# EUROPEAN UNION RISK MANAGEMENT PLAN

## Nplate® (Romiplostim)

| | |
|---|---|
| **Marketing Authorization Holder** | Amgen Europe B.V.<br>Minervum 7061<br>4817 ZK Breda,<br>Netherlands |
| **Version:** | 22.0 |
| **Date:** | 16 November 2023 |
| **Supersedes:** | Version 21.1, dated 09 August 2022 |

## Risk Management Plan (RMP) version to be assessed as part of this application

| | |
|---|---|
| RMP version number: | 22.0 |
| Data lock point (DLP) of this RMP: | 31 July 2023 |
| Date of final sign-off: | 16 November 2023 |
| Rationale for submitting an updated RMP: | Removal of the following safety concern:<br>• Neutralizing antibodies that cross-react with endogenous thrombopoietin [eTPO] |

## Summary of significant changes in this RMP

| Part/Module/Annex | Major Change(s) | Version Number and Date |
|---|---|---|
| Part II: Safety Specification | | |
| SII - Nonclinical Part of the Safety Specification | Updated the relevance to human usage for nonclinical safety findings | Version 22.0, 16 November 2023 |
| SV - Postauthorization Experience | Updated postauthorization exposure data to a cut-off date of 31 July 2023 | Version 22.0, 16 November 2023 |
| SVII - Identified and Potential Risks | The important potential risk of 'neutralizing antibodies that cross-react with eTPO' was reclassified as a not important potential risk and removed from the list of safety concerns. | Version 22.0, 16 November 2023 |
| SVIII - Summary of the Safety Concerns | Updated the safety concerns to align with the changes in Module SVII | Version 22.0, 16 November 2023 |
| Part III: Pharmacovigilance Plan (Including Postauthorization Safety Studies) | The additional pharmacovigilance activity of 'testing for anti-romiplostim and thrombopoietin (TPO) antibody development is available for patients at the request of the treating physician' was removed. | Version 22.0, 16 November 2023 |
| Part V: Risk Minimization Measures (Including Evaluation of the Effectiveness of Risk Minimization Activities) | Updated the safety concerns to align with the changes in Module SVII | Version 22.0, 16 November 2023 |
| Part VI: Summary of the Risk Management Plan | Updated the safety concerns to align with the changes in Module SVII | Version 22.0, 16 November 2023 |
| Part VII: Annexes | | |
| Annex 7 – Other Supporting Data (Including Referenced Material) | References were updated. | Version 22.0, 16 November 2023 |

| | |
|---|---|
| Other RMP versions under evaluation: | |
| RMP version number: | None |
| Submitted on: | Not applicable |
| Procedure number: | Not applicable |
| Details of the currently approved RMP: | |
| Version number: | 21.1 |
| Approved with procedure: | EMEA/H/C/000942/II/0083 |
| Date of approval (opinion date): | 01 September 2022 |
| Qualified Person for Pharmacovigilance (QPPV) Name: | Raphaël Van Eemeren, MSc Pharm and MSc Ind Pharm |
| QPPV oversight declaration: | The content of this RMP has been reviewed and approved by the marketing authorization holder's (MAH) QPPV. The electronic signature is available on file. |

## Table of Contents

## List of Tables

## List of Annexes

## List of Abbreviations

| Term/Abbreviation | Explanation |
|---|---|
| ADR | adverse drug reaction |
| AML | acute myeloid leukemia |
| AMQ | Amgen MedDRA Query |
| ATC | Anatomical Therapeutic Chemical |
| BM | bone marrow |
| CBC | complete blood count |
| CIMF | chronic idiopathic myelofibrosis |
| CIT | chemotherapy induced thrombocytopenia |
| CTCAE | Common Terminology Criteria for Adverse Events |
| DLP | data lock point |
| *E coli* | Escherichia coli |
| EEA | European Economic Area |
| EMA | European Medicines Agency |
| EPAR | European Public Assessment Report |
| eTPO | endogenous thrombopoietin |
| EU | European Union |
| Fc | fragment of an immunoglobulin molecule composed of part of the heavy chains and responsible for binding to antibody receptors on cells and the C1 component of complement |
| FDA | Food and Drug Administration |
| FMEA | Failure Modes Effects Analysis |
| HAT | Home Administration Training |
| HCP | healthcare professional |
| HDMP | high dose methylprednisolone |
| HFE | human factors engineering |
| HI-P | hematologic improvement |
| IgG1 | immunoglobulin G1 |
| INN | International Nonproprietary Name |
| IPSS | international prognostic scoring system |
| IQR | interquartile range |
| IVIG | intravenous immunoglobulin |
| IWG | International Working Group |
| ITP | primary immune thrombocytopenia |
| IV | intravenous(ly) |

| Term/Abbreviation | Explanation |
|---|---|
| KKC | Kyowa Kirin Co., Ltd |
| MAH | marketing authorization holder |
| MDS | myelodysplastic syndrome |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MF | marrow fibrosis |
| NPER | Nplate® Pregnancy Exposure Registry |
| PBRER | Periodic Benefit-Risk Evaluation Report |
| PI | Product Information |
| PL | Package Leaflet |
| PRAC | Pharmacovigilance Risk Assessment Committee |
| PSR | Patient Safety Registry |
| PSR-C | Patient Safety Registry – Canada version |
| PSUR | Periodic Safety Update Report |
| PSUSA | Periodic Safety Update Single Assessment |
| QPPV | Qualified Person for Pharmacovigilance |
| QTc | corrected QT interval |
| RAEB-1 | refractory anemia with excess blasts – 1 |
| RBC | red blood cell |
| reticulin | In this document, reticulin refers to a typically normal component of the bone marrow that can be detected using a reticulin (silver) stain. In contrast, bone marrow fibrosis is detected by specific staining techniques (trichrome among many). Fibrosis includes an expectation of impairment of hematopoiesis. |
| RI-PMBT | request for postmarketing blood tests |
| RMP | risk management plan |
| SC | subcutaneous(ly) |
| SLE | systemic lupus erythematosus |
| SmPC | Summary of Product Characteristics |
| SMQ | Standardised MedDRA Query |
| SOC | standard of care |
| Tg | transgenic |
| TGF-β | transforming growth factor-beta |

| Term/Abbreviation | Explanation |
|---|---|
| TPO | thrombopoietin |
| TPO receptor | Also known as c-Mpl |
| TPO-RA | thrombopoietin receptor agonist |
| TPO-Tg | thrombopoietin transgenic |
| US | United States |
| WBC | white blood cell |

# PART I. PRODUCT(S) OVERVIEW

## Table 1. Product Overview

| | |
|---|---|
| Active substance(s) (International Nonproprietary Name [INN] or common name) | Romiplostim |
| Pharmacotherapeutic group (Anatomical Therapeutic Chemical [ATC] Code) | Antihemorrhagic (B02BX04) |
| Marketing authorization applicant or marketing authorization holder (MAH) | Amgen Europe B.V. |
| Medicinal products to which this Risk Management Plan (RMP) refers | 1 |
| Invented name(s) in the European Economic Area (EEA) | Nplate® |
| Marketing authorization procedure | Centralized |
| Chemical class | A peptibody molecule composed of a human immunoglobulin G1 (IgG1) Fc domain, with each single-chain subunit covalently linked at the C-terminus to a peptide chain containing 2 thrombopoietin (TPO) receptor-binding domains. |
| Summary of mode of action | Romiplostim, a member of the TPO mimetic class, is an Fc-peptide fusion protein (peptibody) that signals and activates intracellular transcriptional pathways via the TPO receptor (also known as c-Mpl) to increase platelet production. |
| Important information about its composition | Romiplostim is produced by recombinant DNA technology in *Escherichia coli* (*E. coli*). |
| Hyperlink to the Product Information (PI) | Link to Nplate® PI on European Medicines Agency (EMA) website: https://www.ema.europa.eu/en/documents/product-information/nplate-epar-product-information_en.pdf |

## Table 1. Product Overview

| | |
|---|---|
| Indication(s) in the EEA | |
| Current (if applicable): | Adults:<br>Nplate is indicated for the treatment of primary immune thrombocytopenia (ITP) in adult patients who are refractory to other treatments (eg, corticosteroids, immunoglobulins).<br>Paediatrics:<br>Nplate is indicated for the treatment of chronic primary immune thrombocytopenia (ITP) in paediatric patients one year of age and older who are refractory to other treatments (eg, corticosteroids, immunoglobulins). |
| Proposed (if applicable): | Not applicable. |
| Dosage in the EEA | |
| Current (if applicable): | The initial dose for romiplostim is 1 μg/kg, administered once weekly as a subcutaneous (SC) injection. The volume of romiplostim to administer is calculated based on body weight, dose required, and concentration of the product. Self-administration of Nplate is not allowed for pediatric patients.<br>Dose adjustments for adults and pediatric subjects should be based on platelet counts measured weekly until stable within the recommended range (once weekly dose increased by increments of 1 μg/kg until the patient achieves a platelet count ≥ 50 x $10^9$/L). Thereafter, platelet counts should be measured at least monthly and appropriate dose adjustments made in order to maintain platelet counts within the recommended range. A maximum once weekly dose of 10 μg/kg should not be exceeded. |
| Proposed (if applicable): | Not applicable. |
| Pharmaceutical form(s) and strength(s) | |
| Current (if applicable): | <u>Powder for reconstitution and SC injection:</u><br>Romiplostim is supplied as a sterile, preservative-free, lyophilized, solid white powder that is reconstituted for SC injection. Three vial presentations are approved, which contain sufficient amounts of active ingredients to provide either 125, 250, or 500 μg romiplostim.<br><u>Powder for reconstitution and SC injection with solvent (reconstitution pack):</u><br>Romiplostim is also supplied in reconstitution packs that contain 250 or 500 μg romiplostim powder in a vial and sterile water for injection (0.72 mL or 1.2 mL, respectively) in a prefilled syringe; the packs also include a plunger rod for pre-filled syringe. |

**Table 1. Product Overview**

| | |
|---|---|
| Pharmaceutical form(s) and strength(s) (continued) | |
| Proposed (if applicable): | Not applicable |
| Is/will the product be subject to additional monitoring in the European Union (EU)? | No |

