Population Based Prospective Annual Assessment of Safety of Romiplostim Treatment in Adult Patients with Chronic Idiopathic (Immune) Thrombocytopenic Purpura (ITP) Based on National Health Registry Systems in Denmark, Sweden, and Norway (Also known as the Nordic Country Patient Registry for Romiplostim [NCPRR])

Product: Romiplostim (Nplate™)

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Study Sponsor:
Amgen Global Safety (AGS) Department
Amgen Inc.
One Amgen Center Drive
Thousand Oaks, CA 91320-1799
805-447-1000

Key Sponsor Contact:
PPD MD, DrPH, Medical Director
Center for Observational Research
1120 Veterans Blvd, So San Francisco, CA, 94080
1-650-244-3622

Key Investigator Contact:
PPD, Professor, MD, DMSc, PhD
Head of Department
Department of Clinical Epidemiology
Aarhus University Hospital
Olof Palmes Allé 43-45
8200 Aarhus N, Denmark
Phone: PPD

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Protocol Synopsis

Population Based Prospective Annual Assessment of Safety of Romiplostim Treatment in Adult Patients with Chronic Idiopathic (Immune) Thrombocytopenic Purpura (ITP) Based on National Health Registry Systems in Denmark, Sweden, and Norway

Product Current Development/Marketing Phase

Post-marketing safety surveillance

Disease and Condition of the Patient Registry

The study titled *Population Based Prospective Annual Assessment of Safety of Romiplostim Treatment in Adult Patients with Chronic ITP Based on National Health Registry Systems in Denmark, Sweden, and Norway* is also known as the "Nordic Country Patient Registry for Romiplostim (NCPRR)." The NCPRR is a patient registry established on the basis of the National Health Registry Systems (NHRS) of 3 Nordic countries: Denmark, Sweden, and Norway. Patients who receive romiplostim therapy between January 2009 and December 2019 will be included in the patient registry through the existing NHRS databases.

The purpose of the NCPRR is to obtain long-term data on the safety of romiplostim therapy and to fulfill romiplostim post-approval pharmacovigilance (PV) requirements.

Primary Objective

- To estimate the incidence rate of increased bone marrow (BM) reticulin and/or BM fibrosis with associated clinical signs[1], confirmed by BM biopsy findings in adults with chronic ITP receiving romiplostim

Secondary Objectives

Potential clinical risks:

- To describe the phenomenon of worsened thrombocytopenia (platelet count significantly reduced to, or below, baseline platelet count levels) after romiplostim cessation among adult chronic ITP patients
- To study the incidence rate of thrombocytosis (platelet count > 450 x 10^9/L) among romiplostim-treated adult chronic ITP patients with/without adverse events
- To describe the incidence rate of thrombotic/thromboembolic events, and the distribution of specific diagnoses of these thrombotic/thromboembolic events for a romiplostim-exposed cohort and an unexposed cohort
- To assess the incidence rate of hematological malignancies and pre-malignant states (focused on acute myelogenous leukemia [AML] and myelodysplastic syndromes [MDS]) for a romiplostim-exposed cohort and an unexposed cohort

[1] Clinical signs: any of the following: splenomegaly, hepatomegaly, leukocytosis, and cytopenia.

- To describe clinically significant bleeding and/or receipt of rescue medication (any new ITP medication prescribed to a chronic ITP patient during romiplostim therapy) in predefined romiplostim therapy periods (Section 7.1)
- To describe the incidence rate of concurrent leukocytosis and anemia (measured by laboratory test results taken within 4 weeks of each other)
- To describe patient safety profiles, including the incidence rate of renal failure among adult chronic ITP patients with renal impairment medical condition at the time romiplostim therapy is initiated
- To measure the impact of the EU dosing rule in the cohort of romiplostim exposed patients

Potential BM abnormal findings:

- To describe the prevalence of reticulin and collagen fiber content in the first BM biopsy of adult chronic ITP patients prior to romiplostim exposure, by splenectomy status
- To assess the incidence of collagen fibrosis with associated clinical signs confirmed by findings in BM biopsies of adults with chronic ITP either receiving or not receiving romiplostim
- To study the incidence of chronic idiopathic myelofibrosis (CIMF, primary myelofibrosis) according to the World Health Organization (WHO) diagnostic criteria for adults with chronic ITP either receiving or not receiving romiplostim
- To assess overall and specific incidence of BM fibrosis, including reticulin and collagen fiber content formation, and CIMF among adult chronic ITP patients using BM data prior to and following romiplostim therapy, regardless of clinical signs and symptoms in adults with chronic ITP either receiving or not receiving romiplostim

Romiplostim Off-label Use:

- To describe the romiplostim utilization pattern in patients without adult chronic ITP

Hypotheses

The NCPRR is descriptive in nature for the purpose of hypothesis generation. There is no specific hypothesis for each specific outcome of interest.

Study Design

The NCPRR is established on the basis of the NHRS of 3 Nordic countries: Denmark, Sweden, and Norway.

The study period will be between 01 January 2009 (starting date) and 31 December 2019 (ending date). Interim study reports will be developed for yearly submission to the Agency. Each annual report will describe events occurring from 01 January through 31 December of the reporting period with cumulative results. All data sources will use the same cutoff date in calendar time, December 31st of the latest year for all data obtained from the NHRS databases. The patient experience (patient time) for all patients who receive at least 1 dose of romiplostim therapy will be

included in the romiplostim exposure cohort after they receive romiplostim. The patient experience with ITP before romiplostim exposure will be included in the romiplostim unexposed cohort along with that for all adult chronic ITP patients who never receive romiplostim therapy during the study period.

Adult chronic ITP cohorts (romiplostim "Exposed Cohort" and "Unexposed Cohort") will include adult patients identified as having chronic ITP (incident and prevalent cases identified through both hospital discharge registry and outpatient clinic registry, as described by Frederiksen and Schmidt, 1999) on or after the starting date, and up to 1 year prior to the ending date. All patients will be followed-up for **at least 1 year and up to 11 years** in either the romiplostim Exposed Cohort or Unexposed Cohort. Incident and recurrent outcomes of interest will be assessed on an annual basis.

All clinical outcomes (eg, thrombotic/thromboembolic events, hematological malignancies, and other potential outcomes of interest) will be identified by International Classification of Diseases – 10th Revision (ICD-10) codes from the NHRS databases (eg, hospital discharge registry, outpatient clinic registry, pathology registry, death registry, cancer registry, birth registry, and prescription registry) or by review of electronic medical records and/or paper medical charts. As needed, suspected and identified cases will be medically confirmed by review of electronic medical records and/or paper medical charts, laboratory test results, BM biopsy reports, pathology data, pharmacy data, and other relevant health records. Laboratory data will be used to determine thrombocytosis and worsened thrombocytopenia after cessation of romiplostim.

Because ITP is a diagnosis of exclusion and secondary causes of thrombocytopenia may be difficult to diagnose, some patients will require review of medical records and laboratory data including bone marrow exams, if any, prior to their first diagnosis of ITP (ICD-10: D69.3-D69.4). These will include the relevant time periods prior to their first diagnosis of ITP for all patients who have a history of any condition from Appendix 2 prior to the first diagnosis of ITP.

Cases with either increased BM reticulin or BM fibrosis (with/without associated clinical signs) and cases of hematological malignancies or disorders (eg, AML and MDS) will be ascertained using electronic medical record review. Confirmation of the diagnosis of reticulin/collagen BM, reticulin/collagen fibrosis or hematological malignancies and disorders will be carried out by evaluation of the results of BM biopsies.

The 3 selected Nordic countries gather all health-related data on their citizens through a complex system of interlinked databases. The Danish government, for example, has compiled nearly 200 registry databases (some initiated in the 1930s) on everything from medical records, hospitalization, prescriptions, laboratory and pathology results, a cancer registry, and death certificates to socioeconomic data regarding jobs and salaries. What makes the databases a prime research tool is the fact that they are all linked by the 10-digit personal identification

number, called CPR, that follows each Danish citizen from birth to death. The NHRS and related databases in Norway and Sweden are similar to Danish system.

Selected data fields for each adult chronic ITP patient (prevalent cases as of 01 January 2009, and incident cases thereafter), and patients who receive romiplostim therapy during the study period, will be extracted and analyzed to evaluate the endpoints listed in Section 6.2. These selected data fields include those for the patient population using other thrombopoietic agents, since these agents could have a confounding impact on the occurrence of study outcomes such as BM fibrosis. In addition, the study will last up to 11 years, and will include both prevalent cases between 1996 and 2008 and incident cases from 2009 to 2018. The diagnoses, treatment procedures, medications, and practice patterns may be significantly changed; therefore, the study will use an inception cohort approach to define the study cohort based upon year of initial ITP diagnosis. Depending upon the sample size, the inception cohorts may be established for the following periods: 1996 to 2000, 2001 to 2005, 2006 to 2010, 2011 to 2015, and 2016 to 2018. Patients and incident rate study outcomes will be compared among these inception cohorts.

To describe the romiplostim off-label utilization pattern, the study will also include patients without an adult chronic ITP diagnosis, but who are exposed to romiplostim. An example would be the inclusion of patients diagnosed with pediatric ITP, MDS, HIV/AIDS diagnoses, and who have received romiplostim therapy. Patients exposed to romiplostim with off-label use will be directly identified by drug codes for romiplostim as the codes are adopted in each participating country.

The selected NHRS databases have been previously used to determine the safety profile of pharmaceuticals, and have been considered among the best PV and epidemiology tools by regulatory authorities, epidemiologists, and safety specialists in both clinical medicine and research communities (Frank, 2000).

Prospective annual analyses will be conducted for the study, in which all proposed research outcomes will be assessed. The annual assessments will be descriptive in nature due to the small sample size and uncertainty of the diagnosis of some outcomes for each assessment. Results from these annual assessments and safety data from other sources (eg, clinical trials, US Patient Safety Registry [PSR], and Canada PSR) will be communicated in the appropriate context to the regulatory agency through submission of the romiplostim Periodic Safety Update Report (PSUR). In the event that a significant risk is observed in an annual assessment, an urgent ad hoc report will be submitted to the regulatory agency in the time frame defined by Amgen Standard Operating Procedures (SOPs).

The registry also can serve as an infrastructure to assess any other newly detected safety signals during post-marketing; however, new research outcomes must be reviewed and approved by the NCPRR Scientific Committee before they may be added to the study. Such modification of the study protocol will be communicated to the regulatory agency.

Primary Endpoints

- Incidence of increased BM reticulin and/or BM fibrosis with associated clinical signs[2], confirmed by findings in BM biopsies among adult chronic ITP patients
- Incidence of reticulin and collagen BM fibrosis (reticulin fibrosis and collagen fibrosis: SNOMED codes: M49000, M49001, M49020, M99611) with associated clinical signs, confirmed by findings in a BM biopsy among adults chronic ITP patients

Secondary Endpoints

Clinical Endpoints:

- Average platelet counts prior to, during, immediately after treatment cessation, and post-romiplostim therapy (study periods are defined in Section 7.1)
- Incidence of thrombocytosis (laboratory confirmation of a platelet count > 450 x 10^9/L) with/without associated symptoms or adverse events among adult chronic ITP patients
- Incidence of thrombotic/thromboembolic events (ICD-10: 180, 126)
- Incidence rate of hematological malignancies focused on AML and/or MDS
- Incidence of clinically significant bleeding and/or receipt of rescue medication for each predefined romiplostim treatment period (Section 7.1)
- Incidence of concurrent leukocytosis and anemia (measured by laboratory test results taken within 4 weeks of each other)
- Description of platelet counts and dose adjustment in µg/kg of romiplostim in patients with cITP according to dose adjustment rules specified in the European SPC

BM Endpoints:

- Prevalence of reticulin and collagen fiber content in the first BM biopsies of adult chronic ITP patients prior to romiplostim therapy by splenectomy status
- Incidence of collagen fibrosis with associated clinical signs confirmed by findings in BM biopsies among adult chronic ITP patients
- Incidence of PMF (primary myelofibrosis, ICD-10: c94.5) according to the WHO diagnostic criteria in adult chronic ITP patients who have BM data prior to and/or post romiplostim therapy
- Overall and specific incidence rate of BM fibrosis, including reticulin and collagen fiber content formation, and PMF among adult chronic ITP patients with BM data prior to and/or post romiplostim therapy
- Association between the aforementioned primary and secondary clinical outcomes and BM abnormal findings

[2] Clinical signs: any of the following: splenomegaly, hepatomegaly, leukocytosis, and cytopenia.

- Association of changes in peripheral blood with listed BM abnormal findings (3 to 6 months prior to, 3 months prior to 3 months post, and 3 to 6 months post-BM abnormal findings)

Romiplostim Off-label Use:

- Romiplostim utilization in patients without adult chronic ITP assessed by underlying disease for which romiplostim is used

Study Setting

The post-marketing romiplostim patient registry will be established on the basis of the NPRS of Denmark, Sweden, and Norway.

Estimated Sample Size

The exact sample size for the NCPRR is unknown, and is projected based upon the estimated national figure of adult chronic ITP patients, as well as the anticipated percentage of adult chronic ITP patients who may be treated with romiplostim. Based upon a conservative estimate, the study will have at least 623 adult chronic ITP patients who will receive romiplostim therapy during the study period, which will equate to more than 4,000 patient-years of follow-up. The NHRS of these 3 countries may also be capable of providing records for approximately 1,860 adult chronic ITP patients who are not exposed to romiplostim, which should provide more than 12,700 patient-years of follow-up data.

Summary of Subject Eligibility Criteria

The study population is chronic ITP patients, defined as those who have been diagnosed with ITP for more than 6 months, and who continually receive ITP treatments (eg, ITP medication), and/or have had a splenectomy procedure. Any adult (≥ 18 years) chronic ITP patient who has received at least 1 dose of romiplostim therapy, and who is registered in the NHRS of Denmark, Sweden, and Norway between 01 January 2009 and 31 December 2018, will be eligible subjects for this study. Patients will be continually followed up after discontinuation of romiplostim therapy.

