, pulmonary embolism) in adult ITP patients who are treated with (a) romiplostim therapy, (b) other TPO-RAs, and (c) other ITP therapies?
3. What is the event rate of pre-malignant states (AML and MDS) in adult ITP patients who are treated with (a) romiplostim therapy, (b) other TPO-RAs, and (c) other ITP therapies?
4. What is the event rate of concurrent leukocytosis and anemia in adult ITP patients who are treated with (a) romiplostim therapy, (b) other TPO-RAs, and (c) other ITP therapies?
5. What is the event rate of acute renal failure in adult ITP patients who are treated with (a) romiplostim therapy, (b) other TPO-RAs, and (c) other ITP therapies?

7. METHODS FOR DATA COLLECTION

A targeted literature review will be conducted to identify studies that report adverse outcomes in adult patients with ITP. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher et al. 2009) will be used to complete the literature review. PRISMA includes a checklist to facilitate clarity and transparency of reporting in a systematic review (see Appendix 1 for the PRISMA elements).

7.1 Study Eligibility

Articles published between 01 January 2005 and 31 August 2019 will be included. Studies published in English as either peer-reviewed journals or conference abstracts will be included. The following additional inclusion criteria will be employed to determine study eligibility.

> **Population**: Studies that include information on treated adult ITP patients from all countries/regions will be included.
>
> **Intervention**: Use of romiplostim in adult ITP patients will be considered for this targeted review. Studies evaluating use of other TPO-RAs (eg, eltrombopag, lusutrombopag, avatrombopag) in adult ITP patients will be also considered. Studies evaluating other ITP therapies will be also considered. See Appendix 2 for the detailed list of interventions.
>
> **Comparator**: The comparator population will be adult ITP patients not treated with romiplostim. See Appendix 2 for the detailed list of comparators.
>
> **Outcome**: Outcomes considered include bone marrow fibrosis/reticulin formation, hematologic malignancy events, thrombotic/thromboembolic events, pre-malignant states (AML or MDS), concurrent leukocytosis and anemia or acute renal failures.
>
> **Study type**: Prospective or retrospective observational cohort studies, clinical trials, case-control studies, and case series will be considered.

The exclusion criteria as follows:

> **Population**: Studies evaluating only the pediatric ITP patients will be excluded. NCPRR studies will be excluded.
>
> **Intervention**: Studies not considering patients on ITP therapy in adult ITP patients will be excluded. See Appendix 2 for the detailed list of interventions.
>
> **Comparator**: Studies without the comparator population (adult ITP patients not treated with romiplostim) will be excluded. See Appendix 2 for the detailed list of comparators.
>
> **Outcome**: Studies with outcomes other than those described for the inclusion criteria will be excluded.
>
> **Study type**: Articles published outside the specified date limits as specified in the inclusion criteria will be excluded. Articles that are not published in English will be excluded. Non-human studies, randomized clinical trials, intervention studies, and case-reports will be excluded. Articles that are opinion pieces, without original data, and case series of less than 20 adult ITP patients will be excluded.

If more than one article from the same study population was published, data from the publication with the longest follow-up or most specifically relevant population and/or outcomes will be extracted. For studies with overlapping data, only those with larger population size, or specifically relevant population and/or outcomes will be considered.

7.2 Study Identification

This systematic literature review will be limited to peer-reviewed published literature to ensure that the research retrieved is based on rigorous methodology and reflects a higher level of evidence. Published studies will include those in journal publications as well as conference abstracts, and information from clinical trials.gov. No other grey literature will be considered.

7.2.1 Identifying Citations (Literature Searches)

The search strategy will be adapted to meet the search specifications of each included database. The search strategy includes search terms, planned date limits, and other suitable filters for each database searched, and is designed such that outcomes of interest and possible stratification variables will be captured in the scope of the literature review. These will be translated into indexed Medical Subject Headings (MeSH) and plain language text-word terms using the National Library of Medicine MeSH thesaurus. The selected terms will be compared to index terms of related published studies to ensure there are no gaps in the chosen search language. Boolean operators will be used to combine the final list of search terms into a comprehensive search strategy. As a final step, limit terms/filters will be added to the search strategy (eg, published after 2005) to ensure only the most relevant studies are included in the final search yield. A draft search strategy is included in Appendix 3.