Page 3 of 3

# PART II. SAFETY SPECIFICATION

## Part II: Module SI - Epidemiology of the Indication(s) and Target Population(s)

### Table 2. Summary of Epidemiology of ITP

| | |
|---|---|
| Incidence | Adult patients:<br>The annual incidence of newly diagnosed ITP in adults is estimated to range from approximately 1.6 to 3.9 per 100 000 persons in studies conducted in Europe, the United States (US), and Asia (Moulis et al, 2014; Kurata et al, 2011; Terrell et al, 2010; Abrahamson et al, 2009; Neylon et al, 2003; Frederiksen and Schmidt, 1999).<br>Pediatric patients:<br>The annual incidence of newly diagnosed ITP in children is estimated to range from approximately 1.9 to 6.4 per 100 000 children in studies conducted in Europe and Asia (Moulis et al, 2014; Kurata et al, 2011; Terrell et al 2010; Yong et al, 2010; Zeller et al, 2005; Sutor et al, 2001). About 25% of newly diagnosed ITP pediatric cases remain thrombocytopenic after 6 months (Bekker and Rosthoj, 2011; Le Meignen et al, 2008; Zeller et al, 2005; Rosthoj et al, 2003; Zeller et al, 2000). |
| Prevalence | Adult patients:<br>Primary immune thrombocytopenia (ITP) prevalence is between 0.09 and 0.81 per 10 000 persons (including adults and children) in the EU. This equates to a prevalent patient population between 4446 and 40 014 persons in the EU (assuming an EU population of 494 million).<br>The 1-year period prevalence of diagnosed ITP in adults (older than 16 or 18 years) is estimated to be from 4.6 to 12.1 per 100 000 persons (Terrell et al, 2012; Bennett et al, 2011; Landgren et al, 2006).<br>Persistence or chronicity is reported to develop in approximately two-thirds of primary adult ITP patients in studies conducted in France (Moulis et al, 2014) and in the US (Gernsheimer et al, 2006).<br>In US-based studies, the estimated 1-year period prevalence for diagnosed ITP lasting 6 or more months is estimated to range from 4.5 per 100 000 in persons aged 1 to 64 years (Segal and Powe, 2006) to 9.5 per 100 000 adults aged 18 to 64 years (Feudjo-Tepie et al, 2008).<br>Pediatric patients<br>Approximately 25% of newly diagnosed ITP pediatric cases remain thrombocytopenic after 6 months (Bekker and Rosthoj, 2011; Le Meignen et al, 2008; Imbach et al, 2006; Zeller et al, 2005; Rosthoj et al, 2003; Zeller et al, 2000; George et al, 1996). The point prevalence of ITP (defined as at least 6 months of illness) in children has been estimated to be 4.6 per 100 000 children (Hedman et al, 1997). |

**Table 2. Summary of Epidemiology of ITP**

| | |
|---|---|
| Demographics of population in the (authorized) (proposed) indication and risk factors for the disease | Adult patients:<br>The risk of ITP among adults increases with age, and there appears to be a female preponderance. Prevalence of ITP has been estimated to be nearly 2 times higher in adults aged 50 years or older than their younger counter parts and twice more common in women than men (Bennett et al, 2011; Feudjo-Tepie et al, 2008).<br>Pediatric patients:<br>The relationship between sex and risk of ITP among children varies by age group. Research has consistently shown a male predominance in children aged younger than 5 years and a female predominance in older age groups (Grainger et al, 2012; Yong et al, 2010; Zeller et al, 2005; Watts, 2004; Sutor et al, 2001; Zeller et al, 2000; Bolton-Maggs and Moon, 1997).<br>Risk factors for the disease include<br>• Chronic lymphocytic leukemia (Visco et al, 2012; Zanotti et al, 2010)<br>• Female gender (Abrahamson et al, 2009)<br>• Autoimmune diseases (Hashimoto's thyroiditis, systemic lupus erythematosus [SLE], psoriasis, and celiac disease) (John and Scharrer, 2012; Olén et al, 2008)<br>• High frequency of certain polymorphisms in the promoter regions of genes coding molecules involved in proinflammatory immune response (Rocha et al, 2010)<br>• Infection with *Helicobacter pylori* (in certain populations, most notably Japan and Italy) (Liebman and Stasi, 2007)<br>• Recent infection in children < 5 years may be a risk factor (Yong et al, 2010)<br>Risk factors for chronicity in adults<br>There are no clear predictors of chronicity in adults.<br>Risk factors for chronicity in children<br>• Insidious onset of symptoms (Elalfy et al, 2010; Glanz et al, 2008; Zeller et al, 2005)<br>• Age ≥ 10 years at presentation (Elalfy et al, 2010; Glanz et al, 2008)<br>• Initial platelet count ≥ 20 x $10^9$/L (Elalfy et al, 2010; Glanz et al, 2008) |

**Table 2. Summary of Epidemiology of ITP**

| | |
|---|---|
| Main existing treatment options | Since ITP in children is usually short-lived with spontaneous recovery, whereas the disease in adults typically has an insidious onset and follows a chronic course, the management of ITP in children and adults differs.<br>Adult patients:<br>First-line or initial treatment for newly diagnosed ITP typically consists of anti-D immunoglobulin, intravenous immunoglobulin (IVIG), and corticosteroids. Second line therapies may include azathioprine cyclosporin A, cyclophosphamide, danazol, dapsone, mycophenolate mofetil, rituximab, splenectomy, vinca alkaloids, and TPO receptor agonists (Neunert et al, 2011; Provan et al, 2010).<br>Splenectomy offers the highest rates of long-term response but is associated with significant side effects (Chaturvedi et al, 2018; Hasan et al, 2009). It is therefore recommended that it be deferred, when possible, until the chronic phase (> 12 months) (Provan et al, 2010).<br>Pediatric patients:<br>Treatment for ITP in children is guided by several factors, including bleeding symptoms, platelet counts, activity profile, and psychosocial issues. A "watch and wait" policy is recommended for newly diagnosed cases lacking significant bleeding symptoms (Provan et al, 2010). As in adults, first-line treatments in childhood ITP include corticosteroids, IVIG, and/or anti-D immunoglobulin (Provan et al, 2010; Neunert et al, 2011). Treatment options in children with persistent or chronic ITP include romiplostim, eltrombopag, dexamethasone, high dose methylprednisolone (HDMP), rituximab, and various salvage treatments for the refractory patient, including azathioprine, cyclosporine, and mycophenolate (Cines and McMillan, 2005). These treatments can have significant side effects and/or convenience issues with respect to their administration. Morbidities associated with these treatments typically result in intermittent use (Provan et al, 2010). Splenectomy is rarely recommended in children due to the extremely low risk of death from ITP (< 0.5%) and the postsplenectomy complications, primarily sepsis (Provan et al, 2010). |

**Table 2. Summary of Epidemiology of ITP**

| | |
|---|---|
| Natural history of the indicated condition in the untreated population, including mortality and morbidity | Adult patients:<br>The rate of true spontaneous recovery of ITP in the absence of treatment is unknown but is likely to be low given that the overall remission rate in both treated and untreated adults has been reported to be between 25% and 30% (Altomare et al, 2016; Moulis et al, 2014; Schiavotto and Rodeghiero, 1993). Thrombocytopenia, when severe (ie, < 30 x $10^9$/L platelet count), can result in spontaneous bruising or bleeding and occasionally can lead to death. As discussed by Lambert and Gernsheimer, 2017, aside from low platelet counts, research has suggested that increased patient age, use of concurrent medications, and male sex are associated with increased bleeding risk. It is recommended that patients who are actively bleeding or deemed at imminent risk of bleeding are treated (Neunert et al, 2011; Provan et al 2010). Mortality rates in the ITP patient population overall (regardless of treatment) may be 1.3 to 2.2 times higher than in the general population (Nørgaard et al, 2011; Portielje et al, 2001; Schoonen et al, 2009), primarily as a result of increased cardiovascular disease, infection, bleeding, and hematological cancer (Frederiksen et al, 2014).<br>Pediatric patients:<br>The rate of true spontaneous recovery of childhood ITP is unknown but it is likely to be relatively high given that approximately 75% of children do not progress to persistent or chronic disease even among those without treatment (Bekker and Rosthoj, 2011; Le Meignen et al, 2008; Imbach et al, 2006; Zeller et al, 2005; Rosthoj et al, 2003; Zeller et al, 2000; George et al, 1996). Primary immune thrombocytopenia in the pediatric population, although rare, can result in significant morbidity and mortality, such as intracranial hemorrhaging (Neunert et al, 2008; Kuhne et al, 2003). Spontaneous recovery is significantly higher in those with abrupt disease onset (symptoms < 14 days), age at onset ≤ 10 years (particularly in infants) and may also be higher in males and in those with a recent infection, platelet count < 5 x $10^9$/L, or wet purpura (Yacobovich et al, 2013). |
| Important comorbidities | • Diabetes (Christiansen, et, 2019; Lozano et al, 2019; Enger et al, 2010)<br>• Hypertension (Christiansen, et, 2019; Lozano et al, 2019; Enger et al, 2010)<br>• Solid tumor malignancy (Christiansen et al, 2019; Lozano et al, 2019)<br>• Peptic ulcer (Christiansen et al, 2019)<br>• Cataract (Enger et al, 2010)<br>• Acute or chronic renal failure (Enger et al, 2010)<br>• Liver disease (Lozano et al, 2019)<br>• Hematological malignancies (Enger et al, 2010)<br>• Cardiovascular conditions (Lozano et al, 2019; Enger et al, 2010)<br>• Other comorbidities (Enger et al, 2010) |

## Part II: Module SII - Nonclinical Part of the Safety Specification

**Table 3. Key Safety Findings From Nonclinical Studies and Relevance to Human Usage**

| Study Type | Important Nonclinical Safety Findings | Relevance to Human Usage |
|---|---|---|
| Toxicity | | |
| • Repeat-dose toxicity | A 4-week, multiple-dose romiplostim toxicology study was conducted in rats (dosages 0 to 100 μg/kg SC or 100 μg/kg IV 3 times weekly). Femoral and sternal bone hyperostosis and bone marrow fibrosis were observed at the end of treatment. Special stains for reticulin and collagen were not performed because distinction between collagen and reticulin fibrosis is not routinely made in general toxicology studies. The increases in bone marrow fibrosis in romiplostim-treated animals were reversed or absent after a 4-week recovery period. No bone marrow fibrosis was observed in chronic studies up to 6 months in duration in monkeys.<br><br>In repeat-dose toxicity studies, red blood cell (RBC) parameters (RBC, hematocrit, and hemoglobin) were mildly decreased in rats at all dose levels and in rhesus monkeys at 5000 μg/kg SC or IV following administration of romiplostim 3 times weekly for 4 weeks. Conversely, the white blood cell (WBC) counts were mildly increased. Romiplostim appeared to have a generalized stimulatory effect on leukocyte production because peripheral blood counts for neutrophils, lymphocytes, monocytes, and eosinophils were increased. Although there was a demonstrable decrease in the RBC parameters in the 1-month studies, there was no effect noted on the erythroid and leukocytic lineages when romiplostim was administered for a longer duration. Specifically, in the 6-month repeat-dose study in which the administration of romiplostim was decreased from 3 times weekly to once weekly, there was no biologically relevant effect on either RBCs or WBCs. | Recommendation for microscopic examination of peripheral blood smear for cellular morphological abnormalities and complete blood count (CBC) prior to and during treatment with romiplostim is included in Section 4.4 of the Summary of Product Characteristics (SmPC).<br><br>Recommendation for a bone marrow biopsy if an abnormal blood smear is observed in patients is included in Section 4.4 of the SmPC. |