Patients are excluded from the cohorts of chronic ITP patients if either of the following is present:

1. Any diagnosis of another condition associated with thrombocytopenia other than chronic ITP listed in Appendix 2 at any time prior to or within 6 months after the qualifying diagnosis for chronic ITP. Examples of thrombocytopenia associated with other diseases and conditions include systemic lupus erythematosus (SLE), HIV infection, hepatitis C virus infection, malignancy, lymphoproliferative disorders, and myelodysplastic syndrome.
2. Lack of a platelet count below 150 x 10^9/L without obvious cause in the 6 months before or after their first ITP diagnosis code

Comparison Group

Adult chronic ITP patients who are never exposed to romiplostim during the study period will be in the comparison group known as the romiplostim Unexposed Cohort. If patients in the comparison

group receive a romiplostim therapy in the subsequent annual assessment period, they will be re-classified into the romiplostim Exposed Cohort. Due to selection bias resulting from confounding by indication, comparative analyses will be inherently challenging to interpret. Therefore, any comparative analysis will be considered as exploratory for signal detection and for the purpose of hypothesis generation. In addition, according to initial dates of receiving romiplostim therapy among patients in Exposed Cohort, the follow-up time period will be separated into 2 periods: (1) follow-up time period prior to romiplostim exposure, and (2) follow-up time period following romiplostim exposure. Patient experiences in the follow-up time period prior to the initial date of receiving romiplostim therapy will be considered as another "within-patient" comparison with the patient experiences during the follow-up time period after the initial date of receiving romiplostim therapy.

Study Period and Method of Follow-up

This registry will be a part of Amgen's global effort to assess the safety of romiplostim treatment. Together with the *US Patient Safety Registry (PSR)*, the *Canada Patient Safety Registry (CPSR)*, the *US Immunogenicity Registry*, and the *US Pregnancy Registry*, Amgen will effectively assess identified and potential risks related to romiplostim therapy. The NCPRR has also been specifically designed to fulfill post-marketing PV requirements from the European regulatory authority, and will continue for 11 years (from 01 January 2009 through 31 December 2019).

Data Collection, Including Safety Data Collection

Although there is no specific need to collect data directly for each individual patient, the study may conduct additional data collection to fill some specific data gaps as needed (eg, BM data confirmation through a standard review process). No direct safety data will be collected from patients through this study, but it is possible that the study may actively review selected medical charts to confirm cases that may identify some adverse events that are specifically linked to romiplostim.

Procedures

Please refer to the study design section above.

Statistical Considerations

The NCPRR is descriptive in nature for the purpose of hypotheses generation. There is no specific hypothesis for each specific outcome of interest.

Patient records will provide person-years of data for each study cohort (Exposed and Unexposed). The incidence rates will be assessed for both the exposure and non-exposure cohorts. The incidence rates will also be assessed for both the follow-up time periods prior to and after the initial date of receiving romiplostim in the Exposed Cohort.

When sample size permits, Kaplan-Meier survival curves will be constructed for patients with events of interest for the Exposed Cohort and Unexposed Cohort.

Due to the intrinsic limitations of this type of observational study, the effects of confounding by indication may bias the results when the incidence rates of study outcomes are compared between the Exposed Cohort and Unexposed Cohort. The effects associated with confounding by indication will be considered in all analyses in order to reduce the possible impact of these effects in the comparison.

In order to reduce the effects of confounding by indication, a propensity score will be developed for each adult chronic ITP patient. A stratified analysis (by propensity score strata, disease severity, and platelet count) and multiple regression analyses will be carried out. As needed, the age-, sex-, and propensity score-matched approach may be also applied to the adult chronic ITP study population. (Inherent limitations related to propensity score are addressed in Section 8).

Cox regression models using romiplostim exposure as a time-varying covariate may be used to compare the event rates among ITP patients and the reference cohort, with an estimation of the hazard ratio and associated 2-sided 95% confidence interval. Other treatment exposures, health status, and disease condition may also be considered for inclusion in the model as time-varying covariates. The analysis will adjust for potential confounders and propensity score. Multiple event models such as Andersen-Gill models may be used to evaluate recurrent events if applicable. However, this analysis is only intended to serve exploratory and hypothesis generation purposes.

Means and 95% confidence intervals of laboratory numerical outcomes (eg, platelet counts) will be obtained and compared between the associated cohorts, and among different predefined time periods related to romiplostim treatment (Section 7.1).

All cases with BM fibrosis will be described in detailed narratives with respect to underlying disease, comorbidities, treatment history, medications, any possible risk factors, and demographic characteristics. This descriptive data will be summarized in the clinical study report.

All romisplostim-exposed patients who develop hematologic malignancies will be described in detailed narratives with respect to underlying disease, comorbidities, treatment history, medications, any possible risk factors, and demographic characteristics. This descriptive data will be summarized in the clinical study report.

Special analyses will be conducted for chronic ITP patients with renal impairment medical conditions at the time romiplostim therapy is initiated. The analysis will include multivariate analysis justifying for renal comorbidities and/or medical history, as well as stratified analysis based on renal impairment status at romiplostim therapy initiated. Other outcomes listed in this study proposal will also be described within each predefined stratum.

Analysis for romiplostim off-label users is descriptive in nature for the purpose of hypothesis generation. The analyses will describe the off-label study population in different study time periods.

Since comparative analyses will be inherently challenging to interpret, any comparative analyses will be considered as exploratory for signal detection and for the purpose of hypothesis generation. The study will also compare the incidence rates from the romiplostim exposed cohort to that from other potential sources where sufficient data may be present:

- Amgen Study 20080092 (Nplate™ Patient Safety Registry – Canada version)
- Amgen Study 20080045 (Nplate™ Patient Safety Registry – US version)
- Amgen Study 20070796 (Determination of Frequency Rates of Bone Marrow Fibrosis and Thrombotic/Thromboembolic Events in Patients with Chronic Immune (Idiopathic) Thrombocytopenic Purpura in Denmark)
- Administrative databases such as SEER, Ingenix, and GPRD, if appropriate data are available at time of analysis
- Published data on the frequency of predefined risks, such as Mufti et al (2007) and Aledort et al (2004)
- Data available from Amgen's ongoing romiplostim clinical program

The safety data will be assessed annually and the findings will be reported in appropriate context to the regulatory agency via the PSUR, and will include the following:

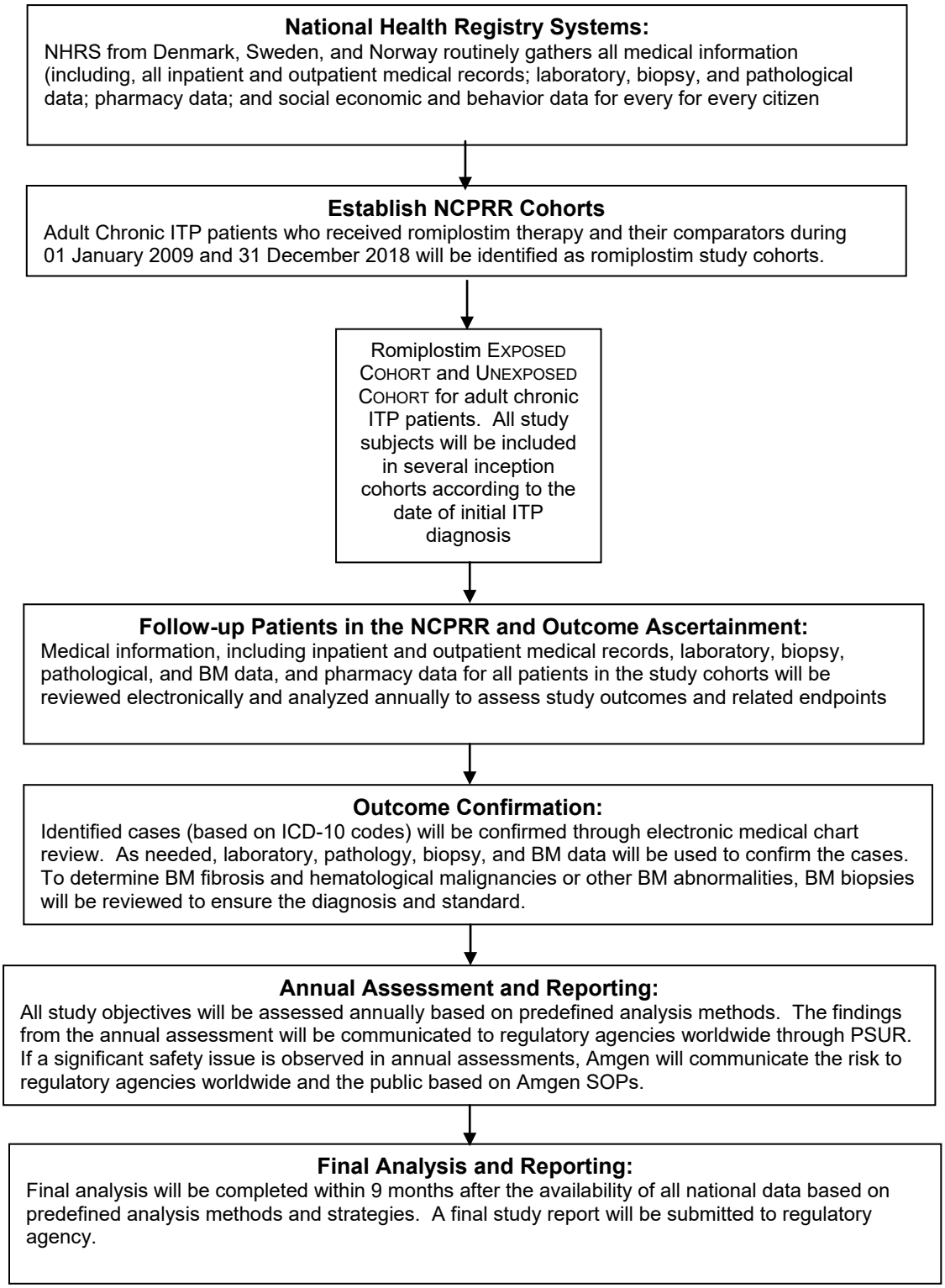
- Total number of subjects and total person-year observation time in each cohort for the current reporting period, and cumulative for all reporting periods
- Current incidence rates of study outcomes based upon data in the current reporting period, and upon cumulative data for all reporting period
- Average platelet counts in predefined romiplostim treatment periods
- Detailed descriptions of each case of BM fibrosis associated with clinical signs in the current reporting period
- Detailed description of hematological malignancy cases (eg, AML and MDS)

A final report to the regulatory agency will be completed within 9 months following the availability of all national data. The final report will be comprehensive for all primary and secondary objectives, and for related outcomes listed in Section 12.

Expected Contribution of Study Results to Current Knowledge

- Determine acute and long-term safety in real life clinical practice
- Describe the impact of romiplostim therapy on platelet count during treatment, and changes after treatment cessation
- Describe the impact of romiplostim therapy on BM fibrosis
- Describe romiplostim off-label utilization pattern

Study Design and Patient Registry Schema



Study Glossary and Definition

Abbreviation/Acronym	Definition
AGS	Amgen Global Safety
AML	Acute myelogenous leukemia
BM	Bone marrow
Chronic ITP cITP	Patients who have been diagnosed with ITP for more than 6 months, and who continually receive ITP treatments (eg, ITP related medication) and/or have had a splenectomy procedure
CIMF	Chronic idiopathic myelofibrosis (primary myelofibrosis)
Confounders	Extraneous factors that account for a difference in disease frequency between the exposure groups; associated factors serving as surrogates for these factors are also commonly called confounders
ICD-10	International Classification of Diseases – 10th Revision
Index date	Date the patient received initial romiplostim therapy in the study period, and the start date of follow-up for each study subject in the Unexposed Cohort
ITP	Idiopathic (immune) thrombocytopenic purpura
Length of disease	Time period from initial diagnosis of the disease to date of study event
MDS	Myelodysplastic syndromes
NCPRR	Nordic Country Patient Registry for Romiplostim
NHRS	National Health Registry System
Propensity score	A propensity score is an estimate of the probability that an observed entity (a person) would undergo the treatment. This probability is sometimes a predictor of outcomes
PSR	Romiplostim Patient Safety Registry designed for the United States
PSUR	Periodic Safety Update Report
PV	Pharmacovigilance
RMP	Risk Management Plan
SAP	Statistical analysis plan

Study Glossary and Definition

Abbreviation/Acronym	Definition
Selection bias	The introduction of error due to systematic differences in the characteristics between those selected and those not selected for a given study. In a sampling bias, the error is the result of failure to ensure that all members of the reference population have a known chance of selection in the sample.
SOP	Standard Operating Procedures
SPC	Summary of Product Characteristics
WHO	World Health Organization
Worsened thrombocytopenia	Platelet count is significantly reduced to or below the baseline platelet count level

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1. OBJECTIVES

The purpose of the Nordic Country Patient Registry for Romiplostim (NCPRR) is to assess the safety of romiplostim in post-marketing clinical practice settings. Since the study period will be of 11 years duration, the study will provide an infrastructure to assess the long-term risk profile of the product. The study may also be used to assess any newly identified safety signals during post-marketing periods. However, the primary purpose of the NCPRR is to fulfill romiplostim post-approval pharmacovigilance (PV) requirements of the European regulatory agency.