Databases to be searched include:

- PubMed, which includes citations from MEDLINE, life science journals, and online books (https://www.ncbi.nlm.nih.gov/pubmed/)
- EMBASE, which includes conference abstracts back to 2009 (https://www.elsevier.com/solutions/embase-biomedical-research); the full list of over 6000 conferences included is available online (https://www.elsevier.com/solutions/embase-biomedical-research/embase-coverage-and-content). Key conferences include:
    - The Annual Meeting of the American Society of Hematology
    - The Congress of the European Hematology Association
    - The Annual Scientific Meeting of the British Society for Haematology
    - The Congress of the International Society on Thrombosis and Haemostasis
    - The Thrombosis and Hemostasis Summit of North America

  - Annual Meeting of the American Society of Clinical Oncology
  - European Society for Medical Oncology Congress
  - International MASCC/ISOO Symposium: Supportive Care in Cancer
- Web of Science, which provides subscription-based access to multiple databases of comprehensive citation data for various academic disciplines (www.webofknowledge.com)

Bibliographies of the selected literature will be also reviewed to find additional references.

Some of the key studies that should be picked up by a search strategy are recent studies published from the Nordic ITP safety cohorts. We will use these as quality assurance checkpoints for the search strategy (see pages 13-14, Section 7.2.1).

These manuscripts include:

1: Adelborg K, Kristensen NR, Nørgaard M, Bahmanyar S, Ghanima W, Kilpatrick K, Frederiksen H, Ekstrand C, Sørensen HT, Fynbo Christiansen C. Cardiovascular and bleeding outcomes in a population-based cohort of patients with chronic immune thrombocytopenia. J Thromb Haemost. 2019 Jun;17(6):912-924. doi: 10.1111/jth.14446. Epub 2019 Apr 19. PubMed PMID: 30933417.

2: Ettrup MS, Jensen AØ, Engebjerg MC, Farkas DK, Nørgaard M, Cha S, Zhao S, Johansen P, Sørensen HT. Bone marrow reticulin and collagen content in patients with adult chronic immune thrombocytopenic purpura: a Danish nationwide study. Am J Hematol. 2010 Dec;85(12):930-4. doi: 10.1002/ajh.21885. PubMed PMID: 20981681.

3: Nørgaard M, Jensen AØ, Engebjerg MC, Farkas DK, Thomsen RW, Cha S, Zhao S, Sørensen HT. Long-term clinical outcomes of patients with primary chronic immune thrombocytopenia: a Danish population-based cohort study. Blood. 2011 Mar 31;117(13):3514-20. doi: 10.1182/blood-2010-10-312819. Epub 2011 Jan 24. PubMed PMID: 21263148.

7.3 Study Selection

To select studies, titles and abstracts will be screened for incidence of bone marrow fibrosis or incidence of hematologic malignancy in adult ITP patients treated with (a) romiplostim therapy, (b) other TPO-RAs, and (c) other ITP therapies including corticosteroids, IVIG (intravenous immunoglobulin), anti-D (Rho[D] immune globulin intravenous), rituximab, splenectomy, cyclophosphamide, dapsone, danazol, cyclosporine A, azathioprine, mycophenolate mofetil, and vinca alkaloids. Abstracts will

be screened and categorized based on primary and secondary outcomes (eg, thrombotic/thromboembolic events, AML or MDS, concurrent leukocytosis and anemia, and acute renal failure).

Clinical trials, prospective or retrospective observational cohort studies, case-control studies, and case series will be included. Full-text articles will be reviewed for the outcomes listed above and any other notable findings. Duplicates will be removed from the search results using automated de-duplication methods and hand screening, and the remaining publications will be imported into Distiller SR. Bibliographies of relevant articles will be also reviewed to identify additional citations of possible interest.

To select the most relevant literature, each publication will be independently reviewed by two research staff members at three stages of this project. First, an independent reviewer will QC 10% of each abstract list from each database to determine agreement. Following this step, the list of full texts will be reviewed twice to determine agreement on all included articles. Finally, after each abstraction, QC will be performed on all data elements extracted for each study (100% QC). Following the abstraction QC, each original abstracter will review the QC done on their abstractions and assess agreement. All disputes will be resolved by a senior researcher. The results will be recorded, maintained and assessed using DistillerSR.

When the review is complete, a PRISMA flow diagram will be constructed to demonstrate the flow of study exclusion at each level, including reasons for exclusion at the level of full-text review.

7.4 Data Abstraction

PRISMA guidelines will be followed to conduct the review, including the data abstraction. For all relevant studies (identified via PubMed, EMBASE, Web of Science, or review bibliographies), data will be abstracted in Distiller SR. The abstraction form will be reviewed prior to any data abstraction to ensure that all appropriate fields are captured, and an initial small sample of articles will be abstracted to determine if the form is able to capture the appropriate information from the articles.