**Table 3. Key Safety Findings From Nonclinical Studies and Relevance to Human Usage**

| Study Type | Important Nonclinical Safety Findings | Relevance to Human Usage |
|---|---|---|
| Toxicity (continued) | | |
| • Tg (transgenic) mouse phenotype | Effects on the renal glomerulus have only been seen in TPO-Tg mice (with high TPO levels and nonpulsatile stimulation). These effects have not been observed in other non-Tg romiplostim treated animals (Shimoda et al, 2007). | Experience is limited in patients with severe renal impairment. Romiplostim should be used with caution in this population. |
| • Reproductive/ developmental toxicity | In rat and rabbit developmental toxicity studies, no evidence of fetal harm was observed at romiplostim exposures up to 11 times (rats) and 82 times (rabbits) higher than the maximum indicated human dose of 10 μg/kg.<br>In mice, at exposures 5 times higher than the maximum indicated human dose, there were reductions in maternal body weight and evidence of increased post implantation loss.<br>In prenatal and postnatal development study in rats, at exposures 11 times the maximum indicated human dose, there was a slight increase in the incidence of perinatal pup mortality.<br>Romiplostim crossed the placental barrier in rats and increased fetal platelet counts at clinically equivalent and higher doses. | There are no or limited amount of data from the use of romiplostim in pregnant women. Romiplostim is not recommended during pregnancy or in women of childbearing potential not using contraception.<br>It is unknown whether romiplostim/metabolites are excreted in human milk. A risk to the newborns/infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from romiplostim therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman. |

**Table 3. Key Safety Findings From Nonclinical Studies and Relevance to Human Usage**

| Study Type | Important Nonclinical Safety Findings | Relevance to Human Usage |
|---|---|---|
| Toxicity (continued) | | |
| • Carcinogenicity | A hypothetical concern regarding hematopoietic growth factors is that they may enhance the growth of existing tumors or promote the growth of new tumors that are influenced by the receptor-ligand axis. A literature review on dysregulated TPO receptor expression indicates that the TPO receptor has been identified on the surface of myeloid or lymphoid cells in patients with MDS or leukemia. There is no confirmed mRNA and/or protein expression on solid tumors (Zhan et al, 2013; Erickson-Miller et al, 2012; Erickson-Miller et al, 2010; Graf et al, 1996; Columbyova et al, 1995). Romiplostim would not be expected to promote growth of solid tumors. | Progression of existing myelodysplastic syndrome (MDS), is documented under Section 4.4 (Special warnings and precautions for use) and Section 4.8 (Undesirable effects) of the SmPC. |
| Safety pharmacology | | |
| • General | No adverse clinical signs or changes in blood pressure, heart rate, corrected QT interval (QTc), or body temperature were attributed to romiplostim administration in cynomolgus monkeys. No central nervous system changes related to romiplostim were noted in rats.<br>In an in vitro receptor screening assay study, there was no binding activity of romiplostim observed on various ion channels (including calcium, potassium, and sodium) predictive of cardiac safety. | Myocardial infarction and heart rate increased are documented under cardiac disorders in Section 4.8 (Undesirable effects) of the SmPC. Headache, dizziness, migraine, paraesthesia, clonus, hypoaesthesia, and hypogeusia are documented under nervous system disorders in Section 4.8 (Undesirable effects) of the SmPC. |

**Table 3. Key Safety Findings From Nonclinical Studies and Relevance to Human Usage**

| Study Type | Important Nonclinical Safety Findings | Relevance to Human Usage |
|---|---|---|
| Other toxicity-related information or data | | |
| • Immunogenicity | Immunogenicity in animals is often not predictive of effects in humans. Romiplostim has no amino acid sequence homology to endogenous thrombopoietin (eTPO) and is immunogenic in mice, rats, rabbits, and monkeys. Binding antibodies to romiplostim developed in all species tested, and neutralizing anti-romiplostim antibodies developed in mice, rats, and monkeys. Although rare instances of anti-TPO binding antibodies developed after dosing in mice, rats, and monkeys, none of these antibodies neutralized the biological effect of TPO. Additionally, there was no evidence of thrombocytopenia in the animals that developed anti-TPO antibodies. The immunogenicity of romiplostim in rats and the induction of a neutralizing antibody response to romiplostim were clearly reflected in the diminution of the platelet response. | Immunogenicity is documented under Section 4.4 (Special warnings and precautions for use) and Section 4.8 (Undesirable effects) of the SmPC. |

Page 4 of 4

# Part II: Module SIII - Clinical Trial Exposure

## Table 4. Total Subject Exposure to Romiplostim in Clinical Trials by Indication and Duration (Safety Analysis Set)

| | Exposure to Romiplostim by Duration | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| PRODUCT | < 1 Year n (subj-yrs)[a] | ≥ 1 Years n (subj-yrs)[a] | ≥ 2 Years n (subj-yrs)[a] | ≥ 3 Years n (subj-yrs)[a] | ≥ 4 Years n (subj-yrs)[a] | ≥ 5 Years n (subj-yrs)[a] | ≥ 6 Years n (subj-yrs)[a] | ≥ 7 Years n (subj-yrs)[a] | Total n (subj-yrs)[a] |
| Phase 1 studies[b] | 56 (1.07) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 56 (1.07) |
| Adult ITP[c] | 414 (192.65) | 633 (1504.40) | 366 (1139.22) | 126 (509.39) | 59 (276.33) | 18 (95.08) | 0 (0) | 0 (0) | 1047 (1697.05) |
| ≤ 12 months | 145 (71.73) | 144 (291.58) | 65 (187.11) | 14 (57.03) | 7 (31.60) | 2 (10.72) | 0 (0) | 0 (0) | 289 (363.30) |
| > 12 months | 269 (120.92) | 488 (1211.49) | 301 (952.11) | 112 (452.36) | 52 (244.73) | 16 (84.36) | 0 (0) | 0 (0) | 757 (1332.41) |
| MDS[d] | 262 (100.69) | 70 (132.42) | 19 (66.26) | 14 (52.90) | 5 (22.02) | 0 (0) | 0 (0) | 0 (0) | 332 (233.11) |
| CIT[e] | 133 (14.81) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 133 (14.81) |

Page 1 of 2

Footnotes, including abbreviations, are defined on the next page of this table

## Table 4. Total Subject Exposure to Romiplostim in Clinical Trials by Indication and Duration (Safety Analysis Set)

| | Exposure to Romiplostim by Duration | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| PRODUCT | < 1 Year n (subj-yrs)[a] | ≥ 1 Years n (subj-yrs)[a] | ≥ 2 Years n (subj-yrs)[a] | ≥ 3 Years n (subj-yrs)[a] | ≥ 4 Years n (subj-yrs)[a] | ≥ 5 Years n (subj-yrs)[a] | ≥ 6 Years n (subj-yrs)[a] | ≥ 7 Years n (subj-yrs)[a] | Total n (subj-yrs)[a] |
| Pediatric ITP[f] | 74 (34.55) | 208 (622.97) | 180 (581.34) | 36 (170.25) | 17 (106.21) | 9 (71.73) | 8 (66.44) | 7 (60.02) | 282 (657.52) |
| ≤ 12 months | 11 (5.11) | 60 (167.71) | 52 (156.09) | 7 (29.85) | 2 (12.30) | 2 (12.30) | 1 (7.01) | 1 (7.01) | 71 (172.82) |
| > 12 months | 63 (29.44) | 148 (455.26) | 128 (425.25) | 29 (140.40) | 15 (93.91) | 7 (59.43) | 7 (59.43) | 6 (53.00) | 211 (484.71) |
| Total | 939 (343.77) | 911 (2259.80) | 565 (1786.82) | 176 (732.53) | 81 (404.56) | 27 (166.81) | 8 (66.44) | 7 (60.02) | 1850 (2603.57) |



adult ITP = adult primary immune thrombocytopenia in subjects≥ 18 years of age; CIT = chemotherapy induced thrombocytopenia; ITP = immune (idiopathic) thrombocytopenic purpura; MDS = myelodysplastic syndrome; n = number of subjects exposed to romiplostim; pediatric ITP = pediatric ITP in subjects≥ 1 and < 18 years of age; subj-yrs = total subject-years of follow-up.

Note: Data is from completed studies, ongoing double-blind CIT studies as of 01 October 2021 (Studies 20140346, 20170770). A study is considered "completed" if a final clinical study report is available or if the study has finished and data have been unblinded.

One [redacted] subject was enrolled in adult ITP Study 20040209 and received at least 1 dose of romiplostim due to protocol deviation.

Extension studies will contribute to the cumulative exposure but not the number of subjects exposed for subjects who received romiplostim in the parent studies.

ITP duration is calculated from the ITP diagnosis to the enrollment of first/parent ITP study. Primary immune thrombocytopenia duration missing for 1 subject from Study 20040209.

Safety Analysis Set includes subjects who received at least 1 dose of investigational product.

[a] Duration of exposure (years) = (last dose date - first dose date + 7)/365.25. If a subject is enrolled in multiple studies, this is the sum of treatment durations of individual studies.

[b] Phase 1 studies include healthy volunteer Studies 20000109, 20040134; Both were randomized double- blinded studies.

[c] Adult ITP studies include Studies 20000137A, 20000137B, 20010218, 20030105, 20030212, 20030213 (adult, extension), 20040209, 20050162, 20060113 (extension), 20060131, 20060216, 20080009, 20080435; Studies 20000137B, 20030105, 20030212, 20060216 were randomized double-blinded studies.

[d] Myelodysplastic syndrome (MDS) studies include Studies 20050159, 20050232A, 20050232B, 20060102, 20060197 (extension), 20060198; Studies 20050232, 20060102, 20060198 were randomized double-blinded studies.

[e] Chemotherapy-induced thrombocytopenia (CIT) studies include Studies 20050144, 20050154; 20140346 (ongoing), 20170770 (ongoing); Study 20050154, 20140346, and 20170770 are randomized double-blinded studies.

[f] Pediatric ITP studies include Studies 20060195, 20080279, 20030213 (pediatric, extension), 20090340 (extension), 20101221 (open-label); Studies 20060195, 20080279 were randomized double-blinded studies.

