PASS Information

Title	Primary Immune Thrombocytopenia Treated with Romiplostim in Routine Clinical Practice: A Retrospective Study from the United Kingdom Immune Thrombocytopenia Registry
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Country of Study	UK
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Marketing Authorisation Holder

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2. List of Abbreviations

Abbreviation	Definition
Anti-D	Rh_o(D) immune globulin
CAG	Confidentiality advisory group
CI	Confidence interval
EMR	Electronic medical record
EOI	Event of Interest
A&E	Accident and Emergency
HES	Hospital Episodes Statistics
HSCIC	Health and Social Care Information Centre
IVIg	Intravenous Immunoglobulin
IQR	Interquartile range
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
SE	Standard Error
TPO-ra	Thrombopoietin receptor agonist
UK	United Kingdom
UKITP Registry	United Kingdom Immune Thrombocytopenia Registry

3. Responsible Parties

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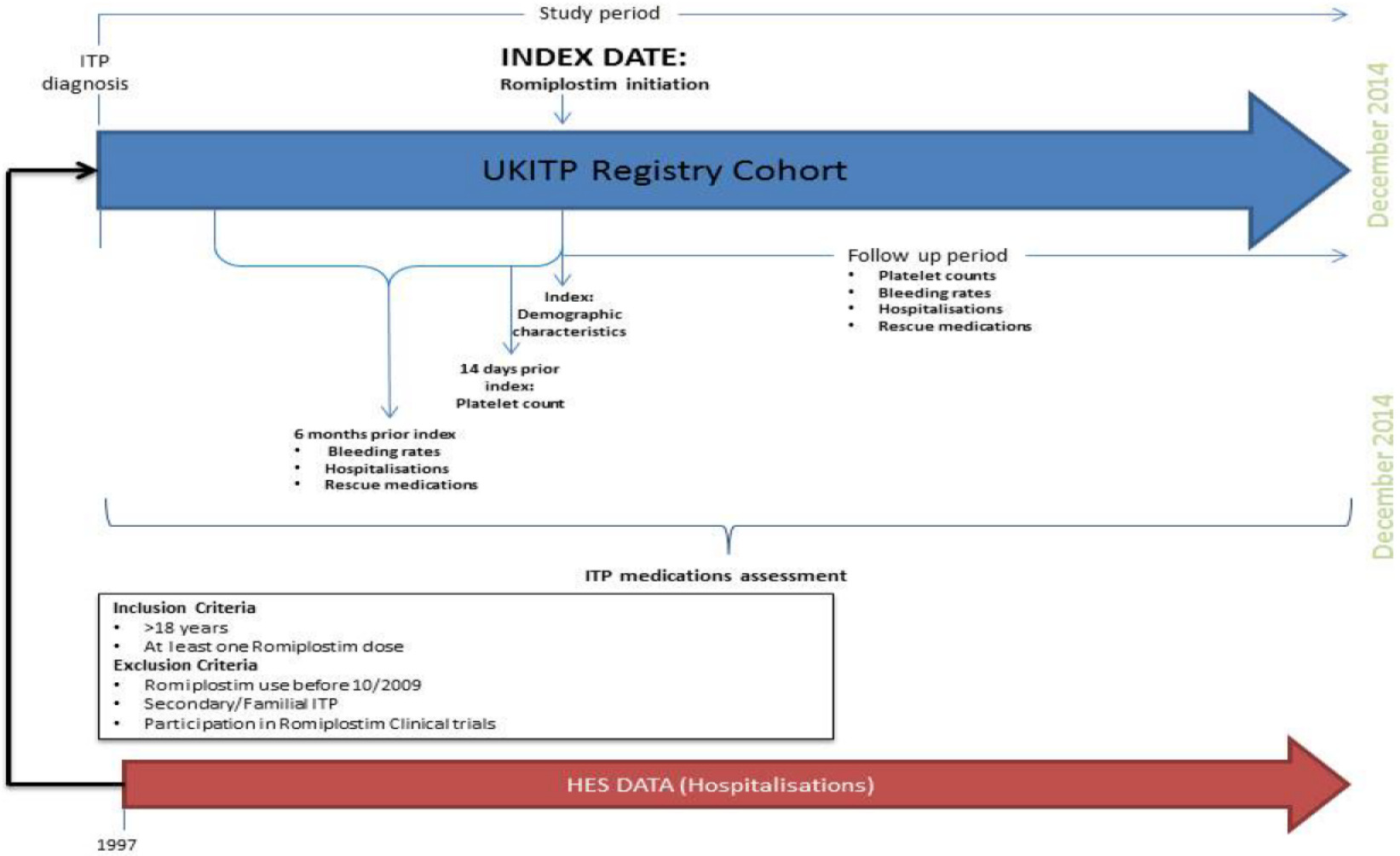
STUDY SCHEMA