Specific items to be extracted will include:

- General information, including title, authors, source, contact address, country
- Year of publication
- Study characteristics, including details of study design and duration/study dates, inclusion/exclusion criteria, TPO-RA use, other medication use, dosage, treatment duration, previous therapies (number and type)
- Participant demographics and disease characteristics including reporting of key confounding factors such as:
    - History of thrombotic events
    - Comorbidities
    - Reason or contraindication they couldn't be treated with romiplostim
    - History of splenectomy
- Safety outcomes (both primary and secondary)
- Quality assessment of study being reviewed via the Newcastle Ottawa scale (http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp). (Appendix 4)
- A draft abstraction table is shown in Appendix 5.

8. DATA SYNTHESIS

8.1 Narrative Summary (Qualitative Synthesis)

A narrative synthesis of the studies included in the systematic literature review will be presented that will describe the overall strength of the collective evidence to address the research questions regarding the incidence of bone marrow fibrosis and incidence of hematologic malignancy in adult ITP patients treated with (a) romiplostim therapy, (b) other TPO-RAs, and (c) other ITP therapies. Tabulated summaries will be presented to explain the characteristics and findings of the included studies. Additional tabulated study summaries will be produced to facilitate review of the evidence available to address each research question by population, intervention, comparator, outcome, study type, and quality. Subgroups of interest include study design, year of testing, gender, country, ethnicity, age, and other reported subgroups. Endpoints that are of greatest interest include incidence of bone marrow fibrosis and incidence of hematologic malignancy in adult ITP patients treated with (a) romiplostim therapy, (b) other TPO-RAs, and (c) other ITP therapies. The structure of the results tables and the information that will be included in each table will be determined after the review is complete.

8.2 Analytical Summary (Quantitative Synthesis)

If sufficient data are available for a given study outcome (eg, incidence of bone marrow fibrosis among adult ITP patients treated with romiplostim) from the literature review, the data may be quantitatively summarized using a meta-analysis. Sufficient data is defined as at least 3 studies within each patient group (romiplostim, other TPO-RAs, or specific therapies within the other ITP therapies group) using the same outcome definition. Meta-analyses will be conducted using Comprehensive Meta-Analysis software (version 3.0; Biostat, Englewood, New Jersey). The results of included study outcomes will be summarized across available studies, weighting all included studies by the inverse of their variance using the method proposed by DerSimonian and Laird (DerSimonian 1986). Heterogeneity between studies in each analysis will be evaluated using the Cochran's Q and I^2 statistical tests. Forest plots will be used to visualize the distribution of included studies in each meta-analysis. If a sufficient number of studies are available ($n \geq 3$), subgroup analyses may be conducted by covariates of interest (eg, treatment line, study design, etc.).

9. STUDY LIMITATIONS

The review will be limited to reports (abstracts and articles) published in English. Results may only be generalizable for the areas and patient groups in which the studies were conducted and are further limited to data provided in the studies as to the demographic and baseline characteristics of the patients, as well as information about disease characteristics and treatment history. The outputs will be examined to determine if the consistency of the outcomes is similar across studies in various geographic areas in order to understand the extent of the generalizability. Missing and/or incomplete data may limit our ability to discuss the results.

10. ETHICAL AND REGULATORY CONSIDERATIONS

10.1 Adverse Events

Reporting of individual adverse events (AE), product complaints (PCs) and other safety findings is not applicable for systematic literature reviews which involve published literature sources, as the safety data from the studies identified will have been previously reported to regulatory agencies, institutional review boards, and ethics committees in accordance with local regulations and routine pharmacovigilance practices.

10.2 Data Management and Quality Control Procedures

Exact duplicates resulting from searching multiple databases will be removed from the search results using automated de-duplication methods and hand screening. The

remaining publications will be evaluated. If more than one article from the same study population was published (based on author names, sample sizes, intervention comparisons or outcomes), data from the publication(s) with the longest follow-up or most specifically relevant population and/or outcomes will be extracted.

Quality control (QC) will be performed at three stages of this project. First, an independent reviewer will QC 10% of each abstract list from each database to determine agreement. Following this step, the list of full texts will be reviewed twice to determine agreement on all included articles. Finally, after each abstraction, QC will be performed on all data elements extracted for each study (100% QC). Following the abstraction QC, each original abstracter will review the QC done on their abstractions and assess agreement. All disputes will be resolved by a senior researcher. The results will be recorded, maintained and assessed using DistillerSR.