*Program: /userdata/stat/amp2/safety/rmp/analysis/eu_2021/tables/t-exp-dur-all.sas*

*Output: t14-05-001-001-exp-dur-all.rtf (Date Generated: 17OCT2021:21:35) Source Data: amp109.c_demog, amp134.demog_a, ped.adsl, itpadl.ds, crtmds.ds, cit.ds, crt.ds, ped.adsl*

## Table 5. Total Subject Exposure to Romiplostim in Clinical Trials by Age Group and Sex, All Studies (Safety Analysis Set)

| | < 18 years | ≥ 18 years to < 65 years | ≥ 65 years | ≥ 75 years |
|---|---|---|---|---|
| Indication | All studies n (subj-yrs)[a] | All studies n (subj-yrs)[a] | All studies n (subj-yrs)[a] | All studies n (subj-yrs)[a] |
| Male | | | | |
| Phase 1 studies[b] | 0 (0) | 56 (1.07) | 0 (0) | 0 (0) |
| Adult ITPc | 0 (0) | 272 (441.57) | 127 (200.18) | 54 (89.44) |
| ≤ 12 months | 0 (0) | 93 (123.47) | 41 (49.82) | 16 (23.26) |
| > 12 months | 0 (0) | 178 (316.76) | 86 (150.36) | 38 (66.18) |
| MDS[d] | 0 (0) | 49 (44.67) | 156 (99.16) | 80 (51.87) |
| CIT[e] | 0 (0) | 50 (5.51) | 34 (2.90) | 7 (0.77) |
| Pediatric ITP[f] | 139 (333.69) | 0 (0) | 0 (0) | 0 (0) |
| ≤ 12 months | 36 (89.75) | 0 (0) | 0 (0) | 0 (0) |
| > 12 months | 103 (243.94) | 0 (0) | 0 (0) | 0 (0) |
| Total | 139 (333.69) | 427 (492.82) | 317 (302.24) | 141 (142.09) |

Page 1 of 2

Footnotes, including abbreviations, are defined on the last page of this table

## Table 5. Total Subject Exposure to Romiplostim in Clinical Trials by Age Group and Sex, All Studies (Safety Analysis Set)

| | < 18 years | ≥ 18 years to < 65 years | ≥ 65 years | ≥ 75 years |
|---|---|---|---|---|
| Indication | All studies n (subj-yrs)[a] | All studies n (subj-yrs)[a] | All studies n (subj-yrs)[a] | All studies n (subj-yrs)[a] |
| Female | | | | |
| Phase 1 studies[b] | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| Adult ITP[c] | 1 (0.58) | 491 (814.20) | 156 (240.53) | 66 (99.70) |
| ≤ 12 months | 0 (0) | 111 (145.39) | 44 (44.63) | 21 (16.17) |
| > 12 months | 1 (0.58) | 380 (668.80) | 112 (195.90) | 45 (83.53) |
| MDS[d] | 0 (0) | 47 (26.54) | 80 (62.74) | 41 (32.99) |
| CIT[e] | 0 (0) | 31 (3.60) | 18 (2.80) | 4 (0.88) |
| Pediatric ITP[f] | 143 (323.83) | 0 (0) | 0 (0) | 0 (0) |
| ≤ 12 months | 35 (83.07) | 0 (0) | 0 (0) | 0 (0) |
| > 12 months | 108 (240.77) | 0 (0) | 0 (0) | 0 (0) |
| Total | 144 (324.42) | 569 (844.34) | 254 (306.07) | 111 (133.58) |



adult ITP = adult primary immune thrombocytopenia in subjects≥ 18 years of age; CIT = chemotherapy induced thrombocytopenia; immune (idiopathic) thrombocytopenic purpura; MDS = myelodysplastic syndrome; pediatric ITP = pediatric ITP in subjects≥ 1 and < 18 years of age; n = number of subjects exposed to romiplostim; subj-yrs = total subject-years of follow-up.

Note: Extension studies will contribute to the cumulative exposure but not the number of subjects exposed for subjects who received romiplostim in the parent studies.

ITP duration is calculated from the ITP diagnosis to the enrollment of first/parent ITP study. Primary immune thrombocytopenia duration missing for 1 subject from Study 20040209.

One [redacted] subject was enrolled in adult ITP Study 20040209 and received at least 1 dose of romiplostim due to protocol deviation.

Includes all completed studies and ongoing double-blind CIT studies as of 01 October 2021 (Studies 20140346, 20170770).

Includes all subjects who received at least 1 dose of romiplostim.

[a] Duration of exposure (years) = (last dose date - first dose date + 7)/365.25. If a subject is enrolled in multiple studies, this is the sum of treatment durations of individual studies.

[b] Phase 1 studies include healthy volunteer Studies 20000109, 20040134; both were randomized double-blinded studies.

[c] Adult ITP studies include Studies 20000137A, 20000137B, 20010218, 20030105, 20030212, 20030213 (adult, extension), 20040209, 20050162, 20060113 (extension), 20060131, 20060216, 20080009, 20080435; Studies 20000137B, 20030105, 20030212, 20060216 were randomized double-blinded studies.
[d] Myelodysplastic syndrome (MDS) studies include Studies 20050159, 20050232A, 20050232B, 20060102, 20060197 (extension), 20060198; Studies 20050232, 20060102, 20060198 were randomized double-blinded studies.
[e] Chemotherapy-induced thrombocytopenia (CIT) studies include Studies 20050144, 20050154; 20140346 (ongoing), 20170770 (ongoing); Studies 20050154, 20140346, and 20170770 are randomized double-blinded studies.
[f] Pediatric ITP studies include Studies 20060195, 20080279, 20030213 (pediatric, extension), 20090340 (extension), 20101221 (open-label); Studies 20060195, 20080279 were randomized double-blinded studies.
*Program: /userdata/stat/amp2/safety/rmp/analysis/eu_2021/tables/t-exp-age-sex.sas*
*Output: t14-05-001-002-exp-age-sex.rtf (Date Generated: 17OCT2021:21:37) Source Data: amp109.c_demog, amp134.demog_a, ped.adsl, itpadl.ds, crtmds.ds, cit.ds, crt.ds, ped.adsl, amp109.c_demog, amp134.demog_a*

## Table 6. Total Subject Exposure to Romiplostim in Clinical Trials in Pediatric Patients by Age Group and Sex, All Studies (Safety Analysis Set)

| | < 1 year old | ≥ 1 to < 6 years old | ≥ 6 to <12 years old | ≥ 12 to <18 years old |
|---|---|---|---|---|
| Indication | All studies n (subj-yrs)[a] | All studies n (subj-yrs)[a] | All studies n (subj-yrs)[a] | All studies n (subj-yrs)[a] |
| Male | | | | |
| Pediatric ITP[b] | 0 (0) | 39 (89.13) | 52 (137.19) | 48 (107.37) |
| ≤ 12 months | 0 (0) | 16 (40.45) | 11 (25.36) | 9 (23.93) |
| > 12 months | 0 (0) | 23 (48.67) | 41 (111.83) | 39 (83.43) |
| Total | 0 (0) | 39 (89.13) | 52 (137.19) | 48 (107.37) |
| Female | | | | |
| Pediatric ITP[b] | 0 (0) | 26 (47.67) | 62 (143.24) | 55 (132.92) |
| ≤ 12 months | 0 (0) | 8 (13.30) | 17 (45.15) | 10 (24.62) |
| > 12 months | 0 (0) | 18 (34.37) | 45 (98.09) | 45 (108.30) |
| Total | 0 (0) | 26 (47.67) | 62 (143.24) | 55 (132.92) |

n = number of subjects exposed to romiplostim; immune (idiopathic) thrombocytopenic purpura; pediatric ITP = pediatric ITP in subjects≥ 1 and < 18 years of age; subj-yrs = total subject-years of follow-up.
Note: Extension studies will contribute to the cumulative exposure but not the number of subjects exposed for subjects who received romiplostim in the parent studies.
One [redacted] subject was enrolled in adult ITP Study 20040209 and received at least 1 dose of romiplostim due to protocol deviation.
Primary immune thrombocytopenia duration is calculated from the ITP diagnosis to the enrollment of first/parent ITP study.
Includes all completed studies.
Includes all subjects who received at least 1 dose of romiplostim.
[a] Duration of exposure (years) = (last dose date - first dose date + 7)/365.25. If a subject is enrolled in multiple studies, this is the sum of treatment durations of individual studies.
[b] Pediatric ITP studies include Studies 20060195 (randomized blinded), 20030213 (pediatric, extension), 20080279 (randomized blinded), 20090340 (extension), 20101221 (open-label).
*Program: /userdata/stat/amp2/safety/rmp/analysis/eu_2021/tables/t-exp-age-sex-ped-all.sas*
*Output: t14-05-001-003-exp-age-sex-ped-all.rtf (Date Generated: 17OCT2021:21:37) Source Data: ped.adsl*

## Table 7. Total Subject Exposure to Romiplostim in Clinical Trials by Product and Race/Ethnic Group (Safety Analysis Set)

| Indication | White n (subj-yrs)[a] | Black or African American n (subj-yrs)[a] | Hispanic or Latino n (subj-yrs)[a] | Asian n (subj-yrs)[a] | Other n (subj-yrs)[a] | Missing / Unknown n (subj-yrs)[a] | Total n (subj-yrs)[a] |
|---|---|---|---|---|---|---|---|
| Phase 1 studies[b] | 30 (0.57) | 1 (0.02) | 0 (0) | 24 (0.46) | 1 (0.02) | 0 (0) | 56 (1.07) |
| Adult ITP[c] | 906 (1394.17) | 25 (37.54) | 42 (88.16) | 67 (169.52) | 6 (7.52) | 1 (0.13) | 1047 (1697.05) |
| ≤ 12 months | 260 (312.21) | 7 (7.91) | 13 (25.65) | 8 (17.41) | 0 (0) | 1 (0.13) | 289 (363.30) |
| > 12 months | 645 (1080.62) | 18 (29.63) | 29 (62.51) | 59 (152.12) | 6 (7.52) | 0 (0) | 757 (1332.41) |
| MDS[d] | 301 (205.58) | 8 (11.65) | 11 (8.27) | 4 (1.55) | 8 (6.06) | 0 (0) | 332 (233.11) |
| CIT[e] | 122 (13.94) | 4 (0.22) | 3 (0.19) | 0 (0) | 4 (0.46) | 0 (0) | 133 (14.81) |

Page 1 of 2

Footnotes, including abbreviations, are defined on the last page of this table

## Table 7. Total Subject Exposure to Romiplostim in Clinical Trials by Product and Race/Ethnic Group (Safety Analysis Set)

| Indication | White n (subj-yrs)[a] | Black or African American n (subj-yrs)[a] | Hispanic or Latino n (subj-yrs)[a] | Asian n (subj-yrs)[a] | Other n (subj-yrs)[a] | Missing / Unknown n (subj-yrs)[a] | Total n (subj-yrs)[a] |
|---|---|---|---|---|---|---|---|
| Pediatric ITP[f] | 213 (515.80) | 24 (41.36) | 3 (12.63) | 17 (31.29) | 25 (56.45) | 0 (0) | 282 (657.52) |
| ≤ 12 months | 54 (138.56) | 4 (6.21) | 0 (0) | 7 (16.36) | 6 (11.69) | 0 (0) | 71 (172.82) |
| > 12 months | 159 (377.23) | 20 (35.15) | 3 (12.63) | 10 (14.93) | 19 (44.76) | 0 (0) | 211 (484.71) |
| Total | 1572 (2130.07) | 62 (90.79) | 59 (109.25) | 112 (202.82) | 44 (70.51) | 1 (0.13) | 1850 (2603.57) |

Page 2 of 2

adult ITP = adult primary immune thrombocytopenia in subjects ≥ 18 years of age; CIT = chemotherapy induced thrombocytopenia; ITP = immune (idiopathic) thrombocytopenic purpura; MDS = myelodysplastic syndrome; n = number of subjects exposed to romiplostim; pediatric ITP = pediatric ITP in subjects ≥ 1 and < 18 years of age; subj-yrs = total subject-years of follow-up.