1.1 Primary Objective

- To estimate the incidence rate of increased bone marrow (BM) reticulin and/or BM fibrosis with associated clinical signs[3], confirmed by BM biopsy findings of adults with chronic ITP receiving romiplostim

1.2 Secondary Objectives

Potential clinical risks:

- To describe the phenomenon of worsened thrombocytopenia (platelet count significantly reduced to, or below, baseline platelet count levels) after romiplostim cessation among adult chronic ITP patients
- To study the incidence rate of thrombocytosis (platelet count > 450 x 10^9/L) among romiplostim-treated adult chronic ITP patients with/without adverse events
- To describe the incidence rate of thrombotic/thromboembolic events and the distribution of specific diagnoses of these thrombotic/thromboembolic events for a romiplostim-exposed cohort and an unexposed cohort
- To assess the incidence rate of hematological malignancies and pre-malignant states (focused on acute myelogenous leukemia [AML] and myelodysplastic syndromes [MDS]) for a romiplostim-exposed cohort and an unexposed cohort
- To describe clinically significant bleeding and/or receipt of rescue medication (any new ITP medication prescribed to a chronic ITP patient during romiplostim therapy) in predefined romiplostim therapy periods (Section 7.1)
- To describe the incidence rate of concurrent leukocytosis and anemia (measured by laboratory test results taken within 4 weeks of each other)

[3] Clinical signs: any of the following: splenomegaly, hepatomegaly, leukocytosis, and cytopenia

- To describe patient safety profiles, including the incidence rate of renal failure among adult chronic ITP patients with renal impairment medical condition when romiplostim therapy is initiated
- To measure the impact of the EU dosing rule in the cohort of romiplostim exposed patients

Potential BM abnormal findings:

- To describe the prevalence of reticulin and collagen fiber content in the first BM biopsy of adult chronic ITP patients prior to romiplostim exposure, by splenectomy status
- To assess the incidence of collagen fibrosis with associated clinical signs confirmed by findings in BM biopsies of adults with chronic ITP either receiving or not receiving romiplostim
- To study the incidence of chronic idiopathic myelofibrosis (CIMF, primary myelofibrosis) according to the WHO diagnostic criteria in adults with chronic ITP either receiving or not receiving romiplostim
- To assess overall and specific incidence of BM fibrosis, including reticulin and collagen fiber content formation, and CIMF among adult chronic ITP patients with BM data prior to and following romiplostim therapy, regardless of clinical signs and symptoms in adults with chronic ITP either receiving or not receiving romiplostim

Romiplostim Off-label Use

- To describe the romiplostim utilization pattern in patients without adult chronic ITP

2. BACKGROUND AND RATIONALE

2.1 Disease and Therapeutic Area

Idiopathic (Immune) thrombocytopenia (ITP) is an autoimmune disorder characterized by platelet destruction caused by antiplatelet autoantibodies, concurrent with evidence of inadequate platelet production by the bone marrow (McMillan, 1981).

The all-cause mortality rate in adult patients treated for ITP is approximately 4% in 75 months (Berchtold and McMillan, 1989). All currently available treatments have substantial morbidities that often require discontinuation of treatment. Thrombocytopenia is resolved in approximately 50% to 75% of patients with ITP after therapy with standard-dose corticosteroids, splenectomy, or both

(Berchtold and McMillan, 1989; Cines and McMillan, 2005). Patients refractory to these treatments may receive other treatments (including pulsed dexamethasone, danazol, colchicine, cyclophosphamide, azathioprine, staphylococcal A immunoadsorption, cyclosporin, anti-immunoglobulin D, or single-agent or combined chemotherapy), but response is generally poor (Berchtold and McMillan, 1989; Cines and McMillan, 2005).

2.2 Romiplostim Therapy for Chronic ITP

Romiplostim is a thrombopoiesis-stimulating protein that targets the thrombopoietin (TPO) receptor. Romiplostim is an Fc fusion protein (peptibody) that increases platelet production through binding and activation of the TPO receptor (also known as c-Mpl), which activates intracellular transcriptional pathways. Romiplostim was initially developed as a treatment for thrombocytopenia associated with adult ITP. Clinical trials in subjects with adult ITP have demonstrated that romiplostim is an effective and safe treatment for ITP. This molecule has the ability to increase platelet counts regardless of splenectomy status.

2.3 Rationale for the NCPRR

Clinical trials have demonstrated that romiplostim is an effective and safe treatment for adult chronic ITP. While romiplostim clinical trials have produced important data about treatment efficacy in controlling ITP, trial data may not fully reflect the diverse population that may receive romiplostim in the post-marketing setting. In addition, since this is an orphan indication, there is inherently some limitation as to the robustness of the long-term safety data. The NCPRR will potentially provide additional real-world data to help address these 2 issues.

The NCPRR will collect data from all romiplostim-treated adult chronic ITP populations in the 3 selected Nordic countries. As a result, data from the NCPRR will be representative of the real-world patient experience. Amgen plans to use the NCPRR as an infrastructure for post-marketing PV to assess the acute and long-term safety of romiplostim therapy. The study will allow Amgen to describe the natural history of the disease and incidence of co-morbidities, and the safety of romiplostim therapy, and will support risk evaluation and mitigation activities.

This registry is part of Amgen's global effort to assess the effects of romiplostim treatment. Amgen will assess observed and potential risks related to romiplostim therapy in the real-world clinical practice setting in this registry and all other pharmacovigilance efforts as listed in Amgen's romiplostim Risk Management Plan (RMP), a global regulatory document that outlines the strategic plan to assess identified

and potential risks of romiplostim. Specifically, the following are some key events noted in the RMP as identified and potential risks based on non-clinical and clinical data:

- Reversible bone marrow fibrosis in animals and increased bone marrow (BM) reticulin in humans. This observation has been identified as a reversible, on-target, expected outcome of stimulation with TPO.
- Transient worsened thrombocytopenia after cessation of treatment has been observed in clinical studies.
- A hypothetical concern regarding hematopoietic growth factors is that they may enhance the growth of existing malignancies or promote the growth of new malignancies that are influenced by the receptor-ligand axis. The TPO receptor is predominantly expressed on cells of the myeloid lineage, and there is no confirmed expression on solid tumors (Graf et al, 1996; Columbyova et al 1995); therefore, it is not expected that romiplostim will promote the growth of solid tumors. In the ITP clinical program, there is no evidence of increased neoplasia, including hematopoietic malignancies; there is, however, a potential risk that TPO receptor agonists may stimulate the progression of existing hematopoietic malignancies or MDS among patients with thrombocytopenia caused by conditions other than ITP. Ongoing clinical studies in other patient populations, including MDS, will help to assess this potential risk.

Other potential risks include:

- Thrombotic/thromboembolic complications
- Progression of increased reticulin to an irreversible BM fibrotic state

In Europe, the product label includes further dose adjustment rules that have been specified by the European regulator as a risk minimization measure of thromboembolic risk and have not been tested in clinical trials.

Dose adjustment rules as specified in the European label

Platelet count (x 10^9 /L)	Action
<50	Increase once weekly dose by 1 mcg/kg
>150 for 2 consecutive weeks[a]	Decrease once weekly dose by 1 mcg/kg
>250[a]	Do not administer, continue to assess platelet count weekly After the platelet count has fallen to < 150 x 10^9 /L, resume dosing with once weekly dose reduced by 1 µg/kg

[a] Due to the inter-individual variable platelet response, in some patients platelet count may abruptly fall below 50 x 10^9 /L after dose reduction or treatment discontinuation. In these cases, if clinically appropriate, higher cut-off levels of platelet count for dose reduction (200 x 10^9 /L) and treatment interruption (400 x 10^9 /L) may be considered according to medical judgment

To address these identified and potential safety issues, Amgen is committed to establishing a comprehensive risk management program which includes cautionary instructions in the prescribing information, PV (both routine and proactive), risk management activities, and additional clinical studies. Amgen believes these actions are appropriate and adequate to manage and minimize the safety risks of romiplostim. As additional safety data becomes available from ongoing and future clinical studies and post-marketing experience, the identified and potential risks will be re-evaluated, and risk management activities will be adjusted.

The NCPRR is specifically designed to fulfill the above post-market PV requirements by the European regulatory authority. In line with these PV requirements, the study assesses acute and long latency effects of romiplostim in real-life clinical practice in three European countries for 11 years (from 01 January 2009 to 31 December 2019).

The National Health Registry System (NHRS) of Denmark, Sweden, and Norway gather all health-related data on their citizens through a complex system of interlinked databases. The Danish government, for example, has compiled nearly 200 registry databases (some initiated in the 1930s) on various datasets from medical records, hospitalization, prescriptions, laboratory and pathology results, cancer registry, and mortality to socioeconomic data on jobs and salaries. The registry databases are population-based and complete. What makes the databases a prime research tool is the fact that they can all be linked by the 10-digit personal identification number (called CPR) that follows each Danish citizen from birth to death (Frank, 2000).

Thereby the entire lifetime information of each romiplostim-exposed patient between 01 January 2009 and 31 December 2019 (11 years) can be extracted and analyzed to meet the needs of post-marketing safety surveillance. The National Health Registry databases of the 3 countries have been previously used to determine the safety profile of pharmaceuticals, and are considered to be among the best PV and epidemiology tools by regulatory authorities, epidemiologists, and safety specialists in both the medical and scientific communities.

2.4 Study Hypothesis

The NCPRR is descriptive in nature for the purpose of hypothesis generation. There is no specific hypothesis for each specific outcome of interest.

3. PATIENT REGISTRY STUDY PLAN

3.1 Registry Design

The NCPRR is established on the basis of the NHRS of 3 Nordic countries: Denmark, Sweden, and Norway.

The study period will be between 01 January 2009 (starting date) and 31 December 2019 (ending date). Interim study reports will be developed for yearly submission to the Agency. Each annual report will describe include events occurring from 01 January through 31 December of the reporting period with cumulative results. All data sources will use the same cutoff date in calendar time, December 31st of the latest year for all data obtained from the NHRS databases. The patient experience (patient time) for all patients who receive at least 1 dose of romiplostim therapy will be included in the romiplostim exposure cohort after they receive romiplostim. The patient experience with ITP time before romiplostim exposure will be included in the romiplostim unexposed cohort, along with that for all adult chronic ITP patients who never receive romiplostim therapy during the study period.

Adult chronic ITP cohorts (romiplostim Exposed Cohort and Unexposed Cohort) include adult patients who are identified as having chronic ITP (incident and prevalent cases through both hospital discharge registry and outpatient clinic registry, as described by Frederiksen and Schmidt, 1999) on or after the starting date, and up to 1 year prior to the ending date. All patients will be followed-up for **at least 1 year and up to 11 years** in either of 2 cohorts: the romiplostim Exposed Cohort or Unexposed Cohort. Incident and recurrent outcomes of interest will be assessed on an annual basis.

All clinical outcomes (eg, thrombotic/thromboembolic events, hematological malignancies, and other potential outcomes of interest) will be identified by International Classification of Diseases – 10th Revision (ICD-10) codes from the NHRS databases (eg, hospital discharge registry, outpatient clinic registry, pathology registry, death registry, cancer registry, birth registry, and prescription registry) or by review of electronic medical records and/or paper medical charts. As needed, suspected and identified cases will be medically confirmed by review of electronic medical records and/or paper medical charts, laboratory testing results, BM biopsy reports, pathology data, pharmacy data, and other relevant health records. Laboratory data will be used to determine thrombocytosis and worsened thrombocytopenia after cessation of romiplostim.

Because ITP is a diagnosis of exclusion and secondary causes of thrombocytopenia may be difficult to diagnose, some patients will require review of NHRS databases, medical records (electronic and/or paper charts), and laboratory data including bone marrow exams, if any, prior to their first diagnosis of ITP. These will include the relevant time periods prior to their first diagnosis of ITP for all patients who have a history of other primary thrombocytopenia (D69.4) or any condition from Appendix 2 prior to the first diagnosis of ITP.

Cases with either increased BM reticulin or BM fibrosis (with/without associated clinical signs) and hematological malignancies (AML and MDS) will be ascertained using electronic medical record review. Confirmation of the diagnosis of BM reticulin/collagen fibrosis or AML/MDS will be accomplished by evaluation of the results of BM biopsies.

Selected data fields of each adult chronic ITP patient (prevalent cases as of 01 January 2009 and incident cases thereafter) and of patients who receive romiplostim therapy during the study period, will be extracted and analyzed to evaluate the endpoints listed in Section 6.2. These selected data fields include those for the patient population using other thrombopoietic agents, since these agents could have a confounding impact on the occurrence of study outcomes such as BM fibrosis. In addition, the study will last up to 11 years and it will include both prevalent cases between 1996 and 2008 and incident cases from 2009 through 2018. The diagnoses, treatment procedures, medication, and practice patterns may be significantly changed; therefore, the study will use an inception cohort approach to define the study cohort based upon year of initial ITP diagnosis. Dependent upon sample size, the inception cohorts can be established as from 1996 to 2000, 2001 to 2005, 2006 to 2010, 2011 to 2015, and 2016 to 2018.

Patients and incidence rate of study outcomes will be compared among these inception cohorts.

To describe the romiplostim off-label utilization pattern, the study will also include patients without an adult chronic ITP diagnosis, but who are exposed to romiplostim. An example would be the inclusion of patients diagnosed with pediatric ITP, MDS, HIV/AIDS diagnoses, and who have received romiplostim therapy. Patients exposed to romiplostim with off-label use will be directly identified by drug codes for romiplostim as the codes are adopted in each participating country.

These selected NHRS databases have been previously used to determine the safety profile of pharmaceuticals, and have been considered one of best PV and epidemiology tools by regulatory authorities, epidemiologists, and safety specialists in both the clinical medicine and research communities (Frank, 2000).

Prospective annual analysis will be conducted for the study, and all proposed research outcomes will be assessed in these annual analyses. The annual assessment will be descriptive in nature due to the small sample size and uncertainty of the diagnosis of some outcomes in each assessment. Results from these annual assessments will be submitted to the regulatory agency in appropriate context through the romiplostim Periodic Safety Update Report (PSUR). In the case a significant risk is observed in an annual assessment, an urgent ad hoc report will be communicated to the regulatory agency in the defined time frame according to Amgen Standard Operating Procedures (SOPs).