10.3 Subject Confidentiality

This study will comply with all applicable laws regarding subject privacy. No direct subject contact or collection of additional subject data will occur. Study results will be in tabular form and aggregate analyses that omits subject identification. Any publications and reports will not include subject identifiers.

11. ADMINISTRATIVE AND LEGAL OBLIGATIONS

11.1 Study Amendments and Study Termination

Amendments must be made only with the prior approval of Amgen. Both Amgen and EpidStrategies reserve the right to terminate participation in the study according to the study contract.

11.2 Study Documentation and Archive

Retention of study documents will be governed by the contractual agreement with EpidStrategies and will be maintained pursuant to Amgen's records retention schedule. A report detailing the methods and results of the literature review and the incidence calculations will be developed. The report will include a diagram demonstrating the flow of study inclusion (PRISMA diagram), the abstraction database, and the summary results of the literature review and meta-analysis calculations.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The results of this review will not be submitted for publication other than submission to a global regulatory authority, EMA.

13. REFERENCES

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14. APPENDICES

Appendix 1. Preferred Reporting Items for Systematic Review of Meta-Analysis (PRISMA) Checklist

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	

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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see item 15).	
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see item 16]).	
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: www.prisma-statement.org.

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Appendix 2. List of Interventions and Comparators

The treatments to be considered in the literature review are listed below.

1. Romiplostim
2. Other TPO-RAs, including eltrombopag, lusutrombopag, and avatrombopag
3. Other ITP treatments, including corticosteroids, IVIG (intravenous immunoglobulin), anti-D (Rho[D] immune globulin intravenous), rituximab, splenectomy, cyclophosphamide, dapsone, danazol, cyclosporine A, azathioprine, mycophenolate mofetil, and vinca alkaloids

Appendix 3. Draft Search Strategy

Term	Ovid-Embase	PubMed
Study population:		
ITP	exp idiopathic thrombocytopenic purpura/ OR (Werlhof* adj1 disease).mp. OR (autoimmune adj1 thrombocytopenia*).mp. OR (immune adj1 thrombocytopenia*).mp.	"Purpura, Thrombocytopenic, Idiopathic"[Mesh]
Inclusion criteria:		
English language	english.lg.	Eng[la]
Publication date: from 01 Jan 2005 to 31 Aug 2019		
Exclusion criteria:		
Case reports	"case report"/	"Case Reports"[pt]
Non-human studies	exp nonhuman/ NOT exp human/	--
Outcomes of interest:		
Bone marrow fibrosis (reticulin formation)	exp myeloid metaplasia/ OR (marrow adj1 fibrosis).mp.	"Primary Myelofibrosis"[Mesh]
Hematologic malignancy	exp hematologic malignancy/ AND (exp epidemiology/ OR (frequenc* or incidence or prevalence or trend* or rate* or proportion* or burden).mp.)	"Hematologic Neoplasms"[Mesh]
Thrombotic/ thromboembolic events	exp thromboembolism/ AND (exp epidemiology/ OR (frequenc* or incidence or prevalence or trend* or rate* or proportion* or burden).mp.)	"Thromboembolism"[Mesh]
Pre-malignant states (acute myelogenous leukaemia, AML, or myelodysplastic syndromes, MDS)	(exp acute myeloid leukemia/ OR exp myelodysplastic syndrome/)	"Leukemia, Myeloid, Acute"[Mesh] OR "Myelodysplastic Syndromes"[Mesh]
Concurrent leucocytosis and anaemia	exp leukocytosis/ AND exp anemia/	"Leukocytosis"[Mesh] AND "Anemia"[Mesh]
Acute renal failure	exp acute kidney failure/	"Acute Kidney Injury"[Mesh] (note: only select articles relating to kidney failure)
Number of hits	2931	71

Appendix 4. Newcastle – Ottawa Quality Assessment Scale

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Exposure categories. A maximum of two stars can be given for Comparability.

Selection

1) Is the case definition adequate?
   a) yes, with independent validation ✸
   b) yes, eg, record linkage or based on self-reports
   c) no description

2) Representativeness of the cases
   a) consecutive or obviously representative series of cases ✸
   b) potential for selection biases or not stated

3) Selection of Controls
   a) community controls ✸
   b) hospital controls
   c) no description

4) Definition of Controls
   a) no history of disease (endpoint) ✸
   b) no description of source

Comparability

1) Comparability of cases and controls on the basis of the design or analysis
   a) study controls for _____ (Select the most important factor.) ✸
   b) study controls for any additional factor ✸ (This criteria could be modified to indicate specific control for a second important factor.)

