1. Executive Summary

1.1. Introduction

Romiplostim was approved in the European Union (EU) via Centralized Procedure on 04 February 2009 for the treatment of adult cITP splenectomised patients who are refractory to other treatments (eg, corticosteroids, immunoglobulins) and as second-line treatment for adult non-splenectomised patients where surgery is contraindicated. As part of the Nplate® (romiplostim) Risk Management Plan, Amgen proposed and implemented an observational study assessing the long-term safety of romiplostim treatment in real-life clinical practice in three Nordic countries (Amgen study identifier 20070797). The Nordic Country Patient Registry for Romiplostim (NCPRR) was designed to assess the long-term risk profile of the product, providing additional long-term data relating to the safety of romiplostim, Specifically, the NCPRR was designed to fulfill the post-marketing pharmacovigilance (PV) requirements of the EMA. The purpose of the NCPRR is to assess the safety of romiplostim in post-marketing clinical practice settings in the Nordic region.

1.2. Primary Objective

• To estimate the event rate of increased BM reticulin and/or BM fibrosis with associated clinical signs, confirmed by BM biopsy findings among adults with cITP who are receiving romiplostim.

The term event rate was used throughout as not all included events were incident.

1.3. Secondary Objectives

Objectives related to other important risks (identified or potential) for romiplostim or aspects of clinical management are as follows:

• To describe the phenomenon of worsened thrombocytopenia (platelet count significantly reduced to, or below, baseline platelet count levels) after romiplostim cessation among adult cITP patients.

• To study the event rate of thrombocytosis (platelet count > 450×10^9/L) among romiplostim-treated adult cITP patients with/without adverse events.

• To describe the event rate of thrombotic/thromboembolic events and the distribution of specific diagnoses of these thrombotic/thromboembolic events in a romiplostim-exposed cohort and in an unexposed cohort.

• To assess the event rate of haematological malignancies and pre-malignant states (focused on acute myelogenous leukaemia (AML) and myelodysplastic syndromes (MDS)) in a romiplostim-exposed cohort and in a romiplostim-unexposed cohort.

• To describe clinically significant bleeding and/or receipt of rescue medications (medications that quickly, even if temporarily, raise platelet counts, including intravenous [IV] immunoglobulin [IVIG], IV Rho immunoglobulin [RhIG], or IV glucocorticoids) in predefined romiplostim therapy periods.

• To describe the event rate of concurrent leucocytosis and anaemia (measured by laboratory test results taken within 4 weeks of each other).

• To describe patient safety profiles, including the event rate of acute renal failure (renal impairment is an important potential risk for romiplostim).

• To measure the impact of the European Union (EU) dosing rule on the cohort of romiplostim-exposed patients.

1.4. Results

This 12th annual and final report includes 6024 patients with chronic immune thrombocytopenia (cITP) with a confirmed ITP-related hospital contact in the period from 01 April 2009 through 31 December 2018 and includes 285 (4.7%) romiplostim-exposed and 5739 (95.3%) unexposed patients. An additional 332 cITP patients have been added to this study since previous report (also covering up to 31 December 2018), including 23 romiplostim-exposed patients.

Females comprised a majority of the unexposed population (57.6%) but were a minority of the romiplostim-exposed population (45.3%). The study population includes 4360 (72.4%) patients with incident cITP at study inclusion, including 212 (4.9%) romiplostim-exposed patients (corresponding to 74.4% of the total romiplostim-exposed patient group).

Romiplostim-exposed patients had a severe ITP profile. In the year prior to cITP diagnosis, romiplostim-exposed patients were observed to have high frequencies of leucocytosis (61.8%), anaemia (9.5%), or an episode of bleeding requiring hospitalisation (29.5%). In the 6 months prior to cITP diagnosis, a high proportion of romiplostim-exposed patients were observed to have had any previous ITP therapies (71.6%), particularly two or more ITP therapies (36.1%). At date of cITP diagnosis, a high proportion of romiplostim-exposed patients had a prior history of splenectomy (26.7%), low platelet count of $<50 \times 10^9$/L in 90 days prior to cITP diagnosis (53.0%),

Charlson Comorbidity Index >2 (13.3%), a high burden of comorbid diabetes (17.9%), and hypertension (30.2%).

During the study period, a total of 37.2% (*n*=106) of the 285 romiplostim-exposed patients had undergone ≥1 bone marrow (BM) biopsy, and 15.8% (*n*=45) had ≥2 BM biopsies. Most of the 285 romiplostim-treated patients (89.8%) did not have a record of a BM biopsy performed either before or after romiplostim exposure or before and after romiplostim exposure. Only 29 had a BM biopsy both before and after romiplostim exposure. Out of these 29 patients, 19 had re-examined samples. Therefore, potential changes in BM reticulin with romiplostim exposure could only be assessed in 19 romiplostim-exposed patients. Worsening of BM reticulin/fibrosis grade (MF grade) after romiplostim exposure was observed in less than five patients. No worsening or unchanged BM grade after romiplostim exposure was found in the remaining patients with re-examined biopsies.