The registry also can serve as an infrastructure to assess any other newly detected safety signals during post marketing. However, new research outcomes must be reviewed and approved by the NCPRR Scientific Committee before they may be added to the study. Such modification of the study protocol will be communicated to the regulatory agency.

3.2 Number of Physicians

The NCPRR is established on the basis of the NHRS databases of Denmark, Sweden, and Norway. The number of physicians is unknown, but all physicians who prescribe romiplostim in Denmark, Sweden, and Norway will be included in the study.

3.3 Study Setting and Source Population

The NCPRR is a prospective annual assessment of study outcomes established on the basis of the NHRS. The study population includes chronic ITP patients, defined as

patients who have been diagnosed with ITP for more than 6 months, and who continually receive ITP treatment (eg, ITP medication) and/or have had a splenectomy procedure. All qualified adult chronic ITP patients will be the source population, regardless of romiplostim therapy status.

To describe the romiplostim off-label utilization pattern, the study will also include patients without an adult chronic ITP diagnosis who are exposed to romiplostim.

3.4 Selection of Participants (or Subject Eligibility)

3.4.1 Inclusion Criteria

Subjects in the NCPRR will be those whose health information is recorded by the NHRS of Denmark, Norway, or Sweden.

The eligible adult cITP romiplostim-exposed patients for the NCPRR must meet all of the following criteria:

- Patients must be 18 years or older at the time of chronic ITP diagnosis,
- Patients will have romiplostim therapy between 01 January 2009 and 31 December 2018, and
- Patients will have at least 6 months of medical information prior to initial date of receiving romiplostim treatment (Index Date), data from which will establish a baseline of study subjects.

The eligible adult cITP romiplostim-unexposed patients for the NCPRR must meet all following criteria:

- Patients must be 18 years or older at the time of chronic ITP diagnosis,
- Patients will not have received romiplostim therapy prior to or during the study period between 01 January 2009 and 31 December 2019, and
- Patients will have at least 6 months of medical information in the study period. The data from this period will establish baseline of subjects in the comparison group.

Eligible romiplostim-unexposed cITP patients will be the source of comparison cohorts for romiplostim-exposed cITP patients. Because potential confounding factors (eg, severity of ITP condition) may cause some biases for the study, however, robust propensity scoring and adjusted analyses will be essential (Section 12). In addition, appropriate contextualization from other recognized data sources will be used in comparisons to address selection biases.

In addition, according to initial dates of receiving romiplostim therapy among patients in the Exposed Cohort, the follow-up time period will be separated into 2 periods: (1) follow-up time period prior to romiplostim exposure, and (2) follow-up time period following romiplostim exposure. Patient experiences in the follow-up time period prior to the initial date of receiving romiplostim therapy will be considered as another "within-patient" comparison with the patient experiences during the follow-up time period after the initial date of receiving romiplostim therapy.

Eligible romiplostim Off-Label-Exposed patients will be any patient who received romiplostim therapy without an adult chronic ITP diagnosis.

3.4.2 Exclusion Criteria

Patients who are enrolled in a clinical trial for other TPO receptor agonists (eg, clinical trials for eltrombopag) will be excluded from the study.

Patients are excluded from the cohorts of chronic ITP patients if either of the following is present:

1. Any diagnosis of another condition associated with thrombocytopenia other than chronic ITP listed in Appendix 2 at any time prior to or within 6 months after the qualifying diagnosis for chronic ITP. Examples of thrombocytopenia associated with other diseases and conditions include systemic lupus erythematosus (SLE), HIV infection, hepatitis C virus infection, malignancy, lymphoproliferative disorders, and myelodysplastic syndrome.
2. Lack of a platelet count below 150 x 10^9/L without obvious cause in the 6 months before or after their first ITP diagnosis code

3.5 Number of Subjects

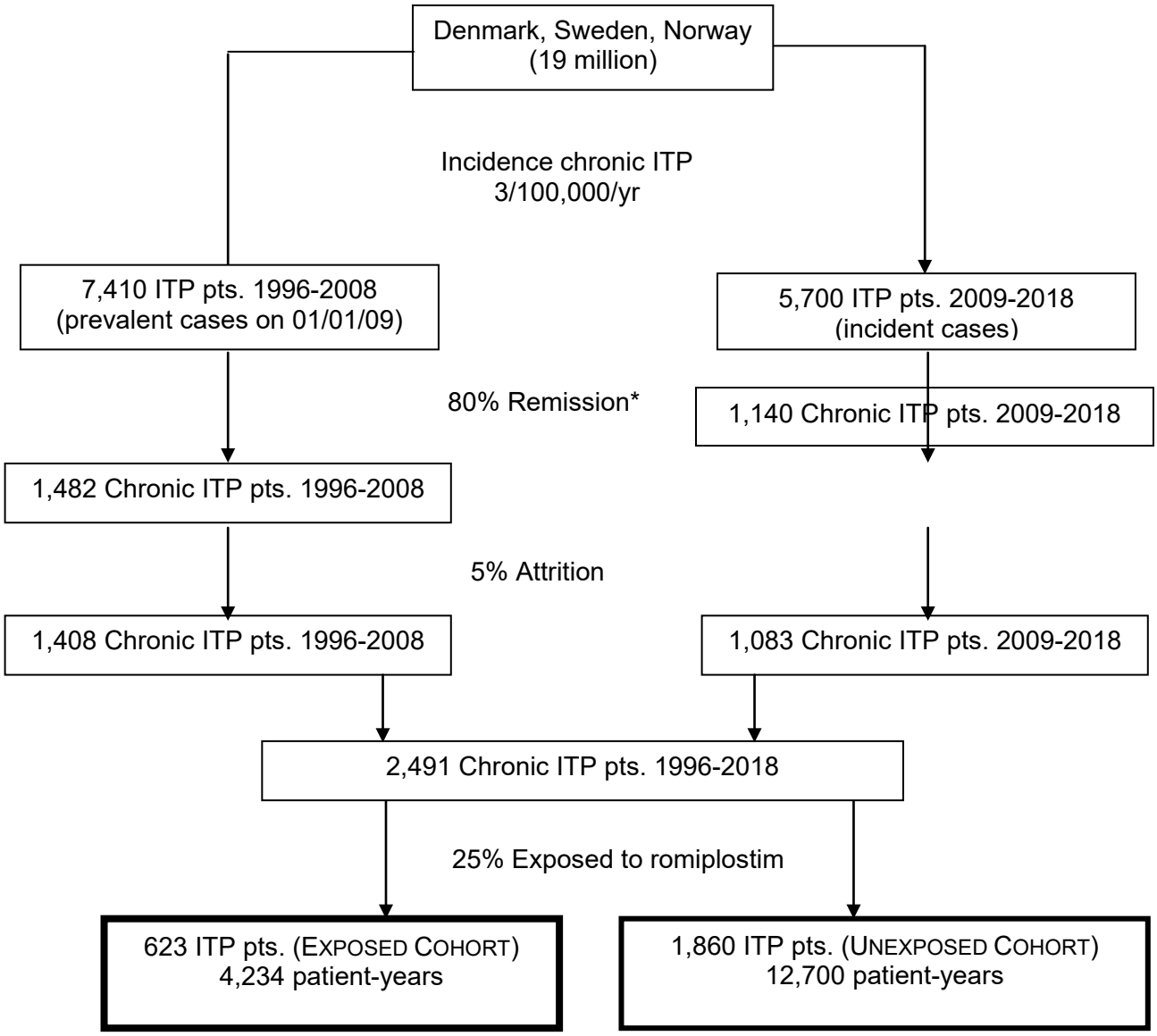
Based upon an exploratory feasibility analysis of the Danish database, the incidence of adult ITP in this country is 3/100,000 per year. Extrapolating this rate to all 3 Nordic countries, there will be 570 newly registered ITP patients per year. Record collection of ITP patients began in 1996; therefore, by the end of 2008, there will be an estimated 7410 patients with ITP. Assuming that 80% of adult ITP patients will have durable remission, 1482 will become chronic ITP patients. This number is reduced to 1408 due to an expected 5% patient attrition over time. By 2008, these patients will constitute the group of prevalent cases eligible for romiplostim. Assuming that the Exposed Cohort will include 25% of the 1408 subjects, 352 patients with chronic ITP will be exposed to romiplostim during the first year post-approval.

For the period 2008 to 2018, there will be 5700 incident cases of adult ITP. Following the assumptions mentioned above, 1140 will become chronic, 1083 will remain after the attrition, and a total of 271 adult chronic ITP patients will receive romiplostim.

In total, there will be 623 patients (4234 patient-years) in the Exposed Cohort. According to the study design, the Unexposed Cohort for adult chronic ITP patients will include 1860 patients, which will account for 12,700 patient-years of follow-up (Figure 1). This is a conservative estimation; the sample size could be larger if the market share of romiplostim is larger than 25% percent.

The number of subjects for the romiplostim-off-label exposure is unknown.

Figure 1. Estimation of Study Sample Size



*Remission includes subjects considered "cured", including acute cases, cases that underwent successful splenectomy, and cases successfully treated with non romiplostim compounds.

3.6 Study Duration for Participants

The study period for the NCPRR will be from 01 January 2009 to 31 December 2019. Patients who receive romiplostim therapy between 01 January 2009 and 31 December 2018 will be selected into the patient registry. Similarly, unexposed patients will be included in the registry Unexposed Cohort between 01 January 2009 and 31 December 2018.

All subjects in the registry will be followed until the end-of-study period (31 December 2019), death, or loss to follow-up, whichever comes first. The specific romiplostim treatment follow-up time periods are defined in Section 7.1.

4. SUBJECT ENROLLMENT

Subject enrollment is dependent on the NHRS. The NCPRR selects eligible study subjects to predefined study cohorts. The patient selection is based on diagnostic codes (ICD-10), medication, laboratory, BM, and pathological data.

4.1 Sub-Patient Group Identification

The adult chronic ITP study population is identified using diagnostic codes (ICD-10: D69.3-D69.4) for at least 6 months after the first primary ITP diagnosis, and as having received at least 1 ITP medication, and/or had a splenectomy procedure during this 6-month time period. Electronic medical records will be reviewed to confirm the diagnosis. Confirmation of the diagnosis of ITP will be carried out by clinical presentations and/or related treatment. Based upon the status of romiplostim therapy, these patients will be segregated into the Exposed Cohort and the Unexposed Cohort. The index date for patients in romiplostim Exposed Cohort is defined as the first date of receiving romiplostim therapy.

The Index Date in the exposed cohort will be the date of first exposure to romiplostim. A patient who has not been exposed to romiplostim will have an Index Date imputed based upon the date of diagnosis using 2 methods: 1) if the date of diagnosis is prior to 01 April 2009, the Index Date will be imputed as 01 April 2009 (the first date of romiplostim availability), and 2) if the date of diagnosis is 01 April 2009 or later, the date of diagnosis will be imputed as the Index Date.

5. DATA COLLECTION PROCEDURES

5.1 Primary Data Collection

The primary data collection for the NCPRR is dependent upon the NHRS. All citizens in Denmark, Sweden, and Norway are included in the systems, and all health care information for each citizen will be included in the system databases. For this reason the NCPRR will not need to actively collect data directly from patients.

Patients with a NHRS diagnosis of ITP of 6 months duration or more are selected for abstraction of medical records and collection of details of the medical history including romiplostim exposure. If a patient was not seen in hospital (in-patient or out-patient

contact, including hematology clinic visits) at least once during the reporting period, the charts for that patients for that reporting period will not be reviewed. When the patient re-appears in the hospital database in following reporting periods, the chart abstraction will resume for that patient.

Because ITP is a diagnosis of exclusion and secondary causes of thrombocytopenia may be difficult to diagnose, some patients will require review of medical records and laboratory data including bone marrow exams, if any, prior to their first diagnosis of ITP (ICD-10: D69.3-D69.4). These will include the relevant time periods prior to their first diagnosis of ITP for all patients who have a history of any condition from Appendix 2 prior to the first diagnosis of ITP.

5.2 Case Ascertainment for Clinical Events

Clinical events (eg, bleeding, thromboembolic, and hematological malignancy endpoints) will be identified and ascertained by ICD-10 diagnostic codes and/or relevant laboratory and pathology data. The detailed diagnostic codes will be provided by the study statistical analysis plan (SAP). All identified cases will be confirmed using electronic medical record review that will be blinded to romiplostim exposure. Patients observed with one of the outcomes of interest during the study will be continually followed for other outcomes until the end of study, death, or loss to follow-up, whichever comes first.

5.3 Case Ascertainment for BM Abnormality

Cases of BM fibrosis with associated clinical signs will be ascertained using electronic medical record review that will be blinded to romiplostim exposure status. Confirmation of the diagnosis of BM fibrosis will be verified by an evaluation of the results of BM biopsies and clinical presentation.

Reticulin and collagen fiber content information will be gathered from BM biopsies. Since BM biopsies are not routinely obtained when treating ITP patients, an estimate of the incidence rate of reticulin and collagen fiber content from this study would likely be inaccurate. For this reason the prevalence rate of reticulin and collagen fiber content and related grading among patients with BM biopsies stained for reticulin and collagen formation will be calculated. Only data from the first BM biopsy prior to romiplostim therapy will be included in the analysis to reduce bias. This analysis will be conducted by splenectomy status.

Adult chronic ITP patients in both the Exposed Cohort and Unexposed Cohort with both positive findings of reticulin and collagen fiber content and repeated BM biopsies will be

assessed to describe disease progression related to changes in reticulin and collagen fiber content in subsequent BM biopsies.

Incidence of BM abnormal findings (eg, PMF, reticulin, and collagen fiber content formation) will be assessed based upon only patients with BM data prior to and post romiplostim therapy.

The relationship between BM findings of reticulin and collagen fiber content and clinical/laboratory findings will be established using data 6 to 3 months prior to, 3 to 0 months prior to, 0 to 3 months post, and 3 to 6 months post-abnormal BM findings (please see Section 12.9 regarding issues related to missing data).