Exposure

1) Ascertainment of exposure
   a) secure record (eg surgical records) ✸
   b) structured interview where blind to case/control status ✸
   c) interview not blinded to case/control status
   d) written self report or medical record only
   e) no description

2) Same method of ascertainment for cases and controls
   a) yes ✸
   b) no

3) Non-Response rate
   a) same rate for both groups ✸
   b) non respondents described
   c) rate different and no designation

NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE (continued)

Selection

1) Representativeness of the exposed cohort
   a) truly representative of the average _____(describe) in the community ✸
   b) somewhat representative of the average _____ in the community ✸
   c) selected group of users eg, nurses, volunteers
   d) no description of the derivation of the cohort

2) Selection of the non exposed cohort
   a) drawn from the same community as the exposed cohort ✸
   b) drawn from a different source
   c) no description of the derivation of the non-exposed cohort

3) Ascertainment of exposure
   a) secure record (eg surgical records) ✸
   b) structured interview ✸
   c) written self-report
   d) no description

4) Demonstration that outcome of interest was not present at start of study
   a) yes ✸
   b) no

Comparability

1) Comparability of cohorts on the basis of the design or analysis
   a) study controls for _____ (select the most important factor) ✸
   b) study controls for any additional factor ✸ (This criteria could be modified to indicate specific control for a second important factor.)

Outcome

1) Assessment of outcome
   a) independent blind assessment ✸
   b) record linkage ✸
   c) self report
   d) no description

2) Was follow-up long enough for outcomes to occur
   a) yes (select an adequate follow up period for outcome of interest) ✸
   b) no

3) Adequacy of follow up of cohorts
   a) complete follow up - all subjects accounted for ✸
   b) subjects lost to follow up unlikely to introduce bias - small number lost - > ____ % (select an adequate %) follow up, or description provided of those lost) ✸
   c) follow up rate < ____% (select an adequate %) and no description of those lost
   d) no statement

Appendix 5. Draft Abstraction Spreadsheet

Note: Spreadsheet was transposed so that all of the fields could be displayed.

Trial/Study Level data	Brief Citation
	Primary data or Pooled data
	Full citation
	PDF obtained? (Y/N)
	Study design (Case series/Cohort/Other)
	NCT number (if applicable)
	Other clinical trial numbers (ie, non-US trial registries)
	Cohort Title (if applicable)
	Inclusion criteria
	Exclusion criteria
	Study dates
	Location (Country)
	Primary Endpoint of Study
	Power Calculation to Determine Sample Size (Y/N)
	Patient N
	Study population (description of patients)
	Follow up time for study outcomes
	Age (stats for all arms participants)
	Sex (% male)
	Race
	Time from Diagnosis
	Analysis plan (for non-compliance); primary outcome
	Analysis plan; safety
	Attrition Rate
	Drug Comparison (Drug Arm 1)
	Drug Comparison (Drug Arm 2)
	Drug Comparison (Drug Arm 3)
	Drug Comparison (Drug Arm 4)
	Notes

Arm Level Data	Arm Number/Letter
	N Patients
	Requested subgroup of interest
	Drug Name (Drug in trial arm)
	Dosage (Dosage in trial arm)
	Cycles (Number of delivered cycles)
	Age
	Sex (% Male)
	Race
	Time from Diagnosis
	Previous ITP Therapies (Y/N)
	Number of Previous ITP Therapies
	Description of Previous ITP Therapies
	Concomitant Treatment (Y/N)
	Concomitant Treatment Description
	Comorbidities (At baseline)
	Median Baseline Platelet Count, x 10^9/L
	Rate of Splenectomy
	Median Time to Splenectomy
	Use of Rescue Medication (Description of Medication - %)
	Use of Additional Therapies (Description of Therapies - %)
	Remission Rate (%)
	Relapse (%)
	Relapse (Definition)
	Median Time to Relapse
	Frequency of myocardial infarction
	Frequency of stroke
	Frequency of deep vein thrombosis
	Frequency of pulmonary embolism
	Event rate of AML
	Event rate of MDS
	Proportion with concurrent leukocytosis
	Proportion with concurrent anemia
	Event rate of acute renal failure
	Comments
	Abstractor Initials
	QC Reviewer Initials