Note: Data is from completed studies, ongoing double-blind CIT studies as of 01 October 2021 (Studies 20140346, 20170770). A study is considered "completed" if a final clinical study report is available or if the study has finished and data have been unblinded. Safety Analysis Set includes subjects who received at least 1 dose of investigational product. Extension studies will contribute to the cumulative exposure but not the number of subjects exposed for subjects who received romiplostim in the parent studies. Primary immune thrombocytopenia duration is calculated from the ITP diagnosis to the enrollment of first/parent ITP study. Primary immune thrombocytopenia duration missing for 1 subject from Study 20040209.

One [redacted] subject was enrolled in adult ITP Study 20040209 and received at least 1 dose of romiplostim due to protocol deviation.

Safety Analysis Set includes subjects who received at least 1 dose of investigational product.

[a] Duration of exposure (years) = (last dose date - first dose date + 7)/365.25. If a subject is enrolled in multiple studies, this is the sum of treatment durations of individual studies.

[b] Phase 1 studies include healthy volunteer Studies 20000109, 20040134; Both were randomized double- blinded studies.

[c] Adult ITP studies include Studies 20000137A, 20000137B, 20010218, 20030105, 20030212, 20030213 (adult, extension), 20040209, 20050162, 20060113 (extension), 20060131, 20060216, 20080009, 20080435; Studies 20000137B, 20030105, 20030212, 20060216 were randomized double-blinded studies.

[d] Myelodysplastic syndrome (MDS) studies include Studies 20050159, 20050232A, 20050232B, 20060102, 20060197 (extension), 20060198; Studies 20050232, 20060102, 20060198 were randomized double-blinded studies.

[e] Chemotherapy-induced thrombocytopenia (CIT) studies include Studies 20050144, 20050154; 20140346 (ongoing), 20170770 (ongoing); Studies 20050154, 20140346 and 20170770 are randomized double-blinded studies.

[f] Pediatric ITP studies include Studies 20060195, 20080279, 20030213 (pediatric, extension), 20090340 (extension), 20101221 (open-label); Studies 20060195, 20080279 were randomized double-blinded studies.

*Program: /userdata/stat/amp2/safety/rmp/analysis/eu_2020/tables/t-exp-race-all.sas*

*Output: t14-05-001-004-exp-race-all.rtf (Date Generated: 17OCT2021:21:38) Source Data: amp109.c_demog, amp134.demog_a, ped.adsl, crtmds.ds, itpadl.ds, cit.ds, crt.ds*

## Part II: Module SIV - Populations Not Studied in Clinical Trials

*SIV.1 Exclusion Criteria in Pivotal Clinical Studies Within the Development Program*

**Table 8. Important Exclusion Criteria in Pivotal Studies Across the Development Program**

| Criterion | Reason for Exclusion | Included as Missing Information (Yes/No) | Rationale |
|---|---|---|---|
| Hypersensitivity to the active substance, to any of the excipients, or to *E coli*-derived proteins | Subjects who are hypersensitive to romiplostim, to any of the excipients, or to *E coli*-derived proteins should not receive romiplostim. | No | Hypersensitivity to the active substance or to any of the excipients or any *E. coli*-derived proteins is a contraindication in the SmPC. |
| Use in pregnant or breastfeeding women | Adequate and well-controlled studies with romiplostim have not been conducted in pregnant women due to the potential risk to the fetus. It is not known whether romiplostim is transferred into human milk. | No | There are no or limited amount of data from the use of romiplostim in pregnant women and it is unknown whether romiplostim/metabolites are excreted in human milk. The SmPC states that romiplostim is not recommended during pregnancy and in women of childbearing potential not using contraception. |
| Use in patients with renal, hepatic, cardiac, or pulmonary impairment | Formal studies were not conducted in subjects with hepatic, cardiac, or pulmonary impairment. | No | A different safety profile in hepatic/renal impairment is not expected due to known romiplostim metabolism. Studies of ITP patients with cardiac/pulmonary impairment are not feasible. |
| Any active malignancy | Active malignancy would interfere with the ability to assess romiplostim efficacy in clinical studies of patients with ITP. | No | Use in chemotherapy-induced thrombocytopenia (CIT) does not represent current approved and recommended use by the MAH. |

Page 1 of 2

**Table 8. Important Exclusion Criteria in Pivotal Studies Across the Development Program**

| Criterion | Reason for Exclusion | Included as Missing Information (Yes/No) | Rationale |
|---|---|---|---|
| History of bone marrow stem cell disorder | Would interfere with the ability to assess romiplostim efficacy in clinical studies of patients with ITP. | No | A different safety profile in patients with a history of bone marrow stem cell disorder is not expected. Romiplostim has been approved with clinical study evidence support in Japan and Taiwan for aplastic anemia refractory to conventional therapy among adult patients. |
| Concurrently receiving rituximab or alkylating agents | Use would interfere with the ability to assess romiplostim efficacy in clinical studies. | No | Anti-cancer therapy (such as rituximab or alkylating agents) induced thrombocytopenia is not an approved indication for romiplostim per the SmPC. |
| Use in pediatric patients (< 1 year of age) | Adequate and well-controlled studies with romiplostim in children from birth to less than 1 year of age have not been conducted. | No | Per the SmPC, romiplostim is not indicated for use in patients below 1 year of age. |
| Use in patients of different racial and/or ethnic origins | Across the clinical development program, the majority of the subjects exposed to romiplostim were white. Experience in patients with different ethnic origins is limited. | No | There is no evidence to date, based on worldwide product use, that there are differences in safety and efficacy that are attributable to differences in race and/or ethnicity. |

*SIV.2 Limitations to Detect Adverse Reactions in Clinical Trial Development Programs*

The clinical development program is unlikely to detect certain types of adverse reactions such as very rare adverse reactions.

The clinical development program is able to detect the adverse drug reactions (ADRs) listed in Table 9.

**Table 9. Limitations Common to all Clinical Trials**

| Ability to Detect Adverse Drug Reactions (ADRs) | Limitation of Trial Program | Discussion of Implications for Target Population |
|---|---|---|
| Rare ADRs | 1850 subjects were exposed to romiplostim in the clinical study program. | There is about 95% probability of observing at least 1 ADR of true frequency rate of 1/617. |
| ADRs due to prolonged exposure | 1850 subjects were exposed to romiplostim in the clinical study program, in which, 565, 176, 81, 27, 8, and 7 subjects were followed for ≥ 2 years, ≥ 3 years, ≥ 4 years, ≥ 5 years, ≥ 6 years, and ≥ 7 years, respectively. | The clinical trial program allowed detection of ADRs after prolonged exposure in a subset of study subjects. |

*SIV.3 Limitations in Respect to Populations Typically Under-represented in Clinical Trial Development Programs*

**Table 10. SIV.2: Exposure of Special Populations Included or Not in Clinical Trial Development Programs**

| Type of Special Population | Exposure |
|---|---|
| Pregnant women[a] | Eleven pregnancies (8 maternal exposure; 3 paternal exposure) were reported across all indications in the clinical development program. |
| Breastfeeding women[a] | There were no lactation exposures reported across all indications in the clinical development program. |
| Patients with relevant comorbidities | |
| Patients with hepatic impairment | A total of 42 (2.3%, 44.68 subject-years) and 12 (0.6%, 11.09 subject-years) subjects with baseline hepatic impairment defined as elevated bilirubin CTCAE v3.0 severity grade 1 and grade 2, respectively, were exposed to romiplostim across all indications in the clinical development program. No subjects had baseline hepatic impairment of grade 3 or 4 severity. |
| Patients with renal impairment | A total of 58 (3.1%; 67.62 subject-years), 4 (0.2%, 3.54 subject-years), and 2 (0.1%, 3.53 subject-years) subjects with baseline renal impairment defined as elevated creatinine CTCAE v3.0 severity grade 1, grade 2, and grade 3, respectively, were exposed to romiplostim across all indications in the clinical development program. No subjects had baseline renal impairment of grade 4 severity. |
| Patients with cardiovascular impairment | Formal studies were not conducted in subjects with cardiac impairment. Subjects with cardiac impairment were excluded from the phase 3 adult ITP pivotal studies. |
| Patients with pulmonary impairment | Formal studies were not conducted in subjects with pulmonary impairment. Subjects with pulmonary impairment were excluded from the phase 3 adult ITP pivotal studies. |
| Patients with a disease severity different from inclusion criteria in clinical trials | Not included in the clinical development program |

Page 1 of 2

Footnotes, including abbreviations, are defined on the next page of this table

## Table 10. SIV.2: Exposure of Special Populations Included or Not in Clinical Trial Development Programs

| Type of Special Population | Exposure |
|---|---|
| Population with relevant different ethnic origin | A total of 1572 (2130.07 subject-years) White,<br>62 (90.79 subject-years) Black or African American,<br>59 (109.25 subject-years) Hispanic or Latino,<br>112 (202.82 subject-years) Asian,<br>44 (70.51 subject-years) other race, and<br>1 (0.13 subject-years) missing/unknown race subjects were exposed to romiplostim across all indications in the clinical development program. No racial/ethnic groups were excluded from clinical studies in ITP. |
| Subpopulations carrying relevant genetic polymorphisms | No information on the use of romiplostim in subjects with genetic polymorphism is available. |
| Pediatric patients (< 1 year of age) | Not included in the clinical development program |
| Elderly patients (≥ 65 years of age) | A total of 571 subjects (317 male subjects [302.24 subject-years] and 254 female subjects [306.07 subject-years]) ≥ 65 years of age were included across all indications in the clinical development program. |
| Use in patients with bone marrow stem cell disorder and/or any active malignancy | These patients were not included in the romiplostim clinical studies in ITP.<br>Total exposure in completed chemotherapy-induced thrombocytopenia (CIT) studies and myelodysplastic syndrome (MDS) studies was 133 subjects (14.81 subject-years) and 332 subject (233.11 subject-years), respectively. |
| Use in patients concurrently receiving rituximab or alkylating agents | A total of 107 subjects (5.8%, 62.18 subject-years) exposed to romiplostim concurrently received rituximab or alkylating agents across all indications in the clinical development program (37 subjects received rituximab concurrently, 27 subjects received alkylating agents concurrently, and 43 subjects received rituximab and/or alkylating agents concurrently). |

Page 2 of 2

CTCAE = Common Terminology Criteria for Adverse Events; ITP = immune (idiopathic) thrombocytopenic purpura; MedDRA = Medical Dictionary for Regulatory Activities; Subject-years = total subject years: (last dose date - first dose date + 7)/365.25.