5.4 Ascertainment for Laboratory Data Outcomes

The effect of romiplostim on thrombocytosis and worsened thrombocytopenia after cessation of romiplostim therapy will be assessed based upon laboratory data. The NHRS contains all laboratory testing results. The study will review all electronic laboratory results through 4 predefined romiplostim study time periods. Two types of data will be obtained: 1) average level of platelet counts for each predefined time period; and 2) frequency of platelet counts above or below the normal range for each predefined time period. Thrombocytosis will also be confirmed by electronic medical chart review, and will be assessed whether it occurs with an adverse experience or not. In addition, rescue medication data for thrombocytopenia will also be obtained, and will be used to adjust for treatment effects in different study periods.

5.5 Standard Review of BM Biopsies and Related Study Plan for Patients with BM Biopsy

BM biopsy-related secondary endpoints of the NCPRR will be based upon all ITP patients who have at least 1 BM biopsy stained for reticulin and collagen registered in the National Pathology Registry (SNOMED: T06000, T06001, T06002 and/or S45410). For the purpose of NCPRR BM study requirements, all BM specimens for adult chronic ITP patients will be requested to be stained for reticulin and collagen.

To ensure these standards, 2 pathologists will independently re-review all BM biopsy specimens. If diagnostic conclusions for a BM biopsy from both pathologists are inconsistent, a third pathologist will re-review the specimen to achieve a final diagnosis. All reviews will be blinded to romiplostim treatment status.

6. DEFINITION OF EXPOSURE, OUTCOME, AND OTHER STUDY VARIABLES

6.1 Exposure

Exposure is defined as the patient receiving romiplostim therapy.

6.2 Outcomes

There are many outcomes in the NCPRR. They are:

Primary Outcome Endpoints:

- Incidence of increased BM reticulin and/or BM fibrosis with associated clinical signs[4], confirmed by findings in BM biopsies among adult chronic ITP patients
- Incidence of reticulin and collagen BM fibrosis (reticulin fibrosis and collagen fibrosis: SNOMED codes: M49000, M49001, M49020, M99611) with associated clinical signs, confirmed by findings in a BM biopsy among adults chronic ITP patients

Secondary Endpoints:

Clinical Endpoints:

- Average platelet counts prior to, during, immediately after treatment cessation, and following romiplostim therapy (study periods are defined in Section 7.1)
- Incidence of thrombocytosis (laboratory confirmation of a platelet count > 450 x 10^9/L) with/without adverse events among adult chronic ITP patients
- Incidence of thrombotic/thromboembolic events (ICD-10: 180, 126)
- Incidence of hematological malignancies (focused on AML and MDS)
- Incidence of clinically significant bleeding and/or receipt of rescue ITP medications for each predefined romiplostim treatment period (Section 7.1)
- Incidence of concurrent leukocytosis and anemia (measured by laboratory test results taken within 4 weeks of each other)
- Description of platelet counts and dose adjustment in mcg/kg of romiplostim in patients with cITP according to dose adjustment rules specified in the European SPC

[4] Clinical signs: any of the following: splenomegaly, hepatomegaly, leukocytosis, and cytopenia.

BM Endpoints:

- Prevalence of reticulin and collagen fiber content in the first BM biopsies of adult chronic ITP patients prior to romiplostim therapy by splenectomy status
- Incidence of collagen fibrosis with associated clinical signs confirmed by findings in BM biopsies among adult chronic ITP patients
- Incidence of PMF (primary myelofibrosis) (ICD-10: c94.5) according to the WHO diagnostic criteria in adult chronic ITP patients who have BM data prior to and/or post romiplostim therapy
- Overall and specific incidence of BM fibrosis, including reticulin and collagen fiber content formation, and PMF among adult chronic ITP patients with BM data prior to and/or post romiplostim therapy
- Association between the aforementioned primary and secondary clinical outcomes and BM abnormal findings
- Association of changes in peripheral blood with listed BM abnormal findings (3 to 6 months prior to, 0 to 3 months prior to, 0 to 3 months post, and 3 to 6 months post-abnormal BM findings)

Romiplostim Off-label Use

- Romiplostim utilization in patients without adult chronic ITP assessed by underlying disease for which the drug is used.

6.3 Other Study Variables – Predictors and Independent Variables

There are many potential predictors for the effectiveness and safety of romiplostim. To further describe the effects of romiplostim therapy, the study will consider the following variables in study cohort establishment and analysis:

Variables considered in study cohort and patient strata establishment will include:

- Sex
- Age
- Race/ethnicity
- Body Mass Index (BMI) and/or Body Surface Index (BSI)
- Year of initial ITP diagnosis (1996 to 2000, 2001 to 2005, 2006 to 2010, 2010 to 2015, and 2016 to 2018)

- Country (the study will be conducted based upon the NHRS from each country, independent of the country considered)
- Adult chronic ITP disease condition: There are many factors that may affect the adult chronic ITP disease condition (eg, length of disease, severity, platelet counts, splenectomy, co-morbidity, and concurrent medication); therefore, a propensity score will be developed to establish the romiplostim Exposed Cohort and Unexposed Cohort for adult chronic ITP patients. The development of a propensity score is discussed in Section 12.3.

Key variables considered in the analysis

- Demographic characteristics (eg, age and sex)
- BMI and/or BSI
- Disease conditions (eg, length of disease, severity, platelet counts, surgical procedure received, splenectomy, etc.)
- Propensity score (will be separated into 5 strata)
- Concurrent medication (eg, thrombopoietic agents)
- Surgical procedures (eg, splenectomy)
- Comorbidities (eg, infections, diabetes and disease or conditions that increase risk of thrombotic event)
- Medication durations and dosage

7. REGISTRY FOLLOW-UP PERIOD, EXPOSURE TIME, AND TIME AT RISK FROM EXPOSURE

7.1 Registry Follow-up Period

The follow-up period will be separated into 4 periods:

- Six months prior to receiving romiplostim therapy: This period is considered a cohort qualification and baseline establishment period. Using this period, the eligibility of subjects will be challenged and confirmed, disease conditions will be assessed, and propensity scores will be assigned for each patient. Based on the information, study cohorts will be established.

- Under treatment period: The period is defined as being from Index Date to 10 days after the last dose of romiplostim medication. During this period, all study outcomes will be assessed except for outcomes related to latency effects and post treatment effects.
- Period immediately after romiplostim treatment cessation: This period is defined as between 10 to 100 days after the last dosing. The period will be used to assess risk of worsened thrombocytopenia after treatment cessation (eg, platelet counts, bleeding, as well as rescue medication usage). As needed, this study will separate this time period into 2 sub-time periods: (3a) time period from 10 to 30 days after the last dose; and (3b) time period from 30 days to 100 days after the last dose.
- Post treatment period: This is defined as the period from 100 days after the last dosing to the end of the study. This period, as well as the aforementioned 3 periods, will be used to study long term effects of romiplostim (eg, malignancies).

7.2 Exposure Time

Exposure time is defined as the period the patient is receiving romiplostim therapy. A patient will be considered to be on "maintenance" therapy when the patient receives the same dose of romiplostim for 4 subsequent weeks.

7.3 Time at Risk

Time at risk for the NCPRR is defined as from time after initial romiplostim exposure to occurrence of outcomes listed in Section 6.2. For patients without these study outcomes, the time at risk will be from the index date to death, loss to follow-up, or the end of study, whichever comes first.

8. POTENTIAL SOURCES OF BIAS IN STUDY DESIGN

There are 4 key potential sources of bias in the study design:

Disease severity: Since romiplostim is more efficacious in treating chronic ITP than currently-marketed products, patients with more severe conditions and longer durations of the disease will receive the treatment, which should be considered as a confounding factor. Such a factor may cause a bias in the evaluation of long-term safety of romiplostim. Patients with a more severe ITP condition, for example, are more likely to have clinically significant bleeding events. Without effective methods to reduce the bias effect, the study results are questionable. To address the issue, propensity scores may be used to create strata in which the patients who are exposed and unexposed are alike

in variables that may affect outcome by forming comparisons between patients at the time of introduction to romiplostim. These variables may include disease severity, duration of disease, prior medications, and other collected variables that influence outcome. However, the prescribing patterns may not be homogeneous across the population, thereby causing minimal overlap in attributes between the exposed and unexposed. Additionally, there may be unobserved (unmeasured) differences that are not represented by the collected data. This could negatively impact the utility of propensity score stratification as there would be fewer unexposed patients with similar characteristics to the exposed patients to select for comparison.

Inconsistent reading of BM biopsy results: Because BM biopsies are taken at different time periods and reviewed by different pathologists, the consistency may be questionable, and may cause some bias. To address this issue, all BM specimens for adult chronic ITP patients will be requested to be stained for reticulin and collagen. In addition, to ensure these standards, 2 pathologists will independently, and in a blinded fashion, review all BM biopsy specimens. If diagnostic conclusions from both pathologists are inconsistent, a third pathologist will re-review the biopsies again to ascertain a final diagnosis.

Case ascertainment and confirmation: Diagnosis based on ICD-10 codes may not be able to correctly determine outcomes. The sensitivity and specificity of diagnosis based on ICD-10 codes for different diseases and conditions and for different cohorts may vary, and may induce a bias. To address this issue, the study will review electronic medical charts to confirm a diagnosis beyond ICD-10, as well as laboratory data and BM biopsy as needed.

Selection bias due to missing values: The study is based on the NHRS databases. Information for some key covariates (eg, laboratory data) may be missing for some patients. It is possible to introduce a selection bias if patients with missing values are excluded from a particular analysis. The missing value issue may also occur in development of propensity score. Patients with missing values will be excluded from the propensity development model. To address this issue, statistical methods will be employed: 1) to evaluate the mechanism of the “missingness” and 2) to impute values for missing variables based on patterns of “missingness”, if necessary.

9. REMOVAL AND REPLACEMENT OF SUBJECTS

Since the NCPRR is based upon real-life clinical practice, all patients will be followed for outcomes. For this reason, there will be no specific procedures for removal and replacement of study subjects.

10. SAFETY DATA COLLECTION, RECORDING, AND REPORTING

The NCPRR is based upon the NHRS databases. Amgen will not collect data directly from patients; however, since the study will review patient medical records, it is probable that some medical records may contain statements that link adverse events to romiplostim therapy. Amgen will instruct all medical chart reviewers to report every adverse event case that is specifically documented (or stated) in medical charts to be linked to romiplostim therapy. The collection, recording, and reporting of these cases will follow Amgen SOPs.

10.1 Safety Event Definitions

10.1.1 Definition of Adverse Events

An adverse event (AE) is any untoward medical occurrence in a patient administered a pharmaceutical product(s) and which does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a product(s), whether or not considered related to the product(s). The definition of an AE includes:

- **Worsening of a pre-existing condition**
- **Events occurring from a medication error or overdose of a product(s), whether accidental or intentional**
- **Events occurring from abuse of a product(s)**
- **Events associated with the discontinuation of the use of a product(s), (eg, appearance of new symptoms)**
- **Any lack or loss of intended effect of the product(s)**

10.1.1.1 Adverse Drug Reactions (ADRs)

AEs that are considered related to the Amgen product(s) are classified as adverse drug reactions (ADRs).

It is the Investigator's responsibility to evaluate if an event is related to an Amgen product prior to reporting the event to Amgen.

10.1.2 Definition of Serious Adverse Events

A serious adverse event (SAE) is any AE as defined above that also:

- **is fatal**
- **is life threatening (places the patient at immediate risk of death)**
- **requires in-patient hospitalization or prolongation of existing hospitalization**
- **results in persistent or significant disability/incapacity**
- **is a congenital anomaly/birth defect**
- **is an "other significant medical hazard" that does not meet any of the above criteria**

A hospitalization meeting the regulatory definition for "serious" is any in-patient hospital admission that includes a minimum of an overnight stay in a healthcare facility.

"Other significant medical hazards" refer to important medical events that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. Examples of such events could include allergic bronchospasm, convulsions, and blood dyscrasias, drug-induced liver injury, events that necessitate an emergency room visit, outpatient surgery, or other events that require other urgent intervention.

10.1.2.1 Serious Adverse Drug Reactions (SADRs)

SAEs that are considered related to the Amgen product(s) are classified as serious adverse drug reactions (SADRs).

It is the Investigator's responsibility to evaluate if an event is related to an Amgen product prior to reporting the event to Amgen.

10.1.3 Definition of Other Safety Findings

Other Safety Findings include:

- **Medication errors, overdose, misuse, or abuse, whether accidental or intentional, involving an Amgen product, regardless of whether associated with an ADR and/or SADR**
- **Pregnancy and lactation exposure regardless of whether associated with an ADR and/or SADR**
- **Transmission of infectious agents regardless of whether associated with an ADR and/or SADR**
- **Reports of uses outside the terms for authorized use of the product including off label use when associated with an ADR and/or SADR**

10.1.4 Definition of Product Complaints

Product Complaints include any written, electronic or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a product or device after it is released for distribution. This includes all components distributed with the product(s) such as packaging, product containers, delivery system, labeling, inserts, etc.

Product Complaints <u>may</u> include but are not limited to issues related to:

- **Appearance (eg, broken, cracks, color, particles, odor)**
- **Labeling (eg, missing, torn, smudged)**
- **Durability (eg, stability issues)**
- **Open packaging**
- **Device damage (eg, pre-filled syringe with bent needle)**
- **Inability of customer to understand product labeling**
- **Inability of customer to deliver the product successfully, including partial or incomplete delivery (eg, defective delivery system [syringe])**

10.2 Reportable Events and Reporting Timeframes

The HCP is responsible for ensuring that all ADRs/SADRs, product complaints and other safety findings for any Amgen product(s) are submitted to Amgen via the supplied Amgen Safety Reporting Forms. See Appendix 3 for a sample Report Form.

