

### Summary Table of Study Protocol

<b>Title</b>	Use of Bone Marrow Biopsies in Patients With Chronic Immune Thrombocytopenia: Predictors For, And Prognosis After – a Nordic Population-based Cohort Study And a Nested Case Control Study
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<b>Research Question and Objectives</b>	Among chronic immune thrombocytopenia (cITP) patients in the Nordic ITP Registry (Amgen study 20070797), the objectives are to: <ol style="list-style-type: none"><li>1) estimate prevalence of previous bone marrow biopsies at date of cITP diagnosis</li><li>2) estimate the incidence of bone marrow biopsy among patients with cITP</li><li>3) identify characteristics associated with an increased risk of having a bone marrow biopsy among patients with cITP</li><li>4) determine whether having a bone marrow biopsy was associated with a higher risk of death, hematological cancer, hospitalized bleeding events, or thrombotic events.</li></ol>
<b>Country(ies) of Study</b>	Denmark, Sweden and Norway
<b>Author(s)</b>	PPD

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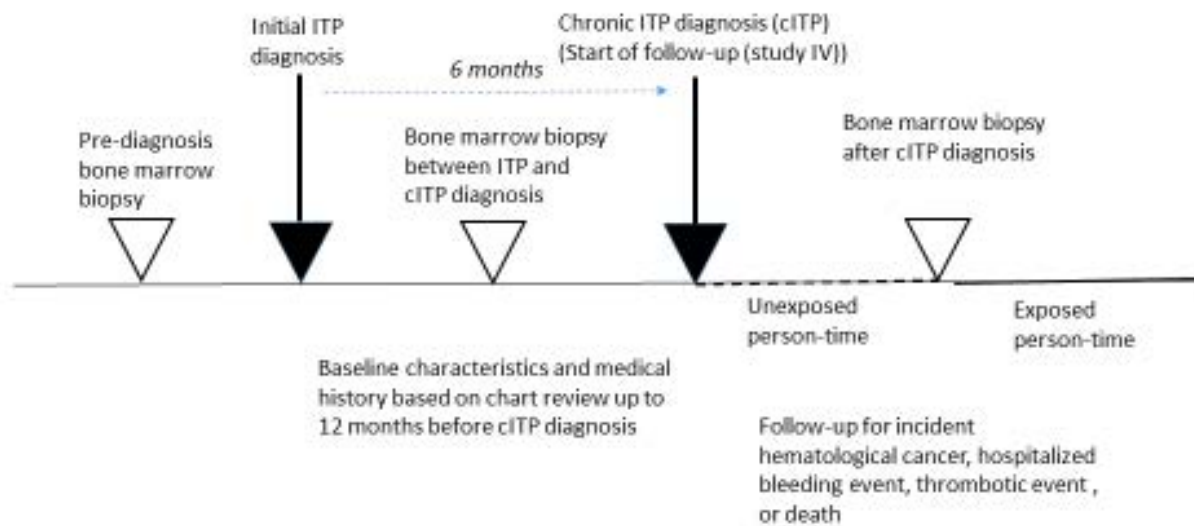
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Figure 1. Study Design Schema



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## 2. List of Abbreviations

ASH - American Society of Hematology

CI - Confidence interval

cITP - Chronic immune thrombocytopenia

IR - Incidence rate

ITP - Immune thrombocytopenia

NA – Not applicable

NCPRR - The Nordic Country Patient Registry for Romiplostim

NHRS - National Health Registry Systems

## 3. Responsible Parties

The project will be conducted by Department of Clinical Epidemiology, PPD [REDACTED], Denmark (Principal Scandinavian Investigator for NCPRR PPD [REDACTED] [REDACTED]) in collaboration with the PPD [REDACTED], Sweden (PPD [REDACTED]); the Department of Internal Medicine, PPD [REDACTED], Norway (PPD [REDACTED]); and PPD [REDACTED] (Lead Nplate Epidemiologist for Europe, PPD [REDACTED]).

## 4. Abstract

Study Title:

Use of bone marrow biopsies in patients with chronic immune thrombocytopenia: Predictors for and prognosis after – a Nordic population-based cohort study and a nested case control study

Study Background and Rationale:

Immune thrombocytopenia (ITP) is an acquired autoimmune disease characterized by low platelet count. It can be an isolated primary condition or it may be secondary to other conditions. According to the American Society of Hematology 2019 guidelines for immune thrombocytopenia, bone marrow examination is not necessary irrespective of age for patients presenting with typical ITP. Bone marrow examination is carried out to rule out leukemia, myelodysplastic syndrome or aplastic anemia. Accordingly, patients with chronic immune thrombocytopenia (cITP) who undergo bone marrow biopsy are not likely to be typical ITP patients. It's hypothesized that they have higher rates of hematological cancer, hospitalized bleeding events, thrombotic events and mortality, compared with cITP patients without bone marrow biopsy. This study will be conducted

to characterize cITP patients who undergo bone marrow biopsy in a population-based setting representing routine clinical practice.

#### Research Question and Objective(s)

- To estimate the prevalence of previous bone marrow biopsies at date of cITP diagnosis
- To estimate the incidence of bone marrow biopsy among patients with cITP
- To identify characteristics associated with an increased risk of having a bone marrow biopsy among patients with cITP
- To determine whether having a bone marrow biopsy is associated with a higher risk of death, hematological cancer, hospitalized bleeding events, or thrombotic events

#### Hypothesis:

No formal hypothesis will be tested and all analyses will be descriptive in nature.