Data is from completed studies, ongoing double-blind CIT studies as of 01 October 2021 (Studies 20140346, 20170770).

[a] Pregnancy and lactation data are extracted from the safety database (cumulative to 31 July 2021) using a particular case type, rather than particular MedDRA search strategies.

## Part II: Module SV - Postauthorization Experience

*SV.1 Postauthorization Exposure*

*SV.1.1 Method Used to Calculate Exposure*

Amgen's estimates of postmarketing patient exposure are in part based on unit sales data (eg, vials or syringes) and in part on observed drug utilization parameters. Worldwide unit sales are reported monthly by country and are converted to a monthly estimate of patient count (when feasible) or person-time using region- and product-specific parameters and algorithms. These parameters include the average number of milligrams per administration, average length of treatment, days between administrations, patient turnover rates, market penetration rates, and average revenue per patient. These drug utilization parameters can change over time to best represent the current patient and market experience.

Postmarketing patient exposure estimates are reported overall and for the following geographic regions: Australia, Canada, Europe (European Union, EEA, Switzerland, and the United Kingdom), United States, and Other (countries, not otherwise specified, where Amgen is the market authorization holder). Patient exposure estimates for countries where market authorization is held by Amgen's licensing partners, such as Japan and neighboring countries, are obtained directly from these companies, may be based on a different set of assumptions, and are reported under a separate paragraph or table in this document.

Estimates of postmarketing exposure are provided by indication (when applicable), sex and these age groups: < 18 years, 18 to 34 years, 35 to 49 years, 50 to 64 years, 65 to 74 years, and ≥ 75 years.

*SV.1.2 Exposure*

The number of person-years exposed to romiplostim through commercial distribution, excluding Kyowa Kirin Co., Ltd (KKC) territories, since the launch to 31 July 2023 are shown in Table 11.

Approximately 525 patients have been exposed to romiplostim through compassionate use programs in Australia (started March 2009) and Europe. Of these, 234 patients were treated in Australia, where the program has now been discontinued. There were 291 patients treated in Europe.

**Table 11. Estimated Number of Patient-years of Exposure to Romiplostim, by Region and Demographic Characteristics, in the Postmarketing Setting**

| Demographic Characteristics | Cumulative Number of Patient-years of Exposure | | | | | |
|---|---|---|---|---|---|---|
| | AU | CA | EUR | US | Other | Total |
| Overall | 3494 | 2088 | 83391 | 69511 | 28146 | 186629 |
| Sex | | | | | | |
| Female | 1801 | 1076 | 42963 | 35825 | 14399 | 96065 |
| Male | 1692 | 1011 | 40428 | 33686 | 13747 | 90564 |
| Age (years) | | | | | | |
| < 18 | 68 | 41 | 1614 | 1347 | 533 | 3602 |
| 18 - 34 | 325 | 194 | 7707 | 6438 | 2492 | 17156 |
| 35 - 49 | 540 | 322 | 12807 | 10700 | 4124 | 28494 |
| 50 - 64 | 1244 | 743 | 29563 | 24685 | 9631 | 65867 |
| 65 - 74 | 603 | 361 | 14507 | 12053 | 5214 | 32738 |
| ≥ 75 | 715 | 428 | 17192 | 14287 | 6150 | 38772 |
| Sex/age (years) | | | | | | |
| Female | | | | | | |
| < 18 | 34 | 20 | 803 | 671 | 259 | 1787 |
| 18 - 34 | 195 | 117 | 4638 | 3874 | 1496 | 10320 |
| 35 - 49 | 321 | 192 | 7610 | 6359 | 2443 | 16924 |
| 50 - 64 | 655 | 391 | 15557 | 12992 | 5054 | 34648 |
| 65 - 74 | 274 | 164 | 6609 | 5490 | 2388 | 14926 |
| ≥ 75 | 322 | 193 | 7746 | 6439 | 2759 | 17460 |

Page 1 of 2

Footnotes, including abbreviations, are defined on next page of this table.

**Table 11. Estimated Number of Patient-years of Exposure to Romiplostim, by Region and Demographic Characteristics**

| Demographic Characteristics | Cumulative Number of Patient-years of Exposure | | | | | |
|---|---|---|---|---|---|---|
| | AU | CA | EUR | US | Other | Total |
| Male | | | | | | |
| < 18 | 34 | 20 | 811 | 676 | 274 | 1815 |
| 18 - 34 | 129 | 77 | 3069 | 2563 | 997 | 6836 |
| 35 - 49 | 219 | 131 | 5196 | 4341 | 1681 | 11 567 |
| 50 - 64 | 589 | 352 | 14 006 | 11 694 | 4578 | 31 219 |
| 65 - 74 | 328 | 196 | 7898 | 6563 | 2826 | 17 812 |
| ≥ 75 | 393 | 235 | 9447 | 7849 | 3392 | 21 315 |

Page 2 of 2

AU = Australia; CA = Canada; EUR = Europe (European Union, European Economic Area, Switzerland, and the United Kingdom); Other = countries, not otherwise specified above, where Amgen is the marketing authorization holder; US = United States

Data cutoff date: 31 July 2023

Note: Numbers may not add to the total due to rounding.

[a] Age and sex breakdowns are based on patient characteristics in MarketScan (from launch to July 2022) and in Optum Clinformatics (after July 2022), US health insurance claims database. Applying these distributions to regions outside the United States requires strong assumptions that are not easily testable.

### Postauthorization Use From Business Partners

Cumulatively through 31 July 2023, an estimated 16 057 patients were exposed to romiplostim in the KKC territories (ie, Japan, South Korea, Hong Kong, Macau, Malaysia, Singapore, Taiwan, Thailand, and China). Exposure in patient-years was not reported by the business partners.

## Part II: Module SVI - Additional EU Requirements for the Safety Specification

*SVI.1 Potential for Misuse for Illegal Purposes*

No evidence to suggest a potential for drug abuse or misuse has been observed.

## Part II: Module SVII - Identified and Potential Risks

*SVII.1 Identification of Safety Concerns in the Initial RMP Submission*

*SVII.1.1 Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP*

Not applicable, as this is not the initial RMP for the product. Please refer to the full safety profile in the SmPC.

*SVII.1.2 Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP*

Not applicable, as this is not the initial RMP for the product. Please refer to the full safety profile in the SmPC.

*SVII.2 New Safety Concerns and Reclassification With a Submission of an Updated RMP*

## Table 12. New or Reclassification of Safety Concerns in the RMP

| Safety Concern | Action Taken | Justification |
|---|---|---|
| Removal of Safety Concerns From the RMP | | |
| Important Potential Risk | | |
| Neutralizing antibodies that cross react with eTPO | Neutralizing antibodies that cross react with eTPO, previously classified as an important potential risk, has been reclassified as a not important potential risk and removed from the list of safety concerns. | As with all therapeutic proteins, there is a potential for immunogenicity with romiplostim. However, the peptide portion of romiplostim has no amino acid sequence homology to eTPO. This lack of amino acid sequence homology reduces the probability that antibodies to romiplostim, if produced, will bind to and neutralize eTPO and cause thrombocytopenia.<br>The clinical evidence to support this as a risk is limited. In the adult ITP safety dataset, there were 4/1046 (0.4%) romiplostim-treated subjects who were positive for neutralizing antibodies to romiplostim postbaseline. Of these, 2 were transient (negative result at the subject's last time point tested) and 2 were persistent (positive result at the subject's last timepoint tested). One subject was positive for neutralizing antibodies to romiplostim at or before baseline. No romiplostim-treated subjects were positive for neutralizing antibodies to TPO post baseline.<br>In the pediatric ITP safety set, 8/282 (2.8%) subjects developed a post baseline, neutralizing antibody-positive result for romiplostim; 4 were transient and 4 were persistent while on study. No subjects were neutralizing antibody positive for TPO at any time in this dataset. Two of 282 (0.7%) subjects experienced an immunogenicity treatment-emergent event (Preferred Terms [PTs]: Drug effect decreased and Neutralizing antibodies positive). One report of a subject who developed positive neutralizing antibody to TPO was received after the data-lock point of this dataset, where a weak positive neutralizing antibody to TPO developed, in the absence of an antibody response to romiplostim, which was suggestive of a pre-existing endogenous antibody response to TPO. |

Page 1 of 2

Footnotes, including abbreviations, are defined on the last page of the table.