4. Abstract

- **Title:**

Primary Immune Thrombocytopenia Treated with Romiplostim in Routine Clinical Practice: A Retrospective Study from the United Kingdom Immune Thrombocytopenia Registry

Version: 1.0

Date: 27 08 2015

Name and affiliation of main authors: PPD (Amgen), PPD (Amgen), PPD (Barts and The London School of Medicine and Dentistry)

- **Rationale and Background:**

Primary Immune Thrombocytopenia is a rare autoimmune blood disorder which is characterised by low platelets count and consequently bleeding. In the adult population, it is estimated to have a prevalence which ranges globally between 9.5 and 58.5 per 100,000 persons and has a yearly incidence of 1.6 to 3.9 per 100,000 persons. It is diagnosed in individuals who present with a platelet count which is below 100 x 10^9/L in the absence of any known thrombocytopenic-causing factors. First line treatment for primary ITP include corticosteroids, intravenous Immunoglobulin (IVIg) and Rh_o(D) immune globulin (anti-D). Patients who are unresponsive to these drugs are considered for second line treatments such as danazol, mycophenolate, azathioprine, cyclosporine, rituximab, and TPO receptor agonists. Romiplostim is a thrombopoietin receptor agonist (TPO-ra) that was recommended by the National Institute for Health and Care Excellence (NICE) in 2011 for the treatment of chronic ITP. NICE recommends the use of romiplostim in accordance with its marketing authorisation; that is in both splenectomised and non-splenectomised (where surgery is contra-indicated) adults when standard treatment options and rescue therapies have failed or the patient has severe disease and is at high risk of bleeding.

Data sources available in the UK to investigate ITP have so far been limited to the General Practice Research Database, a primary care database of 8% of the UK population. Studies based on this data have further described the epidemiology and clinical course of ITP beyond the relatively small number of ITP patients published in the literature at the time. However, ITP is treated mainly in secondary care rather than general practice thus detailed clinical information on comorbidities, medication use (such as romiplostim) and platelet counts may not be complete. Linking with Hospital Episodes Statistics (HES) data can provide further information on hospitalisation events in the GPRD population but does not provide detailed information on treatment in secondary care.

The United Kingdom Immune Thrombocytopenia (UKITP) Registry retrospectively and prospectively collects demographic and ITP-related clinical data (treatment, comorbidities and laboratory results) on ITP subjects who agree to be part of the Registry and its studies. Through a network of 56 centres throughout the UK the Registry has recruited a total of 1153 individuals by July 2014 with comprehensive data collected through notes extraction or during the subjects' clinic visits. According to Schoonen and Fryzek (2007), the maximum prevalence of adult ITP in the UK is 18,057 patients and therefore the registry currently covers approximately 6% of the total ITP population in the country.

This study will help to describe the ITP patient population who has been prescribed romiplostim in the UK in terms of clinical and disease characteristics and provide details on romiplostim use, rate of bleeding and hospitalisation. Moreover, this study will also describe the pattern of rituximab administration in patients who have received romiplostim as an exploratory analysis to investigate the level of use of this drug as second-line therapy.

- **Research Question and Objectives:**

Primary Objective:

- Describe the demographic (sex, age, ethnicity) and clinical characteristics (specific comorbidities, age at ITP diagnosis, at the time of romiplostim initiation (index date).
- Describe ITP medication (before and after index date) and platelet counts prior to and post-index date) in the study population.

Secondary Objective:

- Describe the pattern of romiplostim administration in terms of timing (time from diagnosis), exposure (duration, maximum dose) and pattern (number and duration of courses, discontinuation).
- Estimate the rate of bleeding events prior to and post-index date.
- Estimate the rates of all cause and cause-specific hospitalisations prior to and post-index date
- Estimate the rate of rescue medications use prior and post-index date.