The event rate for thrombocytosis together with any hospital-diagnosed thrombotic/thromboembolic event was 0.01 per 1000 person-weeks (PW) (95% confidence interval [CI]: 0.01-0.02) in 5739 romiplostim-unexposed patients and 0.14 per 1000 PW (95% CI: 0.06-0.27) among 285 romiplostim-exposed patients.

Among 285 romiplostim-exposed patients, the event rates for myocardial infarction, stroke, and deep venous thrombosis were 0.14 per 1000 PW (*n*=8; 95% CI: 0.06-0.27, 0.19 per 1000 PW (*n*=11; 95% CI: 0.10-0.34), and 0.26 per 1000 PW (*n*=15; 95% CI: 0.15-0.44), respectively. Among 5739 unexposed patients, 174 had a myocardial infarction, for an event rate of 0.11 per 1000 PW (95% CI: 0.09-0.12); 206 had a stroke (0.13 per 1000 PW [95% CI: 0.11-0.14]); 125 had deep venous thrombosis (0.08 per 1000 PW [95% CI: 0.06–0.09]); and 109 had a pulmonary embolism (0.07 per 1000 PW [95% CI: 0.05–0.08]).

Among 285 romiplostim-exposed patients, 13 first-time haematological malignancies were reported, for an event rate of 0.23 per 1000 PW (95% CI: 0.12-0.39). The rate of haematological malignancy was higher within the first year of romiplostim treatment and the short interval for pathogenesis (median time 46 weeks) may contribute an argument against causality as most estimates of latency periods for lymphomas range from 2 to 10 years, and for leukemias they range from 1.5 to 35 years. Although latency periods as low as 0.4 years cannot be entirely ruled out (Howard, 2014). Among 5739 unexposed patients, 148 had a first-time haematological malignancy, for an event rate of 0.09 per 1000 PW (95% CI: 0.08-0.11).

In addition to the 285 romiplostim-exposed cITP patients included in this report, an additional 61 other users (“off-label users”) of romiplostim were identified, including nine

potential ITP patients who did not meet the inclusion criteria at the cut-off date for this report.

Since severity of thrombocytopenia may be associated with an increased event rate of some of the secondary objectives, confounding-by-indication is an issue in this obervational study. The confounding in this study arises from an imbalance in covariates, with romiplostim-exposed patients having severe ITP, a great use of glucocorticoids, and high comorbidity burden. Furthermore, patterns of channelling “sicker” ITP patients into romiplostim treatment may change during the study period; romiplostim may be used to treat patients with less severe ITP as physicians gain more experience in prescribing the drug. Post-hoc analyses restricted to subpopulations of patients with lower platelet counts and/or treatment with second-line therapies addressed some confounding. However, the effects of residual confounding cannot be excluded. Therefore, romiplostim-exposed and unexposed comprise different patient populations that are not comparable due to confounding. In addition, due to the small sample size, the annual assessments are descriptive in nature. Thus, comparison of the results between exposed and unexposed patients, originating from the descriptive analyses, should be avoided.

1.5. Conclusion

This large observational study has provided valuable information about the use of romiplostim in routine clinical practice and additional safety data for romiplostim use among cITP patients, in particular by providing absolute event rates that can be compared with other romiplostim-exposed cohorts in trials and in routine clinical care. The study is the only multinational cITP cohort including virtually all cITP patients in three countries combining data from population-based health databases with detailed data from medical records collected in hospital settings (inpatient or outpatient) with comprehensive ascertainment of romiplostim exposure by medical record review of all confirmed cITP patients. The study reflects routine clinical care within a total of 6024 cITP patients, but only 285 romiplostim-exposed patients. Uptake of romiplostim in the three countries has been lower than originally expected at the study design stage in 2008, resulting in a limited number of romiplostim-exposed patients available for analysis. Furthermore, a relatively low proportion of romiplostim-exposed patients underwent BM biopsy, with an even smaller proportion undergoing repeat biopsy. Therefore, potential changes in BM reticulin with romiplostim exposure could only be assessed in 19 exposed patients who had a BM biopsy both before and after romiplostim exposure and whose samples could be re-examined. Among these 19 patients, any

temporal relationship between exposure to romiplostim and changes to BM as assessed by biopsy is limited. This may be indicative of clincians unwilling to recommend invasive testing unless necessary in a real world practice. Overall, the event rates for the study outcomes were low and statistically imprecise, but they are in line with the rates reported in a clinical trial. Direct comparison of exposed and unexposed patients should be interpreted very cautiously due to the challenges of confounding by indication.