**Table 12. New or Reclassification of Safety Concerns in the RMP**

| Safety Concern | Action Taken | Justification |
|---|---|---|
| Removal of Safety Concerns From the RMP | | |
| Important Potential Risk | | |
| Neutralizing antibodies that cross react with eTPO | Neutralizing antibodies that cross react with eTPO, previously classified as an important potential risk, has been reclassified as a not important potential risk and removed from the list of safety concerns. | Cumulatively through the data-lock point (31 July 2022) of Periodic Benefit Risk Evaluation Report (PBRER) #21, there were no cases from the clinical trial setting and 538 cases with 553 events in the postmarketing setting identified using the Immunogenicity Amgen Medical Dictionary for Regulatory Activities (MedDRA) Query (AMQ) (Broad) search strategy. Of the 553 events in the postmarketing setting, there were 6 events with the PT of Neutralizing antibodies positive and 4 events with the PT of Antibody test positive. A review of the cases did not identify any new information to support further characterization of the risk.<br>Even though antibody testing is provided at the request of the treating physician, there have been very limited requests for testing in the postmarketing setting. In the global postmarketing setting, 21 samples were submitted in 2021 and 11 samples in 2022, with only 1 sample being neutralizing antibody positive against romiplostim. All samples tested were negative for antibodies against eTPO.<br>No new safety information pertaining to this risk has been identified from the ongoing review of the clinical trial data and postmarketing data received through continued safety surveillance.<br>The overall risk and the public health impact is negligible given the limited evidence to support this as a risk. This risk is adequately described in the SmPC under Special warnings and precautions for use, Section 4.4 (Loss of response to romiplostim), and Undesirable effects, Section 4.8 (Immunogenicity). There are no additional risk minimization activities and no additional risk characterization is planned.<br>Therefore, based on the above, this risk will be removed from the list of safety concerns and continue to be monitored via routine pharmacovigilance activities. |



eTPO = endogenous thrombopoietin; ITP = primary immune thrombocytopenia; MedDRA = Medical Dictionary for Regulatory Activities ; PBRER = Periodic Benefit Risk Evaluation Report; PT = Preferred Term; SmPC = Summary of Product Characteristics; TPO = thrombopoietin

*SVII.3 Details of Important Identified Risks, Important Potential Risks, and Missing Information*

*SVII.3.1 Presentation of Important Identified Risks and Important Potential Risks*

## Table 13. Important Identified Risk: Romiplostim Medication Errors (Dosing/Administration)

| | |
|---|---|
| Potential mechanisms | As romiplostim is administered in small volumes, and small differences in dose may have large effects on platelet counts, there is a potential for adverse events related to medication errors to occur.<br>Overdose may result in an excessive increase in platelet counts associated with thrombotic/thromboembolic complications; underdose may result in low platelet counts that can lead to an increased risk of bleeding events. |
| Evidence source(s) and strength of evidence | Although a low number of reports of medication error were received from clinical studies, postmarketing data has provided real-world examples of the kinds of medication error that are possible. |
| Characterization of the risk | |
| Frequency | Medication errors were identified using the Medication errors SMQ (broad and narrow search).<br>**Adult ITP safety set:** There have been no reported cases involving a medication error with an adult subject in the clinical trial setting.<br>**MDS disease-related thrombocytopenia safety set:** There was 1 reported case in the clinical trial setting involving a medication error (serious) of overdose with an opiate and not romiplostim with an adult subject in Study 20060198.<br>**Pediatric ITP safety set:** There have been 2 reported events of medication error (nonserious) in 2/282 romiplostim-treated subjects in the pediatric ITP safety set (0.7%; 95% CI: 0.1, 2.5). Study duration adjusted rate was 0.3/100 subjects-years (95% CI: 0.0, 1.1). One subject was rolled over onto Study 20090340 on 25 June 2014 from Study 20080279. The starting dose was assigned as 1 µg/kg (last dose in Study 20080279 was 10 µg/kg on 29 October 2013). The site mistakenly dosed the subject with 10 µg/kg romiplostim. No adverse events were associated with the medication error. The second reported (nonserious) case of medication error in the pediatric clinical trial setting involved a subject in Study 20090340 who accidently took his mother's Synthroid (levothyroxine). |
| Severity | **ITP safety sets**: No medication error events were reported from the adult ITP safety set and those reported from the pediatric ITP safety set were of mild or moderate severity. |
| Reversibility | Sequelae of medication error resulting in overdose or underdose of romiplostim may include increase or decrease, respectively, in platelet count. Reversibility of these sequelae will depend on the degree of dosing error and adherence to the dose adjustment guidance for romiplostim based on platelet count. |

Page 1 of 2

Footnotes, including abbreviations, are defined on the last page of this table.

**Table 13. Important Identified Risk: Romiplostim Medication Errors (Dosing/Administration)**

| | |
|---|---|
| Long-term outcomes | Long-term outcomes were evaluated based on reoccurrence of an event from the search strategy for this risk 1 year or longer after the initial occurrence. The evaluation is limited to the available data from 1 year or longer follow-up after initial occurrence of the risk.<br>There were no recurrent events at ≥ 1 year of initial occurrence in the ITP safety sets. |
| Impact on quality of life | Medication errors may affect individual subjects in different ways. In the event of overdose, platelet counts may increase excessively and result in thrombotic/thromboembolic events. There is also a potential for underdose leading to increased risk of bleeding. |
| Risk groups or risk factors | Subjects with ITP receiving (and/or self-administering [adult subjects]) treatment with romiplostim. |
| Preventability | The SmPC provides clear guidance on dose calculation and adjustment, reconstitution (as well as dilution if required – when individual patient dose is less than 23 μg), and administration, and recommendations for the use of syringes with 0.01 mL graduations for low volume administration. Both the SmPC and Package Leaflet include information on romiplostim total vial content and deliverable product/volume as well as describes the cap colour for different vial presentations.<br>In addition, provision of a dose calculator is available for physicians involved in the prescribing of romiplostim to adult and pediatric patients in order to simplify the calculation of the correct dose and guide to the correct reconstitution, dilution (if required) and administration procedures.<br>For self-administration by adult patients:<br>Patient educational material on self-administration, designed for adult patients, is provided (ie, a HAT pack). A guide and checklist for adult patient selection and training is also provided for HCPs. Contents of the HAT pack are listed in Annex 6. |
| Impact on the risk-benefit balance of the product | This risk has been incorporated in the benefit-risk assessment with overall benefit-risk balance remaining positive. The consequences of medication error with romiplostim, including overdose and underdose, could potentially have significant clinical impact; however, with the appropriate routine risk minimization through labelling and additional risk minimizations measures in place to communicate to physicians the correct procedures for handling, reconstitution, dilution (if required), and administration procedures of romiplostim, the risk-benefit balance remains favorable. |
| Public health impact | Due to the relatively small number of patients exposed to the drug, and the low number of medication error events reported in both the clinical study and postmarketing setting, the public health impact is considered to be low.. |

Page 2 of 2

CI = confidence interval; HAT = home administration training; HCP = healthcare professional; ITP = immune (idiopathic) thrombocytopenic purpura; MDS = myelodysplastic syndrome; MedDRA = Medical Dictionary of Regulatory Activities; SmPC = Summary of product characteristics; SMQ = Standardised MedDRA Query

SVII.3.2 Presentation of the Missing Information

Not applicable.

## Part II: Module SVIII - Summary of the Safety Concerns

### Table 14. Summary of Safety Concerns

| | |
|---|---|
| Important identified risks | Romiplostim medication errors (dosing/administration) |
| Important potential risks | None |
| Missing information | None |

## PART III: PHARMACOVIGILANCE PLAN (INCLUDING POSTAUTHORIZATION SAFETY STUDIES)

### *III.1 Routine Pharmacovigilance Activities*

Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection are presented in Table 15.

**Table 15. Specific Adverse Reaction Follow-up Questionnaires**

| Follow-up Questionnaire (Annex 4) | Safety Concern(s) | Purpose |
|---|---|---|
| Nplate (Romiplostim) safety questionnaire for medication errors | Romiplostim medication errors (Dosing/Administration) | Monitor and evaluate postmarketing and clinical study safety data in order to further characterize the nature of romiplostim medication errors. |

### *III.2 Additional Pharmacovigilance Activities*

There are no planned or ongoing category 1 to 3 postauthorization studies.

### *III.3 Summary Table of Additional Pharmacovigilance Activities*

There are no planned or ongoing romiplostim category 1 to 3 studies.

## PART IV: PLANS FOR POSTAUTHORIZATION EFFICACY STUDIES

No efficacy studies that are specific obligations and/or conditions of the marketing authorization are planned or ongoing.

# PART V: RISK MINIMIZATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMIZATION ACTIVITIES)

## Risk Minimization Plan

*V.1 Routine Risk Minimization Measures*

**Table 16. (Table Part V.1) Description of Routine Risk Minimization Measures by Safety Concern**

| Safety Concern | Routine Risk Minimization Activities |
|---|---|
| Important Identified Risks | |
| Romiplostim medication errors (Dosing/administration) | Routine risk communication:<br>• SmPC Section 4.2<br>• SmPC Section 4.4<br>• SmPC Section 4.8<br>• SmPC Section 4.9<br>• SmPC Section 6.5<br>• SmPC Section 6.6<br>• PL Section 3<br>• PL Section 6<br>Routine risk minimization activities recommending specific clinical measures to address the risk:<br>• Detailed instructions for calculation, reconstitution, dilution (if required), and administration procedures are provided in SmPC Section 4.2<br>• Recommendation to discontinue Nplate and monitor platelet counts if an overdose result in an excessive increase in platelet counts associated with thrombotic/thromboembolic complication is included in SmPC Section 4.4 and Section 4.9<br>Other risk minimization measures beyond the PI:<br>• Pack size: None<br>Legal status: Restricted medical prescription |

PI = Prescribing Information; PL = Package Leaflet; SmPC = Summary of Product Characteristics

*V.2 Additional Risk Minimization Measures*

**Table 17. Additional Risk Minimization Measure Healthcare Professional Educational Guide: Dosing Calculator for Physicians Involved in the Prescribing of Romiplostim to Adults and Children > 1 Year of Age**

| | |
|---|---|
| Objectives | Educational material will be provided to address the following risks:<br>• Medication errors (dosing/administration) |
| Rationale for the additional risk minimization activity | • To communicate to physicians the appropriate Nplate dose calculation.<br>• To communicate to physicians the correct procedures for handling, reconstitution, dilution (if required), and administration procedures of Nplate |
| Target audience and planned distribution path | Target audience includes physicians. Distribution can be hard copy or any other means as deemed appropriate, in accordance with national competent authority requirements |
| Plans to evaluate the effectiveness of the interventions and criteria for success | The effectiveness of the dosing calculator will be evaluated via<br>• Collection and assessment of process metrics (eg, overall distribution)<br>• Postmarketing and clinical study data and report in PBRER/PSURs |
| Evaluation of the effectiveness of risk minimization activities | Safety assessment based on the postmarketing and clinical study data indicates no change in the risk benefit profile. |

PBRER = Periodic Benefit Risk Evaluation Report; PSUR = Periodic Safety Update Report

**Table 18. Additional Risk Minimization Measure: Healthcare Professional and Patient Educational Guide: Home Administration Training Pack to Physicians Who Express an Interest in Initiating Self-administration for Specific Adult Subjects**

| | |
|---|---|
| Objectives | Educational material will be provided to address the following risks:<br>• Medication errors (dosing/administration) |
| Rationale for the additional risk minimization activity | To communicate to physicians and patients who are self-administering of the correct procedures for reconstitution and administration of Nplate.<br>To communicate to physicians the monitoring needed for subjects who self-administer Nplate. |
| Target audience and planned distribution path | Target audience include physicians and adult patients. Distribution can be hard copy or any other means as deemed appropriate, in accordance with national competent authority requirements. |
| Plans to evaluate the effectiveness of the interventions and criteria for success | The effectiveness of the HAT pack will be evaluated via<br>• Collection and assessment of process metrics (eg, distribution):<br>• Assessment of outcome measures: It was measured by Study 20120269 and Human Factors Engineering (HFE) study and there are no plans to measure further<br>• Postmarketing and clinical study data and report in PBRER/PSURs<br>Criteria for success:<br>• Safety assessment based on the postmarketing and clinical study data indicates no change in the risk benefit profile |

Page 1 of 2

Footnotes, including abbreviations, are defined on the last page of this table.