- **All clearly documented SADRs, product complaints and other safety findings, including pregnancy and/or lactation, are to be reported to Amgen within 1 business day of the HCP's date of awareness.**
- **ADRs that do not meet serious criteria are to be collected in the study database and must be reported in the final study report.**

11. STUDY SIZE CONSIDERATION

A total estimate of 623 patients (4,234 patient-years) will comprise the Exposed Cohort. According to the study design, the Unexposed Cohort for adult chronic ITP patients will include 1860 patients, and will account for 12,700 patient-years of follow-up (Figure 1). This is a conservative estimation.

The study will compare chronic ITP patients who received romiplostim with those patients who do not receive romiplostim. This study will collect approximately 4,234 patient-years of romiplostim-exposed patient information during the 11 years of follow-up. Although the background incidence rate of study outcomes in chronic ITP patients is unknown, this sample size has a greater than 80% probability of detecting a difference in a range of relative risks from 2 to 4 where the background incidence ranges for 0.5% to 5%.

12. STATISTICAL ANALYSIS

12.1 Data Editing

Data in the NCPRR has been collected and collated in the NHRS database, and there will be no data editing required.

12.2 Exploratory and Descriptive Analysis

Since the study is descriptive in nature for the purpose of hypothesis generation, the analyses will describe the study population and outcomes in all study cohorts, as well as in different follow-up time periods (prior to and post Nplate exposure time periods). This will include:

- Total number of subjects and total person-year observation time in each cohort in the current reporting period, and cumulative for all reporting periods
- Current incidence rates of study outcomes based on data in the current reporting period and in the cumulative data for all reporting periods
- Average platelet count in predefined romiplostim treatment periods
- Detailed descriptions of each case with increased BM reticulin and / or BM fibrosis associated with clinical signs in the current reporting period
- Detailed description of hematological malignancy cases (eg, AML) and cases of MDS

Detailed descriptions of cases with BM reticulin, BM fibrosis, hematological malignancies, secondary thrombocytopenia, or clustering of events may require a narrative description of diagnoses and therapies leading to events in order to provide context for medical interpretations. In addition, the following descriptive analyses will also be conducted:

- A tabular summary (frequency, total patient-years of observation, rate) for patients' demographic and clinical characteristics between the Exposed Cohort and Unexposed Cohort, and among inception cohorts
- A tabular summary (frequency, total patient-years of observation, rate) for baseline laboratory findings of patients between study cohorts

The romiplostim utilization pattern in adult chronic ITP patients will also be assessed (eg, demographic characteristics of users, the condition or characteristics of the disease for which the drug is used, the kind of health professional who prescribes the drug, and how patients are dosed). This descriptive analysis may also compare the utilization patterns between the romiplostim Exposed Cohort and Unexposed Cohort, as well as among inception cohorts to determine the potential selection bias. In this analysis, demographic characteristics, clinical conditions of underlying diseases, and other potential confounders will be measured and compared. Stratified analyses and a multiple regression analysis will be used as needed to determine major imbalances of patient populations between romiplostim users and non-users. The analysis will be used as the basis to determine measurable selection bias. However, non-measurable selection bias cannot be addressed by the study, which is a major limitation and adds a challenge with regard to the interpretation of study results.

12.3 Development of a Propensity Score of Romiplostim Treatment for the Chronic ITP Population

There are many factors that may affect the adult chronic ITP disease condition (eg, age, sex, length of disease, severity, platelet counts, splenectomy, co-morbidities, and concurrent medications). To reduce potential effects from confounding by indication of romiplostim therapy, a propensity score will be developed to create a pseudo-randomization in balancing important factors that might affect the outcomes between the romiplostim Exposed Cohort and Unexposed Cohort for chronic ITP patients. The propensity score is defined as the conditional probability of being treated given a set of important and relevant covariates. The logistic regression method will be used to develop the propensity score for the severity of the ITP condition. The variables to be considered may include, but are not limited to, age, sex, BMI/BSI, country, year of ITP diagnosis, length of disease, average platelet counts, lowest platelet counts, splenectomy, major comorbidities, and prior ITP medications (type and frequency), and frequency and severity of bleeding events. While the propensity score is being developed, other methods, such as stratification by country or by a span of years associated with changing practice patterns will be investigated. The aforementioned variables to be included in the propensity score development model will be updated and modified based upon the findings from an Amgen-sponsored historical study to be based upon the Danish Health Registry System Database for chronic ITP patients (Study 20070796) and expert opinions. The dependent variable for the model is romiplostim therapy (yes or no). The propensity model will be refined with every annual analysis based on newly available data. The propensity score will be reassigned to each patient for each annual analysis and the final analysis; therefore, the propensity-score for each subject in the cohorts reported in each annual and the final analysis may be different. However, variables involved in the propensity score development model will be the same throughout unless some new variable emerged during the 11-year study period. The data used to develop a propensity score will be from 6 months prior to the Index Date of receiving romiplostim therapy, and data from 6 months prior to the Index Date that is randomly selected from romiplostim-unexposed chronic ITP patients. To ensure the sensitivity and specificity of the propensity score, sensitivity analyses will be conducted for each established propensity model. The sensitivity and specificity test will be conducted using medical records for selected clinical characteristics, features, severity measures, and potential confounders.

The distribution of propensity scores for the Exposed Cohort and Unexposed Cohort will be graphically presented in a figure. Patients with very low or very high propensity scores whose scores are non-overlapping with patients in comparison cohorts will be excluded from (or trimmed from) the analysis. The "trimming" method will remove outliers from the analysis to reduce selection bias and the impact of patients with extreme conditions. This may impact the statistical power to evaluate any differences between the exposed and unexposed groups. A reduced sample size would reduce the probability of detecting a difference in a range of relative risks from 2 to 4 where the background incidence ranges from 0.5% to 5% (refer to Appendix 1 for exact power). Based upon the distribution of propensity scores, 5 strata will be developed and used in the analysis. Propensity scores will also be used in multiple regression analysis as a covariate. Important variables including age, sex, ITP diagnostic year and disease duration that contribute to the propensity score can also be independently included in multiple regression analysis as additional covariates, which constitute a "Doubly Robust" model.

The propensity score, along with age, sex and diagnosis year will be used as needed to match the Exposed Cohort and Unexposed Cohort among adult chronic ITP patients.

12.4 Analysis for Long-term Effects

Analysis for long-term effects will be descriptive in nature. As the selection bias resulting from confounding by indication for this study could be very large, and as some impacts are not measurable, comparative analyses will be inherently challenging to interpret. For these reasons any comparative analyses must be considered as exploratory for signal detection and for the purpose of hypothesis generation. The incidence rates of clinically significant bleeding (inpatient and outpatient) and/or rescue medication use will be described for the Exposed Cohort and Unexposed Cohort:

- Kaplan-Meier survival curves will be constructed for patients with bleeding events for the Exposed Cohort and Unexposed Cohort.
- As needed, a Cox model with romiplostim exposure as a time-varying covariate will be used to compare the total event-free survival rates among exposed ITP patients and the unexposed cohort, with an estimation of the relative risk and associated 95% confidence interval. This analysis will adjust for potential confounders and propensity scores. Stratification by propensity score, significant year spans, and country may be considered for this analysis, although such an analysis will only be for exploratory and hypothesis generating purposes. Other treatment exposures,

health status, and disease conditions may also be considered for inclusion in the model as time-varying covariates.

Comparison of platelet counts in predefined time periods (prior to, during, immediately after treatment cessation, and post treatment) between the Exposed Cohort and Unexposed Cohort:

- Mean and SD
- As needed, a multiple regression will be used to test the difference between the Exposed Cohort and Unexposed Cohort. However, such an analysis will only be for exploratory and hypothesis-generating purposes.

Comparison of long-term safety (eg, thromboembolic risk, thrombocytosis, hematological malignancies, focused upon AML, and MDS), including:

- Description of rare and long latency events: Some events (eg, AML and MDS) are too few to conduct any meaningful statistical analysis or comparison. The study will provide detailed case descriptions for each case observed.
- Incidence rate of these events will be calculated.

12.5 Description of Transient Worsened Thrombocytopenia After Romiplostim Treatment Cessation

The analysis will be conducted for the Exposed Cohort in chronic ITP patients.

The comparison will be based upon platelet counts among four predefined study time periods (Section 7.1).

- Comparison of mean (SD) platelet counts in four study time periods between study cohorts.
- Multiple regression to determine if the phenomenon of transient worsened thrombocytopenia exists after adjusting for other potential confounders and propensity scores. The propensity score-stratified analysis will also be used.

12.6 Comparisons of Outcomes that are Dependent on BM Data

1) Frequency and incidence of increased BM reticulin and/or BM fibrosis with associated clinical signs[5], confirmed by findings in a BM biopsy and 2) frequency and incidence of collagen fibrosis with associated clinical signs confirmed by findings in BM biopsies will be analyzed between the Exposed Cohort and Unexposed Cohort in all adults with chronic ITP:

[5] Clinical signs: any of the following: splenomegaly, hepatomegaly, leukocytosis, and cytopenia.

- Since the sample size could be very small, the detailed description of each identified case will be listed in the report.
- If there is a sufficient sample size, a formal statistical analytic comparison, as described in Section 12.4, will be conducted.

Description of prevalence rate of reticulin and collagen formation among chronic ITP patients:

- This analysis will be conducted based upon all eligible adult chronic ITP patients in the period prior to romiplostim treatment by splenectomy status. Only initial BM results will be used in the analysis to reduce potential selection bias caused by repeated testing for BM with abnormal findings.
- Prevalence of patients with reticulin and collagen formation in BM will be assessed. No comparison will be conducted; however, the descriptive analysis will be used to describe demographic characteristics, clinical features, and laboratory findings.

1) Frequency and incidence of chronic idiopathic myelofibrosis (primary myelofibrosis) according to the WHO diagnostic criteria, and 2) overall and specific incidence rates of BM fibrosis findings, including reticulin and collagen fiber content formation, and chronic idiopathic myelofibrosis in the Exposed Cohort and Unexposed Cohort in adult chronic ITP patients who have BM data prior to and post romiplostim therapy:

- Since the sample size could be very small for these outcomes, the detailed description of each identified case will be listed in the report.
- If there is a sufficient sample size (e.g., approximately 10 per treatment group for each covariate considered), a formal statistical analytic comparison, as described in Section 12.4, will be conducted.

2) Association of splenomegaly and/or hepatomegaly with BM fibrosis and 2) association of changes in peripheral blood prior to and following the finding of reticulin and collagen fiber content or formation (reticulin grading 1 to 3):

- The association tests will be based on data 3 to 6 months prior to, 0 to 3 months prior to, 0 to 3 months post, and 3 to 6 months post-positive findings in BM biopsies.
- 2XN tabulation will be created and chi-square tests for categorical variables will be used to test the association.
- Multiple regression and logistic analysis will be used to investigate romiplostim's effect after adjusting for other confounders, if feasible.

12.7 Stratified Analysis

Stratified analyses will be used as needed. The following are some variables to be considered as stratification factors:

- Sex and age (< 18, 18 to 30, 31 to 50, 51 to 70, and 71+)
- BMI and/or BSI
- Propensity scores (5 strata)
- Initial platelet level (< 10×10^9, 10 to 30×10^9, $\geq$ 30 to 50×10^9)
- Length of chronic ITP since diagnosis (< 1 year, 1 to 3 years, 4+ years)
- Year of initial ITP diagnosis (1996 to 2000, 2001 to 2005, 2006 to 2010, 2011 to 2015, and 2016 to 2018)
- Splenectomy (yes or no)
- Receiving immunosuppressive therapy
- Concomitant bleeding disorder/history of significant bleeding
- Any significant span of years (based on changing practice patterns)
- Country (if practice patterns differ among studied countries)

12.8 Comparison of Study Outcomes with External Data Sources

Since selection bias caused by confounding by indication for this study could be very large and some impacts are not measurable, in addition to internal comparison the study will compare the incidence rates from the romiplostim-exposed cohort to that from other potential sources where sufficient data may be present:

- Amgen Study 20080092 (Nplate™ Patient Safety Registry – Canada version)
- Amgen Study 20080045 (Nplate™ Patient Safety Registry – US version)
- Amgen Study 20070796 (Determination of Frequency Rates of Bone Marrow Fibrosis and Thrombotic/Thromboembolic Events in Patients with Chronic Immune (Idiopathic) Thrombocytopenic Purpura in Denmark)
- Administrative databases such as SEER, Ingenix, and GPRD, if appropriate data are available at time of analysis

- Published data on the frequency of predefined risks, such as Mufti et al, 2007 (J Supp Oncol 2007;5(S2):80-81) and Aledort et al, 2004. (Am J Hematol. 2004;76(3):205-213)
- Data available from Amgen's ongoing romiplostim clinical program

The signals and/or hypothesis will be generated based upon both internal and external comparison data, with great caution and appropriate contextualization applied.

12.9 Missing Data and Loss to Follow-up

Since this study is based on the NHRS, missing data and patients being lost to follow-up are a relatively minor issue. The study estimates that less than 5% of ITP patients will be lost to follow-up due to emigration to other countries. Since the study is able to assess all electronic medical records of study subjects, any missing data for outcomes of interest will be retrieved from medical chart reviews. Through the medical chart review, the study will distinguish missing values from those unknown or not tested. The analysis will treat missing and unknown values differently, although the study will not be able to retrieve all missing data for covariates. Appropriate approaches to missing data will be explored depending on the ascertainment of the missingness mechanism.

12.10 Analysis for Chronic ITP Patients with Renal Impairment

Since sample size could be very small, safety assessment for these renal functional impaired patients will be mainly focused on individual case description and line listing. When sample size is sufficient to conduct statistical analysis, special analyses will be conducted for chronic ITP patients with renal impairment medical conditions at the time romiplostim therapy is initiated. The analysis will include multivariate analysis and stratified analysis:

- Multivariate analysis will used to justify for renal comorbidities and / or medical history (see Section 12.2, 12.3, and 12.4).
- Stratified analysis based on renal impairment status will be conducted to describe patient's safety profile, including incidence rate of renal failure within each renal impairment stratum. Other outcomes listed in this study proposal will also be described within each predefined stratum.