Exploratory objective:

- Describe the pattern of rituximab administration in patients who have received romiplostim.
- Describe the primary and secondary endpoints in the study population categorised by splenectomy status at index date.

- **Study Design:**

This study is a retrospective cohort study using data from the UK ITP Registry which involves both retrospective and prospective data collection from patient records.

- **Population:**

Subjects will be selected from the UKITP Registry population for whom there is complete data up to end December 2014. All subjects who were 18 years and over at diagnosis of primary ITP (secondary or familial ITP cases are not included) and received at least one dose of romiplostim after UK launch in October 2009 will be included. Subjects who are identified to have had secondary ITP or who took part in any romiplostim clinical trial will be excluded.

- **Baseline, Index Date and Follow-up:**

Index date will be defined at the first time use of romiplostim. Demographic characteristics will be assessed at index date. Comorbidities will be assessed during a period of one year prior to index date. Prior platelet counts will be assessed for a period of 14 days prior to index date. Prior bleeding rates, hospitalisations and rescue medication use will be assessed for 6 months prior to index date. Follow-up will start at the index date to until a subject exits the registry for any reason or the end of the study period (i.e. end of December 2014), whichever comes first. The number and sequence

of ITP medications will be assessed during the period from ITP diagnosis until end of study period.

- **Variables:**

Primary Endpoint/Outcomes:

Demographic (sex, age, ethnicity) and clinical characteristics (specific comorbidities, age at ITP diagnosis,) will be described using descriptive statistics. The number and proportion of patients receiving ITP medications will be described as well as the sequence of medications. Minimum, maximum and pooled platelet counts will be summarised by different time periods, before (14 days) and after index date. Continuous variables will be described using means (standard deviation) and medians (interquartile range, minimum and maximum values) and categorical variables will be describe using frequencies and percentages.

Secondary Endpoints/Outcomes:

- The pattern of romiplostim administration will be described after index date, including duration of administration and maximum dose, number of courses, course duration and number of subject with maximum dose greater than 10mcg/kg.
-Rate of bleeding events prior to (6 months) and post-index date.
-Rate of all cause and cause-specific hospitalisation events prior to (6 months) and post-index date.
-Rate of rescue medication use (IVIg, IV steroids/methylprednisolone, platelet transfusions and IV Rho Ig) prior (6 months) and post-index date.

- **Data Sources:**

The UKITP Registry is the primary source of data for this study. It is a natural cohort of individuals with primary ITP who have volunteered to contribute their demographic and clinical data to be used in the Registry's studies. Currently, the Registry has a network of 56 centres throughout the UK through which it recruits its subjects.The Registry has also linked its subjects' records to those managed by the Health and Social Care Information Centre (HSCIC), namely Hospital Episodes Statistics (HES), and as such, HES data will be used to provide estimates on hospitalisation in this study.

- **Study Size:**

The UKITP Registry cohort contains comprehensive data on over 1150 individuals, of whom at least 84 have received romiplostim. Of those, we expect approximately 30 to also have received rituximab.

- **Data Analysis:**

This analysis is descriptive in nature and no formal hypothesis will be tested. To describe the cohort's characteristics, univariate analysis will be adopted using frequencies and percentages for categorical variables and the mean (standard deviation) and median (interquartile range, minimum and maximum value) for continuous variables. For measuring rate of events of interest in person-time, the number of events during the time at risk will be divided by the total person-time at risk. Rates for bleeding, hospitalisation and rescue medications will also be calculated and plotted at intervals over time before and after index date. A 95% confidence interval (Poisson) will be generated for each estimate. Random effects models will be employed to account for the within-patient correlation, induced by multiple platelet counts per patient. For a full description of statistical analysis methods, refer to Section 9.7.