**Table 18. Additional Risk Minimization Measure: Healthcare Professional and Patient Educational Guide: Home Administration Training Pack to Physicians Who Express an Interest in Initiating Self-administration for Specific Adult Subjects**

| | |
|---|---|
| Evaluation of the effectiveness of risk minimization activities | Human factors engineering (HFE) study: Results from the HFE study in 29 ITP subjects and 1 caregiver of an ITP subject did not show any failures resulting from improper reconstitution in self-administration. Four failures (out of 120 sample injections; 3.3%) were the result of drawing less than the intended amount of reconstituted drug; participants either misjudged the reference point of the plunger head or counted in the wrong direction on the syringe.<br>Failure modes effects analysis (FMEA) study: Improper reconstitution was considered a low risk, and drawing an insufficient amount of reconstituted product was considered a low to medium risk, depending on the cause. Both of these ratings are due to the kit's instructions, the kit's design, visible detection by the subject, and availability of training/education from kit and HCP.<br>Study 20120269: Results from this study showed that most adult subjects (87.5%) were able to administer romiplostim correctly without HCP intervention after the HAT pack training. An HCP intervened in 5 instances to correct the administration of romiplostim at the first standard-of-care 4-week visit. For each of these instances, there are instructions and specific wording in the current HAT pack training materials which explain the corresponding risk minimization steps to be taken. The results of this study highlight the importance of adult patient selection by the physician and supervising the adult patient or caregiver again after the first 4 weeks of self-administration (as required by the EU SmPC and the HAT pack training materials). |

Page 2 of 2

EU = European Union; FMEA = failure modes effects analysis; HAT = home administration training; HCP = healthcare professional; HFE = human factors engineering; ITP = idiopathic (immune) thrombocytopenic purpura; PBRER = Periodic Benefit Risk Evaluation Report; PSUR = Periodic Safety Update Report; SmPC = Summary of Product Characteristics

*V.3 Summary of Risk Minimization Measures*

**Table 19. (Table Part V.3) Summary Table of Pharmacovigilance Activities and Risk Minimization Activities by Safety Concern**

| Safety Concern | Risk Minimization Measures | Pharmacovigilance Activities |
|---|---|---|
| Important Identified Risks | | |
| Romiplostim medication errors (dosing/ administration) | Routine risk minimization measures:<br>• SmPC Section 4.2, where detailed dosing instructions are provided<br>• SmPC Section 4.4, where recommendation to monitor platelet counts is given<br>• SmPC Section 4.8<br>• SmPC Section 4.9, where recommendation to monitor platelet counts is given<br>• SmPC Section 6.5<br>• SmPC Section 6.6<br>• PL Section 3<br>• PL Section 6<br>• Legal status: Restricted medical prescription<br>Additional risk minimization measures:<br>• Dosing calculator<br>• HAT pack (intended for use with adult patients) | Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:<br>• adverse event follow-up form for adverse reaction: Nplate (Romiplostim) safety questionnaire for medication errors<br>Additional pharmacovigilance activities:<br>• None |

HAT = home administration training; PL = Package Leaflet; SmPC = Summary of Product Characteristics

## PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

### Summary of Risk Management Plan for Nplate® (romiplostim)

This is a summary of the risk management plan (RMP) for Nplate®. The RMP details important risks of Nplate®, how these risks can be minimized, and how more information will be obtained about Nplate®'s risks and uncertainties (missing information).

Nplate®'s summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Nplate®, should be used.

This summary of the RMP for Nplate® should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all of which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Nplate®'s RMP.

### I. The Medicine and What it is Used for

Nplate® is used to treat adult patients with primary immune thrombocytopenia (ITP) and children aged 1 year and over with chronic ITP who may or may not have had their spleen removed and who have previously been treated with corticosteroids or immunoglobulins, where these treatments don't work (see SmPC for the full indication). It contains romiplostim as the active substance and it is given by subcutaneous injection.

Further information about the evaluation of Nplate®'s benefits can be found in Nplate®'s EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage. Link to product's EPAR summary landing page on the EMA webpage: https://www.ema.europa.eu/en/medicines/human/EPAR/Nplate

### II. Risks Associated With the Medicine and Activities to Minimize or Further Characterize the Risks

Important risks of Nplate®, together with measures to minimize such risks and the proposed studies for learning more about Nplate®'s risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be:

- Specific Information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals.
- Important advice on the medicine's packaging;
- The authorized pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;

- The medicine's legal status — the way a medicine is supplied to the public (eg, with or without prescription) can help to minimize its risks.

Together, these measures constitute *routine risk minimization* measures.

In the case of Nplate®, these measures are supplemented with *additional risk minimization measures* mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed including Periodic Safety Update Report (PSUR) assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of Nplate® is not yet available, it is listed under 'missing information' below.

*II.A. List of Important Risks and Missing Information*

Important risks of Nplate® are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Nplate®. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected.

| **List of important risks and missing information** | |
|---|---|
| Important Identified Risk | • Romiplostim medication errors (dosing/administration) |
| Important Potential Risk | None |
| Missing Information | None |

*II.B. Summary of Important Risks*

| **Important identified risk: Medication errors** | |
|---|---|
| Evidence for linking the risk to the medicine | Although a low number of reports of medication error were received from clinical studies, postmarketing data has provided real-world examples of the kinds of medication error that are possible. |
| Risk factors and risk groups | Subjects with ITP receiving (and/or self-administering [adult subjects]) treatment with romiplostim. |
| Risk minimization measures | Routine risk minimization measures:<br>• SmPC Section 4.2<br>• SmPC Section 4.4<br>• SmPC Section 4.8<br>• SmPC Section 4.9<br>• SmPC Section 6.5<br>• SmPC Section 6.6<br>• PL Section 3<br>• PL Section 6<br>• Pack size: None<br>• Legal status: Restricted medical prescription<br>Additional risk minimization measures:<br>• Dosing calculator<br>• Home administration training pack |

*II.C. Postauthorization Development Plan*

*II.C.1. Studies Which Are Conditions of the Marketing Authorization*

There are no studies which are conditions of the marketing authorization or specific obligation of Nplate®.

*II.C.2. Other Studies in Postauthorization Development Plan*

There are no studies required for Nplate®.

## Annex 4. Specific Adverse Drug Reaction Follow-up Forms

### Table of Contents

Follow-up forms

| Follow-up Form Title | Version Number | Date of Follow-up Version |
|---|---|---|
| Nplate (Romiplostim) safety questionnaire for medication errors | Not applicable | 04 August 2022 |

AMGEN®

# NPLATE (Romiplostim) Safety Questionnaire for Medication Errors

AER #



## 1. PATIENT INFORMATION

Patient Initials (Confidential)

Age at Time of Event

Gender: ☐ Male ☐ Female

Weight: _____ lb _____ kg

Date of Event (dd/mm/yyyy)

Date of this Report (dd/mm/yyyy)

## 2. NPLATE ADMINISTRATION INFORMATION

Start date (dd/mm/yyyy): _____ Stop date: _____

Last dose received (mcg): _____ Intended dose (mcg): _____ Batch/Lot # _____

Platelet count before error: _____ x $10^9$/L Date: _____

Who administered the drug when the error occurred?

☐ Healthcare Professional (specify): ☐ Physician ☐ Nurse ☐ Pharmacist

☐ Patient ☐ Caregiver (not healthcare professional)

☐ Other (specify): _____

## 3. MEDICAL HISTORY (If not previously reported, please provide as much detail as possible.)

## 4. TYPE OF MEDICATION ERROR (Please describe how the error occurred, check all that apply and provide additional details in Section 6.)

☐ Prescribing error: ☐ Incorrect dose calculation ☐ Other (specify) _____

☐ Improper storage: _____

☐ Dispensing error: _____

☐ Preparation error: ☐ Incorrect reconstitution/dilution ☐ Incorrect diluent ☐ Other (specify) _____

☐ Administration error: ☐ Incorrect route of administration ☐ Other (specify) _____

☐ **Consequences of error**: ☐ Error resulting in overdosage ☐ Error resulting in underdosage ☐ Error resulting in unclear dosage

Other (specify) _____

☐ Repetitive error for the same patient: How many times? _____ ☐ Same type of error or different types of errors? _____

## 5. FACTORS INVOLVED IN MEDICATION ERROR (Please check all that apply.)

Health Authorities have identified various factors for medication errors. Please check all that apply in this case.

☐ Poor communication
☐ Confusing package leaflet
☐ Lack of employee knowledge
☐ Dispensing error
☐ Misinterpreted handwriting
☐ Labeling packaging
☐ Confusing patient pack material
☐ Drug name confusion
☐ Lack of training
☐ Lack of patient understanding about drug's directions
☐ Other, specify: _____

## 6. CLINICAL SEQUENCE OF EVENTS (If not previously reported, please provide as much detail as possible.)

Please provide the chronological clinical sequence of events (with dates). Please provide as much detail as possible as to how the medication error occurred and at what step in the process did the error occur. Continue overleaf if necessary.

Did any adverse events occur in association with the medication error? ☐ No ☐ Yes If yes, please provide details and any corrective action taken:

Platelet count after dosage associated with the medication error: _____ x $10^9$/L Date (dd/mm/yyyy): _____

Was there anything that could have helped prevent this error? ☐ No ☐ Yes
Please specify:

Amgen
Office Fax:

**REPORTER** Name:
Address:
City: State/
Country: Province:
Email: Postal Code:
Phone: (include country code)

**Signature** _____
**Title** _____ **Date** _____

## Annex 6. Details of Proposed Additional Risk Minimization Activities (if applicable)

### Approved key messages of the additional risk minimization measures

- **Additional risk minimization measures**

The MAH shall agree the details of the following educational tools with the National Competent Authorities and must implement such programme nationally.

**Dose calculator**

- Physicians involved in the prescribing of romiplostim are provided with a dosing calculator to simplify the calculation of the correct dose and as a guide to the correct reconstitution, dilution (if required) and administration procedures.

**Home Administration Training (HAT) pack**

- Physicians who express an interest in initiating self-administration for specific patients are provided with a HAT pack for those patients. The HAT pack includes materials for HCPs on how to select and train patients for self-administration of romiplostim; and for patients, in order to help them with the process of preparation and self-administration of the correct dose of romiplostim.
- As self-administration of Nplate is not allowed for paediatric patients, the HAT pack is intended for use with adult patients and not with paediatric patients.