1 LIST OF ABBREVIATIONS

AML	Acute myeloid leukemia
CI	Confidence interval
cITP	Chronic immune thrombocytopenia
CLL	Chronic lymphocytic leukemia
CVA	Cerebrovascular accident
DVT	Deep vein thrombosis
EMA	European Medicines Agency
FDA	U.S. Food and Drug Administration
ITP	Immune thrombocytopenia
MDS	Myelodysplastic syndrome
MF	Marrow fibrosis
MI	Myocardial infarction
NCPRR	Nordic Country Patient Registry for Romiplostim
NR	Not reported
PASS	Post Authorization Safety Study
PE	Pulmonary embolism
PICOS	Population, Intervention, Comparator, Outcome, and Study type
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analysis
QC	Quality control
RCT	Randomized controlled trial
TE	Thrombotic event
TIA	Transient ischemic attack
TPO-RA	Thrombopoietin receptor agonist

2 EXECUTIVE SUMMARY

2.1 Introduction

Thrombopoietin receptor agonists (TPO-RA), such as romiplostim and eltrombopag, are approved to treat adult patients with immune thrombocytopenia (ITP). The purpose of this literature review was to assess safety outcomes in adult ITP patients treated with TPO-RA and other ITP therapies. Safety outcomes of interest included bone marrow changes, hematopoietic malignancies and pre-malignant states, and thromboembolic events.

2.2 Methods

Articles published between 1 January 2005 and 31 August 2019 were included in this review. Studies were required to be published in English as either peer-reviewed journal

articles or conference abstracts. Additional inclusion criteria were made according to PICOS (Population, Intervention, Comparator, Outcome, and Study type).

Literature searches were conducted in the PubMed, Embase, and Web of Science databases using the search strings in Table 11-1. The articles were de-duplicated by title, author, and abstract. The review was conducted according to Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines. The de-duplicated abstracts were reviewed first at the level of title and abstract to exclude irrelevant studies. Remaining articles were then reviewed at the level of full text by two independent reviewers (100% quality control [QC]). Bibliographies of relevant reviews were searched by hand for additional citations of interest.

An extraction database was developed based on the protocol. Articles marked as relevant at the full text review stage were extracted into the database. The complete extraction database is available on request. Extracted data elements included study characteristics, population demographics and disease characteristics, and safety outcomes. Additionally, risk of bias in individual studies was evaluated using the Cochrane Risk of Bias Tool for clinical trials and the Newcastle Ottawa Scale for observational studies.

In several cases, multiple articles from the same trial or study population were published. The article with the longest follow-up, most recent data, or most specifically relevant population was selected for inclusion into the review. Studies from the same trial or study population reporting unique outcomes (eg, bone marrow fibrosis and thromboembolic events) were both included.

Data were quantitatively summarized using meta-analytical techniques where sufficient data were available. Sufficient data required at least 3 studies reporting the same drug and the same outcome, defined in a similar manner across studies (eg, incidence of myocardial infarction among patients treated with romiplostim). If fewer than 3 studies were found, only a narrative review was performed.

Meta-analyses were conducted using Comprehensive Meta-Analysis software (version 3.0; Biostat, Englewood, New Jersey). The results of included study outcomes were summarized across available studies, weighting all included studies by the inverse of their variance using the method proposed by DerSimonian and Laird (DerSimonian and Laird 1986). Heterogeneity between studies in each analysis was evaluated using the Cochran's Q and I^2 statistical tests.

2.3 Results

2.3.1 Data sources

A total of 99 publications comprising 32 clinical trials, 59 observational studies and 8 pooled studies were identified. Forty studies (43.5%) were conducted in Europe, 15 in Asia (16.3%), 11 in the US (12.0%), 7 in multiple countries (7.6%), 2 in Australia (2.2%), 1 in the Middle East (Tunisia) (1.1%) and 15 studies (16.3%) in an unspecified study location. Median sample size was 103 (interquartile range: 50 to 227), and maximum follow-up time ranged from 30 days to 16 years. Large studies (>200 patients) included an observational cohort of romiplostim patients followed for up to 2 years (N = 340, Steurer et al. 2017), a phase 3b open-label trial of romiplostim in 407 patients (Janssens et al. 2015), a phase 2/3 trial of eltrombopag with follow-up up to 8 years (N=302, Wong et al. 2017), and a retrospective cohort of eltrombopag users followed for

up to 15 months (N=220, Gonzalez-Lopez, Fernandez-Fuertes, et al. 2017). The reporting of outcomes was heterogeneous (eg, inferences derived from secondary-use medical data, serious or non-serious events, treatment-related serious adverse events), limiting comparisons across studies. There were insufficient studies to perform meta-analyses in any outcome other than thromboembolic events.

2.3.2 Bone marrow fibrosis or reticulin formation

Changes to patients' bone marrow included presence of bone marrow fibrosis, changes in reticulin, and/or presence of collagen fibers. Among romiplostim-treated patients, individual studies and large pooled-data analyses reported incidence of bone marrow reticulin/collagen AE (from biopsies taken at investigators' discretion) of 0.4 to 1.3 per 100 patient-years. Incidence proportions of bone marrow fibrosis AEs ranged from 0% to 2.2%. Increased reticulin was observed in 0.3% to 2.1% of patients in pooled studies, while incidence proportions in individual studies ranged from 0% to 6.3% of all ITP patients, and up to 28.9% of a subset selected for biopsy. The presence of bone-marrow collagen was observed in 0% to 1.5% of patients. No pooled analyses were available for eltrombopag-treated patients, but among individual studies the incidence proportion of bone marrow fibrosis AEs ranged from 0% to 6%, increased reticulin ranged from 0% to 1.1% and the presence of collagen ranged from 0.8% to 4% of treated patients. Two studies evaluating thrombopoietin receptor agonists (TPO-RAs) in general reported bone marrow fibrosis incidence proportions (as a percentage of only tested patients) of 12.5% and 19%, and one reported a change in the prevalence of MF-0, from 67% pre-treatment to 21% a median of 17 months post-treatment.

2.3.3 Hematologic malignancy

Incidence proportions for hematological malignancies ranged from 0% to 1.7% for romiplostim- and from 1% to 1.5% for eltrombopag-treated patients. Among patients treated with other non-TPO-RA interventions (including rituximab, intravenous immunoglobulin, splenectomy, danazol, prednisone, prednisolone, methylprednisolone, azathioprine, cyclophosphamide, cyclosporin, and vincristine) the incidence proportion for hematological malignancies ranged from 0% to 8.6%.

2.3.4 Thromboembolic events

Incidence of thromboembolic (TE) events among romiplostim-treated patients were reported for pooled studies with incidence rates ranging from 0.1 to 6 TE events per 100 person-years. Among individual studies the incidence proportions of TE events for romiplostim- and eltrombopag-treated patients ranged from 0% to 10.6%, and 0% to 14.3% of patients, respectively. Meta-analyzed TE incidence proportion was 4.0% (95% confidence interval [CI]: 2.9-5.6%) for romiplostim-treated patients, 5.0% (CI: 3.9-6.4%) for eltrombopag-treated patients, and 5.3% (CI: 4.0-7.0%) among patients treated with other ITP treatments (ie, splenectomy, rituximab, and others). There were no statistically significant differences identified for TE events generally, but there were significantly fewer deep vein thromboses (DVTs) observed among TPO-RA patients than among pooled data for patients treated with rituximab or splenectomy.