- **Milestones:** Start of data collection in September 2015, end of data collection by December 2015, and final report by December 2016

5. Amendments and Updates

None (first version)

6. Milestones

Milestone	Planned date
Start of data collection	September 2015
End of data collection	December 2015
Final report of study results	December 2016

7. Rationale and Background

7.1 Disease and Therapeutic Area

Primary immune thrombocytopenia (Primary ITP) is a rare bleeding disorder. Its pathophysiology is increasingly explained within an autoimmune paradigm in which circulating platelets are destroyed or its megakaryocytic production is compromised by one's own immune responses (1). In the adult population, it is estimated to have a prevalence which range between 9.5 and 58.5 per 100,000 persons and has a yearly incidence of between1.6 to 3.9 per 100,000 persons (2-5). Primary ITP is diagnosed in individuals who present with low platelet count (100 x 10^9/L) and through the elimination of any secondary causes of thrombocytopenia (6). The symptoms can range from mild bruising to severe bleeding such as cerebrovascular haemorrhage (7). About a third of individuals with primary ITP can spontaneously recover, but the rest can relapse following treatment, which can range from days to decades, or can have longer lasting manifestations of symptoms and lowered platelet count (8). Death from bleeding complications has been estimated to be lower than 14% in the ITP population (5, 7). The 5 year mortality rate from primary ITP has been estimated using longitudinal studies at around 22-24% (9, 10).

The treatment paradigm for primary ITP has undergone several changes over time but the therapeutic aim has remained the same, to increase and maintain platelet count in order to prevent recurrence of a platelet count drop and bleeding. Corticosteroid and/or other IVIg or AntiD are the first line therapies. Failure to respond to these therapies would result in second line treatment options, such as Danazol, Mycophenolate, Azathioprine, Cyclosporine, Rituximab, and TPO receptor agonists. Splenectomy is also a second line choice for those who can undergo this surgical intervention. The detailed recommendations how these treatments can be applied are found in the International Consensus report on the investigation and management of ITP (which is employed in the UK) and the ASH's evidence-based practice guideline for ITP (6, 11).

Romiplostim (Nplate®) is a therapeutic agent that was recommended by NICE in 2011 to treat chronic ITP. It is a thrombopoietin (TPO) mimetic agent which acts as an agonist

at thrombopoietin receptors to stimulate the production of platelets production. The NICE recommendation for romiplostim is as follows:

"Romiplostim is recommended as an option for treating adults with chronic immune (idiopathic) thrombocytopenic purpura, within its marketing authorisation (that is, in adults who have had a splenectomy and whose condition is refractory to other treatments, or as a second-line treatment in adults who have not had a splenectomy because surgery is contraindicated), only if: their condition is refractory to standard active treatments and rescue therapies, or they have severe disease and a high risk of bleeding that needs frequent courses of rescue therapies and if the manufacturer makes romiplostim available with the discount agreed in the patient access scheme."(12)

Since recommendation for use in the UK, its efficacy in clinical trial populations is well published but there is limited published evidence about its use in real life settings in the UK. This present study therefore aims to describe the use of romiplostim in a natural cohort of individuals with primary ITP within the UK, to describe platelet count pattern, and estimate the rate of bleeding events, hospitalisation and rescue medication use before and after receiving this drug. The study will also describe how rituximab was prescribed among patients who also received romiplostim.

7.2 Rationale

The incidence of ITP in the UK was estimated based on an analysis of the UK population from the General Practice Research Database (GPRD) from 1990 to 2005. Schoonen et al estimated an incidence of 3.9 per 100,000 patient-years (95% CI: 3.7 to 4.1) (5). Satia et al estimated average ITP incidence in the UK to be 3.0 per 100,000 patient-years also from the GPRD (13). The GPRD has also been used by a number of studies to provide further descriptive epidemiology on ITP in the UK including studies on comorbidities (14), prevalence (3) and thromboembolic events (15).These studies have further described the epidemiology and clinical course of ITP beyond the relatively small number of ITP patients published in the literature at the time. However, ITP is treated mainly in secondary care and detailed clinical information on comorbidities, medication use (such as romiplostim), and platelet counts may not be complete.

In 2007, Amgen initiated a European single arm, non-interventional, long term observational study (20070225) of adult patients with ITP in order to collect such information. This study aimed to describe the patient profile (in terms of demographics, ITP and romiplostim history and splenectomy status), romiplostim utilisation and dosing requirements, concomitant ITP therapies, adverse drug reactions, clinically relevant bleeding events, healthcare resource utilization, and reasons for romiplostim discontinuation. The study enrolled subjects from 7 European countries: Austria, Belgium, Czech Republic, France, Greece, Portugal, and Sweden, but did not include any patients from the UK.