12.11 Analysis for Romiplostim Off-label Users

Analysis for romiplostim off-label users is descriptive in nature for the purpose of hypothesis generation. The analyses will describe the off-label study population in different study time periods. Analysis will include:

- Total number of subjects and total person-year observation time for all off-label users, as well as in each major underlying disease/condition cohort in the current reporting period, and cumulative for all reporting periods
- Description analysis for romiplostim-off-label utilization pattern, including
- Underlying disease for which the drug is used
- Underlying disease characteristics (eg, length, stage, and severity of underlying diseases)
- Demographic characteristics

12.12 Annual Analysis and Early Stopping Guidelines

Since this study will be used to fulfill the European regulatory agency requirements, annual assessments are planned. For each pre-specified analysis scheduled, the NCPRR investigators will conduct an annual analysis based on available data. The analysis will be limited to the analyses described in Section 12. The annual analysis results will be communicated to the regulatory agency through PSURs.

There are no pre-defined early stopping rules for this study.

13. LIMITATIONS

The major limitations in the NCPRR study design are:

- The sample size is relatively small: ITP is an orphan disease and the population available for the study is limited (estimated at only 623 adult chronic ITP patients). The small sample size will limit assessment of risk for some rare events (eg, AML or MDS). To address this issue, Amgen will conduct an all patient registry in the US (US PSR) and a selected patient registry in Canada (CAN PSR), and some rare events may be effectively assessed by combining the findings of these studies.
- Limited countries are involved: The study will only include data from 3 Nordic countries, and may not represent romiplostim's benefit/risk profile of experiences for the entire European population, given that the health care system and practice patterns of ITP treatments may be different among countries. The key purpose of the study is to assess effect of romiplostim, and by creating a reasonable

comparison group such an assessment can be achieved. Amgen also plans to conduct a drug utilization study in most European countries which will provide information on how romiplostim will be used in these countries under different health care systems and practice guidelines.

- Section 8 has identified four potential sources of bias in the study design. Although several methods have been considered in the study design to address these issues, it is probable the residual of these biases may still remain (eg, unmeasured selection bias due to physicians' prescribing behavior and selection bias caused by excluding patients with missing values).
- Comparability of the exposed and unexposed to reduce bias in the analysis of the outcomes may not be achieved. It is possible that propensity score adjustment will not be adequate to reduce the confounding by indication. In this scenario, caution should be taken that the comparative analyses will be inherently challenging to interpret due to the potential for bias. The context for results observed for romiplostim-treated patients should be considered in relationship to not only internal comparisons within the Nordic registry, but too other potential sources of information (Section 12.8) for establishing that context as well.

14. ETHICAL AND REGULATORY OBLIGATIONS

14.1 Informed Consent

Since the NCPRR is based upon the NHRS databases, it will not be necessary to obtain patient consent to obtain data. Study results will only be presented in an aggregate form so that individuals will not be identified.

The NCPRR may request a review of an individual patient's electronic medical records, however, as well as assessment of a patient's biological samples (eg, BM). Communication with potential investigators of the study has confirmed that it will not be necessary to obtain informed consent from patients when detailed chart reviews and BM biopsy staining and reviews are conducted.

15. COMMUNICATION OF STUDY RESULTS

15.1 Communication of Study Results to Regulatory Agencies

The health risk findings of the registries associated with Amgen products must be reported to regulatory agencies according to local and international requirements. Depending on the nature of the result and the regulations applied, the results may need

to be reported in an expedited manner (eg, as "new relevant safety information"). In any case, results of all registry studies of drug safety should be included in Amgen's periodic aggregated regulatory reports, such as the PSUR and similar regulatory documents, with appropriate contextualization provided.

The NCPRR will conduct an assessment annually. The assessment results will be submitted to regulatory agencies worldwide through the PSUR.

16. ADMINISTRATIVE CONSIDERATIONS

16.1 The NCPRR International Investigator Study Team (IIST) Responsibilities

The NCPRR IIST is responsible to the NCPRR for:

- Maintaining IRB approval for the Registry study
- Developing the Statistical Analysis Plan (SAP) for the NCPRR
- The collection, management, and follow-up qualified study subjects prospectively
- Establishing and managing the Registry databases
- Compiling research data based upon the NCPRR study objectives from the NHRS
- Providing all relevant single case and aggregate clinical data, including all predefined adverse event data to Amgen and the Advisory Committee for review
- Providing data, including both individual case and cumulative data, that is specifically requested to be reviewed by the NCPRR SAC
- Collaborating with Amgen scientists to develop interim, ad hoc, and final study reports to be reviewed by the NCPRR SAC
- Being available to answer questions and facilitate requests for additional data
- Collaborating with Amgen for routine auditing
- Working with Amgen to prepare publications resulting from the Registry

16.2 Registry Coordination Center & Investigator Team Leader Responsibilities

Registry Coordination Center and Investigator Team Leader are responsible for:

- Oversight of the registry team's responsibilities
- Ensure effective communication between Amgen and the Investigators
- Manage the service agreement between Amgen and the Investigators, and the related budget

16.3 Amgen Responsibilities

An Amgen cross functional team that consists of Global Safety Officers (GSO), Global Development Leaders (GDL), Epidemiologists from PV-Epidemiology and the Global Epidemiology team, and Safety Biostatisticians will provide scientific and technical support to the NCPRR conduct and the NCPRR SAC activities. Their representatives will participate in the NCPRR Scientific Advisory Committee (SAC) meeting. Amgen's responsibilities to the NCPRR and the NCPRR SAC are to:

- Review and approve final study design and methodologies, and study protocol finalization prior to the study initiation
- Coordinate with the IIST to develop the analysis plan before the study initiation
- Ensure that study data meets regulatory standards for data quality management and auditing
- Collaborate with IIST investigators to develop interim, ad hoc, and final study reports to be reviewed by the NCPRR
- Communicate with regulatory authorities on study design, protocol, study results and other pertinent information
- Fulfill Amgen's regulatory responsibilities, including development and submission of annual interim reports and the final study report to the regulatory agency
- Be available to answer questions and facilitate requests for additional data at the meeting, as well as outside of the meeting
- Communicate to the NCPRR SAC any decisions made concerning NCPRR SAC recommendations and notify the NCPRR SAC of all changes to the protocol or the NCPRR conduct
- Archive NCPRR SAC records (by the NCPRR SAC Liaison)
- Schedule NCPRR SAC meetings and prepare meeting agendas
- Collaborate with the IIST to prepare relevant publications.

17. APPENDICES

Appendix 1. Probability of Detecting Specified Relative Risk for Estimated Incidence Rates for the Study Sample Size

Estimated Background Incidence Rate (%)	Relative Risk				
	1.25	1.50	2.00	3.00	4.00
	Power (%)				
0.1	4	9	26	69	92
0.2	6	16	50	94	99
0.5	13	40	89	99	99
1.0	24	70	99	99	99
2.0	46	99	99	99	99
5.0	85	99	99	99	99

Appendix 2. Conditions Associated with Thrombocytopenia Other Than cITP

Diseases and Condition	ICD-10 Codes
Hereditary syndromes and Immunodeficiency:	
Alport syndrome	Q87.8
Fanconi anemia	D61.0B
May Hegglin anomaly	D72.0 (genetic abnormalities of leukocytes)
CVI (hypogammaglobulinemia)	D80.0, D80.1 (hereditary and nonfamilial hypogammaglobulinemia)
IgA deficiency	D80.2
IgG subclass 2 deficiency	D80.3
Low C4 counts	D84.1 (defects in the complement system)
Systemic “Global” autoimmunity:	
Evans syndrome and autoimmune hemolytic anemia	D69.3 & D59.0/D59.1
Systemic lupus erythematosus (SLE)	M32
Infections:	
HIV/AIDS	B20-B24
Hepatitis C	B17.1, B18.2
Lymphoproliferative disorders Malignant:	
Solid tumor	C00-C80
Hematological malignancies	C81-C96
Lymphoproliferative disorders non-Malignant:	
Autoimmune lymphoproliferative syndrome type I (ALPS) (or Canale-Smith syndrome)	D36.0 (benign neoplasms of lymph nodes)
Liver disorders:	
Diseases of liver	K70-K77
Bone marrow disorders	
Agranulocytosis	D70
Aplasia pure red cell	D60
Aplastic anaemia,pancytopenia	D61.0, D61.1, D61.2, D61.3, D61.9
Bone marrow transplant rejection	T86.0
Bone marrow tumour cell infiltration	Z94.8
Myelodysplastic syndrome	D46
Myelofibrosis	C94.5
Myeloproliferative disorder	D47.1
Other transplants, incl. bone marrow	Z94.8
Other disorders involving platelets	
Allergic purpura	D69.0
Qualitative platelet defects	D69.1
Secondary thrombocytopenia	D69.5
Antiphospholipid syndrome	D68.8 (coagulation defects)
Disseminated intravascular coagulation	D65
Hemolytic-uremic syndrome	D59.3
Thrombocytopenia neonatal	P61.0
Thrombotic thrombocytopenic purpura	M31.1
von Willebrand's disease	D68.0
Wiskott-Aldrich syndrome	D82.0

Appendix 3. Sample Safety Reporting Form

Project ID:	AMGEN	Safety Reporting Form Secondary Data Collection	Date of Report:
		Fax reports to: Local Amgen office at:	<<populate LAO fax here or delete language>>

1. Indicate event type: ☐ SADR/Other safety finding ☐ SADR/Other safety finding with Product Complaint ☐ Product Complaint only

2. Vendor Contact Details			3. Reviewer (if other than Vendor)		
name	*phone*	*fax*	*Name or ID*	*phone*	*fax*
address			*address*		
city	*state/province*		*city*	*state/province*	
postal code	*country*		*postal code*	*country*	

4. HCP Contact Details (whose documentation was reviewed)			5. Patient			
name			*Initials (optional)*	*Sex* ☐ F ☐ M	*Age (at time of event)*	*Was consent obtained to follow-up with HCP?* ☐ Yes ☐ No
country						
address						
city	*state/province*	*postal code*	*Weight* ☐ lbs ☐ kg	*Height* ☐ in ☐ cm	*Race*	
phone	*fax*					

6. Medical History (include primary diagnosis)	7. Suspect Product Information (include dosing details)				
	Product: _____				
	Indication: _____				
	Start Date (day month year)	Stop Date (day month year)	Dose	Route	Freq
Pregnant? ☐ Yes ☐ No Lactating? ☐ Yes ☐ No	Prefilled Syringe? ☐ Yes ☐ No		Lot # _____ ☐ Unknown to Reporter		Vial size
Allergy: _____	Other Device _____				

8. SADR, other safety finding, or product complaint information

Finding: (List main event first; one event per line)	Onset Date (day month year)	Resolved Date (If patient died, list date of death) Cause of Death: _____ (provide autopsy report) (day month year)	Hospitalization: Hospitalized? ☐ Yes ☐ No; Hospitalization Prolonged? ☐ Yes ☐ No; Admitting dx _____ (provide discharge summary); Date Admitted (day month year); Date Discharged (day month year)	Serious Criteria (1=persistent or significant disability/ incapacity 2=congenital anomaly/ birth defect 3=significant medical hazard)	Action Taken (1=none 2=dose reduced 3=dose increased 4=drug withdrawn 5=Drug rechallenge (state outcome))	Outcome (1=resolved 2=resolved w/ sequelae 3=resolving 4=event ongoing 5=died of event)	Severity (1=mild 2=moderate 3=severe 4=life-threatening 5=fatal)	Relationship to Product/ Device (Indicate below (x) whether finding was related to the Product and/or Device?) Product	Device

9. Description: chronological summary of symptoms or product complaint from above (signs, diagnosis, treatment, concomitant medications including those used to treat event.)

Reporter Signature: _____ Page 1 of ____

The data provided by you will be transferred as a report to Global Safety at Amgen Inc (USA) and will be exclusively used for safety and quality purposes

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18. REFERENCES

Aledort LM, Hayward CPM, Chen M-G, Nichol JL, Bussel J. Prospective screening of 205 patients with ITP, including diagnosis, serological markers, and the relationship between platelet counts, endogenous thrombopoietin, and circulating antithrombopoietin antibodies. *Am J Hematol*. 2004;76(3):205-213.

Berchtold P, McMillan R. Therapy of chronic idiopathic thrombocytopenic purpura in adults. *Blood*. 1989;74:2309-2317.

Cines DB, McMillan R. Management of adult idiopathic thrombocytopenic purpura. *Ann Rev Med*. 2005; 56:425-442.

Columbyova L, Loda M, Scadden DT. Thrombopoietin receptor expression in human cancer cell lines and primary tissues. *Cancer Res*. 1995;55:3509-3512.

Frank L. Epidemiology. When an entire country is a cohort. *Science*. 2000;287:2398-2399.

Frederickson H, Schmidt K. The incidence of idiopathic thrombocytopenia purpura in adults increases with age. *Blood*. 1999;94:909-913.

Graf G, Dehmel U, Drexler HG. Expression of thrombopoietin and thrombopoietin receptor MPL in human leukemia-lymphoma and solid tumor cell lines. *Leuk Res*. 1996;20:831-8.

McMillan R. Chronic idiopathic thrombocytopenic purpura. *N Engl J Med*. 1981;304:1135-1147.

Mufti G, Bagg A, Hasserjian R, et al. Bone marrow reticulin in patients with immune thrombocytopenic purpura. *J Supp Oncol*. 2007;5(S2):80-81.

Superseding Amendment 4

Protocol Title: Population Based Prospective Annual Assessment of Safety of Romiplostim Treatment in Adult Patients with Chronic Idiopathic (Immune) Thrombocytopenic Purpura (ITP) Based on National Health Registry Systems in Denmark, Sweden, and Norway

Amgen Protocol Number 20070797

Amendment Date: 18 December 2012

Rationale:

The protocol changes update the safety reporting language to be consistent with the requirements of the EU directive of 02 July 2012 and include a sample of the updated safety reporting form (FORM-067757).