- Study Design/Type  
A Nordic population-based cohort study and a nested case control study.
- Study Population or Data Resource  
The studies will be conducted using data from The Nordic Country Patient Registry for Romiplostim (NCPRR, Amgen study 20070797), which includes data from the National Health Registry Systems (NHRS) in Denmark, Sweden, and Norway during 2009–2016 enriched with data from medical record reviews.
- Summary of cITP patients Eligibility Criteria  
All adult ( $\geq 18$  years) cITP patients in Denmark, Sweden and Norway with cITP defined as two or more ITP diagnoses at least 6 months apart within the study period, were included if ITP diagnoses could be confirmed by the medical record review.
- Exclusion criteria:
  - A diagnosis consistent with secondary ITP within 5 years before the date of cITP
  - No recorded platelet count below  $150 \times 10^9/L$  according to the medical record
  - A secondary cause of thrombocytopenia stated in the medical record.
- Follow-up  
Patients will be followed from date of their cITP diagnosis until death, emigration, or end of follow-up (31 December 2017)

- Variables
  - *Outcome Variable(s)*

Bone marrow biopsy (and biopsy date for cases, or biopsy index date for controls) (objectives 1, 2 and 3), death, hematological cancer, hospitalized bleeding events, and thrombotic events (objective 4)
  - *Exposure Variable(s)*

Bone marrow biopsy (objective 4)
  - *Other Covariate(s)*

Age group, sex, country, year of cITP diagnosis, specific comorbidities, previous bleeding episodes (yes/no), lowest platelet count within 90 days before index date, previous splenectomy, previous bone marrow biopsy, previous treatment with cITP medication (within one year before cITP diagnosis date, one year or more before cITP diagnosis date, or never), previous number of ITP treatments, type of previous ITP treatment

- Study Sample Size

More than 5000 patients with cITP; approximately 540 of these patients had at least one bone marrow biopsy after cITP diagnosis.

- Data Analysis

Analyses will include the prevalence of bone marrow biopsies conducted before the date of first ITP diagnosis and between first ITP diagnosis and date of cITP diagnosis, overall and by baseline characteristics. The cumulative incidence of bone marrow biopsies in cITP patients, overall and by baseline characteristics will be estimated, while assuming death to be a competing risk, and estimated as a function of time since cITP diagnosis.

The nested case control analyses will estimate the frequencies and proportions of potential predictors for cases and controls, respectively. Conditional logistic regression analysis will be used to estimate odds ratios associating suggested predictors with occurrence of bone marrow biopsy while adjusting for age group, sex, country, previous bleeding episodes (yes/no), lowest platelet count, and previous cITP medication within 6 months of cITP diagnosis date.

For the prognostic cohort study, analyses will include bone marrow biopsy as a time varying exposure. All cITP patients will be followed-up until death, hematological cancer, hospitalized bleeding events, and thrombotic events from date of cITP.



Patients will contribute time at risk in the “no bone marrow biopsy” cohort until they have a bone marrow biopsy. These patients will enter the bone marrow biopsy cohort at the date of eventual bone marrow biopsy. Kaplan Meier curves will be constructed for mortality for the two cohorts and mortality rates will be computed. Incidence rates of hematological cancer, hospitalized bleeding events and thrombotic events for the two cohorts will be estimated. Cox regression will be used to compare mortality and other outcomes between the two cohorts using “no bone marrow biopsy” person-time as reference, while adjusting for baseline variables.

## **5. Amendments and Updates**

NA

## **6. Rationale and Background**

### **6.1 Diseases and Therapeutic Area**

Immune thrombocytopenia (ITP) is an acquired autoimmune disorder characterized by isolated thrombocytopenia due to immune-mediated accelerated platelet destruction and suppressed platelet production. ITP is currently classified as chronic (cITP) if the duration is 12 months or more. The estimated annual incidence of ITP is 1–3 per 100,000 adults ([Moulis et al, 2014](#); [Terrell et al, 2010](#); [Abrahamson et al, 2009](#); [Frederiksen et al, 1999](#)). At the time of romiplostim approval in Europe the definition for cITP was ITP lasting at least 6 months and as this study uses data collected since 1996, it is the definition that will be used in this study.

### **6.2 Rationale**

The ITP diagnosis is made by exclusion of secondary causes of thrombocytopenia: there is no diagnostic test to confirm the diagnosis. The American Society of Hematology (ASH) 2011 and 2019 guidelines for ITP state that there is no evidence for an age-threshold in which bone marrow biopsy should be required as part of the diagnostic work-up for ITP ([Neunert et al, 2019](#); [Neunert et al, 2011](#)). Accordingly, the ASH guideline recommendations specify that a bone marrow biopsy is not necessary in patients presenting with typical ITP - irrespective of age. It is, however, recommended that patients suspected of ITP – due to abnormalities in complete blood count, peripheral blood smear (other than thrombocytopenia), and microcytic anemia attributed to chronic blood loss - should be further investigated, for example with a bone marrow biopsy ([Neunert et al, 2019](#)).

Consequently, ITP patients who undergo bone marrow biopsy are likely to represent a selected group of patients with less typical disease and higher chance of secondary