The results of this European study show that the safety and efficacy profile of romiplostim when used in routine clinical practice is consistent with the efficacy data from clinical studies (16). The study showed that patients achieved sustained increases in platelet counts and a notable reduction in grade ≥3 bleeds. Patients also received similar doses as those reported in the pivotal randomised controlled clinical trials with no

new safety signals and few patients discontinuing romiplostim due to adverse drug reactions (ADRs).

The retrospective cohort study described in this document will help to describe the ITP patient population who has been prescribed romiplostim in the UK using the first available data source to contain the required information. This study will describe the clinical and disease characteristics of patients who have been prescribed romiplostim in the registry and provide details on romiplostim and rituximab use, platelet counts, rates of bleeding, hospitalisation and rescue medication use. This information will contribute to the available published data on ITP patients in the UK as well as strengthen access to romiplostim and support the use of romiplostim in European markets.

8. Research Question and Objectives

Primary Objective:

- Describe the demographic (sex, age, ethnicity) and clinical characteristics (specific comorbidities, age at ITP diagnosisof patients who have received romiplostim at the time of romiplostim initiation (index date).
- Describe ITP medication use since diagnosis (before and after index date) and platelet counts prior to and post-index date in the study population.

Secondary Objectives:

- Describe the pattern of romiplostim administration in terms of timing (time from diagnosis), exposure (duration, maximum dose) and pattern (number and duration of courses, discontinuation).
- Estimate the rate of bleeding events prior to and post-index date.
- Estimate the rates of all cause and cause-specific hospitalisations prior to and post-index date.
- Estimate the rate of rescue medication use prior to and post-romiplostim initiation.

Exploratory objective:

- Describe the pattern of rituximab administration in patients who have received romiplostim.
- Describe the primary and secondary endpoints in the study population categorised by splenectomy status at index date

9. Research Methods

9.1 Study Design

This study is a retrospective cohort study using data from the UK ITP Registry which involves both retrospective and prospective data collection.

9.2 Setting

9.2.1 Study population

The UKITP Registry has now collected ample longitudinal data on 1,400 consented primary ITP patients, of which over 1150 have complete and comprehensive demographic data and biological samples (1,138 blood and 150 saliva samples). This will allow the conduct of adequately powered studies to understand the disease's aetiology and epidemiology, and the effectiveness of contemporary ITP treatment paradigms to improve outcomes. According to Schoonen and Fryzek (2007), the maximum prevalence of adult ITP in the UK is 18,057 patients and therefore the registry is expected to cover around 6% of the total ITP population in the country.

As of December 2014, approximately 84 subjects were found to have received at least one dose of romiplostim. This group of subjects will form the study sample and a sub-cohort of subjects who received rituximab within this sample will also be defined. No survey has been conducted to date to establish how many haematology teams across the National Health Service care for patients with primary ITP. The Registry is the largest pool of subjects with primary ITP in the UK and can be regarded as the most comprehensive sample of the primary ITP population for the UK.

9.2.2 Eligibility criteria

9.2.2.1 Inclusion Criteria

This study will include all adults (18 years and over at ITP diagnosis) from the Registry who had at least one dose of romiplostim after launch in the UK in October 2009. Although, most patients would have received romiplostim after the NICE recommendation in April 2011, some patients may have obtained it through individual funding requests. Any patients included during this time will be checked.

9.2.2.2 Exclusion Criteria

The Registry does not recruit any individuals who are diagnosed to have secondary or familial ITP. Should any subjects be identified to have secondary or familial ITP while the data is being prepared for analysis, they will be excluded. Subjects identified to have been involved in clinical trials for romiplostim in the past will also be excluded from this study.

9.2.3 Baseline covariate assessments and Follow up

9.2.3.1 Study period

The UKITP Registry cohort consists of data collected throughout the lifetime of its subjects. The study period is defined from the date of ITP diagnosis until end of follow-up or 31st December 2014 (the date the cohort was closed for this study), whichever comes first. ITP medications will be assessed during the period from ITP diagnosis until end of study period.

9.2.3.2 Baseline period and Index Date

Index date will be defined as the first time use of romiplostim. Demographic characteristics will be assessed at index date. Comorbidities will be assessed for a period of one year prior to index date. Prior platelet counts will be assessed in a period of 14 days prior to index date . Prior bleeding rates, hospitalisations and rescue medications will be assessed during 6 months prior to index date .