Description of changes:

Insert addtional protocol text for safety data collection, recording, and reporting after introductory paragraph in Section 10.

After:

The NCPRR is based upon the NHRS databases. Amgen will not collect data directly from patients; however, since the study will review patient medical records, it is probable that some medical records may contain statements that link adverse events to romiplostim therapy. Amgen will instruct all medical chart reviewers to report every adverse event case that is specifically documented (or stated) in medical charts to be linked to romiplostim therapy. The collection, recording, and reporting of these cases will follow Amgen SOPs.

Insert

10.1 Safety Event Definitions

10.1.1 Definition of Adverse Events

An adverse event (AE) is any untoward medical occurrence in a patient administered a pharmaceutical product(s) and which does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a product(s), whether or not considered related to the product(s). The definition of an AE includes:

- **Worsening of a pre-existing condition**
- **Events occurring from a medication error or overdose of a product(s), whether accidental or intentional**
- **Events occurring from abuse of a product(s)**
- **Events associated with the discontinuation of the use of a product(s), (eg, appearance of new symptoms)**
- **Any lack or loss of intended effect of the product(s)**

10.1.1.1 Adverse Drug Reactions (ADRs)

AEs that are considered related to the Amgen product(s) are classified as adverse drug reactions (ADRs).

It is the Investigator's responsibility to evaluate if an event is related to an Amgen product prior to reporting the event to Amgen.

10.1.2 Definition of Serious Adverse Events

A serious adverse event (SAE) is any AE as defined above that also:

- **is fatal**
- **is life threatening (places the patient at immediate risk of death)**
- **requires in-patient hospitalization or prolongation of existing hospitalization**
- **results in persistent or significant disability/incapacity**
- **is a congenital anomaly/birth defect**
- **is an "other significant medical hazard" that does not meet any of the above criteria**

A hospitalization meeting the regulatory definition for "serious" is any in-patient hospital admission that includes a minimum of an overnight stay in a healthcare facility.

"Other significant medical hazards" refer to important medical events that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. Examples of such events could include allergic bronchospasm, convulsions, and blood dyscrasias, drug-induced liver injury, events that necessitate an emergency room visit, outpatient surgery, or other events that require other urgent intervention.

10.1.2.1 Serious Adverse Drug Reactions (SADRs)

SAEs that are considered related to the Amgen product(s) are classified as serious adverse drug reactions (SADRs).

It is the Investigator's responsibility to evaluate if an event is related to an Amgen product prior to reporting the event to Amgen.

10.1.3 Definition of Other Safety Findings

Other Safety Findings include:

- **Medication errors, overdose, misuse, or abuse, whether accidental or intentional, involving an Amgen product, regardless of whether associated with an ADR and/or SADR**
- **Pregnancy and lactation exposure regardless of whether associated with an ADR and/or SADR**
- **Transmission of infectious agents regardless of whether associated with an ADR and/or SADR**
- **Reports of uses outside the terms for authorized use of the product including off label use when associated with an ADR and/or SADR**

10.1.4 Definition of Product Complaints

Product Complaints include any written, electronic or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a product or device after it is released for distribution. This includes all components distributed with the product(s) such as packaging, product containers, delivery system, labeling, inserts, etc.

Product Complaints may include but are not limited to issues related to:

- **Appearance (eg, broken, cracks, color, particles, odor)**
- **Labeling (eg, missing, torn, smudged)**
- **Durability (eg, stability issues)**
- **Open packaging**
- **Device damage (eg, pre-filled syringe with bent needle)**
- **Inability of customer to understand product labeling**
- **Inability of customer to deliver the product successfully, including partial or incomplete delivery (eg, defective delivery system [syringe])**

10.2 Reportable Events and Reporting Timeframes

The HCP is responsible for ensuring that all ADRs/SADRs, product complaints and other safety findings for any Amgen product(s) are submitted to Amgen via the supplied Amgen Safety Reporting Forms. See Appendix 3 for a sample Report Form.

- **All clearly documented SADRs, product complaints and other safety findings, including pregnancy and/or lactation, are to be reported to Amgen within 1 business day of the HCP's date of awareness.**
- **ADRs that do not meet serious criteria are to be collected in the study database and must be reported in the final study report.**

Add:

Appendix 3. Sample Safety Reporting Form

Project ID:	AMGEN	Safety Reporting Form Secondary Data Collection	Date of Report:
	Fax reports to: Local Amgen office at:	<<*populate LAO fax here or delete language*>>	

1. Indicate event type: ☐ SADR/Other safety finding ☐ SADR/Other safety finding with Product Complaint ☐ Product Complaint only

2. Vendor Contact Details			**3. Reviewer (if other than Vendor)**		
name	*phone*	*fax*	*Name or ID*	*phone*	*fax*
address			*address*		
city	*state/province*		*city*	*state/province*	
postal code	*country*		*postal code*	*country*	

4. HCP Contact Details (whose documentation was reviewed)			**5. Patient**			
name			*Initials (optional)*	*Sex* ☐ F ☐ M	*Age (at time of event)*	*Was consent obtained to follow-up with HCP?* ☐ Yes ☐ No
country						
address						
city	*state/province*	*postal code*	*Weight* ☐ lbs ☐ kg	*Height* ☐ in ☐ cm	*Race*	
phone	*fax*					

6. Medical History (include primary diagnosis)	**7. Suspect Product Information (include dosing details)**				
	Product: _____				
	Indication: _____				
	Start Date (day month year)	Stop Date (day month year)	Dose	Route	Freq
Pregnant? ☐ Yes ☐ No Lactating? ☐ Yes ☐ No	Prefilled Syringe? ☐ Yes ☐ No		Lot # _____ ☐ Unknown to Reporter		Vial size
Allergy: _____	Other Device _____				

8. SADR, other safety finding, or product complaint information

Finding: (List main event first; one event per line)	Onset Date (day month year)	Resolved Date (If patient died, list date of death) Cause of Death: _____ (provide autopsy report) (day month year)	Hospitalization: Hospitalized? ☐ Yes ☐ No; Hospitalization Prolonged? ☐ Yes ☐ No; Admitting dx _____ (provide discharge summary); Date Admitted (day month year)	Date Discharged (day month year)	Serious Criteria: 1=persistent or significant disability/ incapacity 2=congenital anomaly/ birth defect 3=significant medical hazard	Action Taken: 1=none 2=dose reduced 3=dose increased 4=drug withdrawn 5=Drug rechallenge (state outcome)	Outcome: 1=resolved 2=resolved w/ sequelae 3=resolving 4=event ongoing 5=died of event	Severity: 1=mild 2=moderate 3=severe 4=life-threatening 5=fatal	Relationship to Product/ Device (indicate below (x) whether finding was related to the Product and/or Device?): Product	Device

9. Description: chronological summary of symptoms or product complaint from above (signs, diagnosis, treatment, concomitant medications including those used to treat event.)

Reporter Signature: _____ Page 1 of ____

The data provided by you will be transferred as a report to Global Safety at Amgen Inc (USA) and will be exclusively used for safety and quality purposes

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Amendment 3

Protocol Title:

Population Based Prospective Annual Assessment of Safety of Romiplostim Treatment in Adult Patients with Chronic Idiopathic (Immune) Thrombocytopenic Purpura (ITP) Based on National Health Registry Systems in Denmark, Sweden, and Norway

Amgen Protocol Number 20070797

Amendment 3 Date: **14 May 2012**

Rationale:
This amendment is being made to recognize changes and clarify aspects of the protocol as follows:

- Update of Study contacts to reflect current information
- Replacement of Finland with Norway as a participating country along with designation of Nordic for Scandinavian in study and country description (NCPRR for SCPRR)
- Addition of a secondary objective to measure the impact of the EU dosing rule in the cohort of romiplostim exposed patients and related endpoints to describe platelet count and monitored dosage adjustment
- Clarification of annual calendar year interim study reports for calendar date cut-off for all data sources and emphasis on cumulative data
- Clarification of chronic ITP cohort with cohort exclusion criteria for 1) thrombocytopenia not due to ITP by specific diagnoses in Appendix 2 and 2) lack of a platelet count below 150 x 10^9/L without obvious cause in the 6 months before or after their first ITP diagnosis code
- Expansion of time window for exclusion criteria for thrombocytopenia not due to ITP from any time prior to the first available code for ITP to 6 months after the qualifying ITP diagnosis
- Clarification that some clinical outcomes (eg, those derived from platelet counts) may be identified from review of medical records such that not all clinical outcomes are solely identified through ICD-10 codes from the NHRS databases
- Clarification that identification of off-label use of romiplostim will follow adoption of national drug codes for romiplostim
- Clarification that primary data collection (abstraction of charts) on an annual basis will be exclusive to patients who were seen in hospital (inpatient or outpatient) contact including hematology clinic visits during each reporting period
- Addition that patient centered narratives will be added to interim and final reports for romiplostim-exposed patients who develop hematologic malignancies and other conditions, BM reticulin, BM fibrosis, hematological malignancies, secondary thrombocytopenia, or clustering of events in order to illustrate underlying risk factors
- Clarification that comparison of Study results to those from other sources will be limited to those with sufficient data

- Clarification that final report will be completed within 9 months following the availability of all national data (previous protocol versions did not anticipate data lag for availability of NHRS data, medical record chart abstraction, and time for analysis)
- Clarification that patients will be considered to be on “maintenance” therapy when the patient receives the same dose of romiplostim for 4 subsequent weeks
- Delete appendices 1 and 2 which were not referenced in the body text of the protocol (each consisted of a single placeholder page with the short name of an external study)

Description of Changes

Section: Global, Protocol amendment date

Change: Amendment date changed to 14 May 2012 from 30 July 2009

Section: Global

Change: Replaced: SCPRR with: **NCPRR**

Section: Global

Change: Replaced: Finland with: **Norway**

Section: Global: Protocol Title

Replace:

Population Based Prospective Annual Assessment of Safety of Romiplostim Treatment in Adult Patients with Chronic Idiopathic (Immune) Thrombocytopenic Purpura (ITP) Based on National Health Registry Systems in Denmark, Sweden, and Finland

With:

Population Based Prospective Annual Assessment of Safety of Romiplostim Treatment in Adult Patients with Chronic Idiopathic (Immune) Thrombocytopenic Purpura (ITP) Based on National Health Registry Systems in Denmark, Sweden, and **Norway**

Section: Global

Renumber Appendices after deletion of appendices 1 and 2

Section: Short title

Replace:

(Also known as the Scandinavian Country Patient Registry for Romiplostim [SCPRR])

With:

(Also known as the **Nordic** Country Patient Registry for Romiplostim [**NCPRR**])

Amendment #2

Protocol Title: Population Based Prospective Annual Assessment of Safety of Romiplostim Treatment in Adult Patients with Chronic Idiopathic (Immune) Thrombocytopenic Purpura (ITP) Based on National Health Registry Systems in Denmark, Sweden, and Finland

Amgen Protocol Number (20070797)

Amendment Date: July 30, 2009

Rationale:

Development and refinement of the Statistical Analysis Plan for Protocol 20070797, the *Population Based Prospective Annual Assessment of Safety of Romiplostim Treatment in Adult Patients with Chronic Idiopathic (Immune) Thrombocytopenic Purpura (ITP) Based on National Health Registry Systems in Denmark, Sweden, and Finland* (also known as the Scandinavian Country Patient Registry for Romiplostim [SCPRR]), has resulted in language changes to objectives and study design. This revised language has been reflected in this amendment to protocol 20070797, and comprise the key changes specified below.

CCI [redacted]

Description of Changes:

Section: Cover Page,

Addition: **Amendment 2**

Date: **30 July 2009**

Section: **Protocol Synopsis, Disease and Condition of the Patient Registry**

Replace: The study titled *Population Based Prospective Annual Assessment of Safety of Romiplostim Treatment in Adult Patients with Chronic ITP Based on National Health Registry Systems in Denmark, Sweden, and Finland* is also known as the "Scandinavian Country Patient Registry for Romiplostim (SCPRR)." The SCPRR is a patient registry established on the basis of the National Health Registry Systems (NHRS) of three ~~Scandinavian~~ countries: Denmark, Sweden, and Finland. Patients who receive romiplostim therapy between January 2009 and December 2019 will be included in the patient registry through the existing NHRS databases.

CCI [redacted]

Amendment #1

Protocol Title: Population Based Prospective Annual Assessment of Safety of Romiplostim Treatment in Adult Patients with Chronic Idiopathic (Immune) Thrombocytopenic Purpura (ITP) Based on National Health Registry Systems in Denmark, Sweden, and Finland

Amgen Protocol Number (20070797)

Amendment Date: April 17, 2009

Rationale:

Following approval of Protocol 20070797, the *Population Based Prospective Annual Assessment of Safety of Romiplostim Treatment in Adult Patients with Chronic Idiopathic (Immune) Thrombocytopenic Purpura (ITP) Based on National Health Registry Systems in Denmark, Sweden, and Finland* (also known as the Scandinavian Country Patient Registry for Romiplostim [SCPRR]), the Amgen Study Team and International Investigators have collaborated to define the roles and responsibilities for those who will administer the registry protocol. These administrative duties have been amended to protocol 20070797, and comprise the key changes specified below.

CCI [redacted]

Description of Changes:

Section: Cover Page,

Addition: **Amendment Date: 17 April 2009**

Replace: Key CRO Contact: PPD PhD
Institute for Statistical & Epidemiological Cancer Research
Pieni Roobertinkatu 9
FI-00130 Helsinki, Finland
phone PPD
email:

With: PPD **MD, PhD**
Department of Genetic Epidemiology,
Folkhälsan Research Center, Biomedicum Helsinki
Haartmansgatan 8
PB 63 (C312), FIN-00014 HU
phone: PPD
email: PPD

CCI [redacted]