9.2.3.3 Study Follow-up Period

Follow-up will start at first exposure to romiplostim Follow-up will continue post-index date until a subject exits the study for any reason (e.g. leave study the registry, death, or loss to follow up) or the end of the study period (i.e. end of December 2014), whichever comes first.

9.3 Variables

Demographic and clinical characteristics:

- Sex (male, female): (n, %)
- Ethnicity (White, African / Caribbean, Asian, Mixed, Other): (n, %)
- Specific comorbidities (listed in Annex 6)
- Age at ITP diagnosis (years)
- Age at registration (years)
- Age at index date (years)
- Year of diagnosis (year)
- ITP therapy use prior to and after romiplostim initiation;
    - Number and type of medications: (n,%)
    - Sequence of therapies after ITP diagnosis
    - Number of transfusions (blood and platelets)

Pattern of romiplostim administration:

- Time from diagnosis to index date (years)
- Number of romiplostim courses
- Number and proportion of patients with dose >10mcg/Kg/wk (n,%)
- Total treatment duration and by courses (weeks)
- Time in-between courses (weeks)
- Maximum dose per patient and by course (mcg/kg)
- Number and proportion of discontinuations
- Time from index date to last dose for those who discontinued

Platelet counts, bleeding events, hospitalisations and rescue medication use

- Platelet counts prior to and after index date ($x10^9$/L)
- Rate of bleeding events prior to and after index date (events/person time) Rate of hospitalisations prior to and after index date (events/person time)
- Rate of rescue medication (IVIg, IVsteroids, platelet transfusions and IV Rho Ig) use prior to and after index date (events/person time)

Pattern of rituximab administration

- Total treatment duration and by courses (weeks)
- Number of courses

9.4 Data Sources

The UKITP Registry is a national registry which enrols subjects with primary ITP from different parts of the UK. Currently, the Registry has 56 centres, with at least one centre in Scotland, Wales and Northern Ireland (Appendix A). The Royal London Hospital (RLH; part of Barts Health NHS Trust) is the largest secondary and tertiary centre for ITP care and jointly hosts the core UKITP Registry team with Barts and The London School of Medicine and Dentistry, Queen Mary University London.

The Registry actively encourages participation from other haematology teams across the UK and those with an interest to join contact the Registry team to initiate the process. Potential sites do not require Site Specific Assessment (SSA) and only need approval from their local R&D to initiate recruitment for the Registry. After the R&D approval is obtained sites are able to enrol subjects locally. Each site has its own local Principal Investigator (PI) who is responsible for the study coordination locally which includes recruitment, data collection, biological sample collection, and liaising with the core Registry team.

The Registry team is responsible for operations and coordinating the overall data collection from the regional centres within the NHS. Recruitment occurs via the Registry's centres throughout the UK and at the Royal London Hospital (RLH). Regional centres collaborate with the Registry on a voluntary basis. Data is collected from the subject's medical notes, hospital electronic records, and from the data received from the subject's General Practitioner. This is done at the time of enrolment and as the data become available, or at a minimum annually during follow up. Certain information is also directly reported by the subjects to their clinician who can directly enter information to the data collections forms for the medical notes reviewer to extract from. Medical record reviewers can be consultant haematologists, research nurses, data managers, research administrators, and research assistants and are responsible for data extraction. Should they require any advice or guidance on data extraction or other study-related issues, they can contact the core Registry team at the RLH. All collected data are entered on the Registry's online database and backed up regularly. The fields collected from medical records which are relevant for this study are presented in appendix B.

To obtain a more complete medical history and understanding of the subject's interaction with the NHS, the Registry liaises with the Health and Social Care Information Centre (HSCIC) to receive Hospital Episodes Statistics (HES) for subjects enrolled in the registry. The HES data consists of inpatient, outpatient, accident and emergency, and critical care datasets in which the NHS numbers, names, addresses and date of birth are used to link the records of patients in the HSCIC to those in the registry. The detail around the HES data received from the HSCIC is as follows:

i. Inpatients dataset (Admitted Patients Data) contains the primary reasons for admission given in the form of International Classification of Disease version 10 (ICD-10) diagnoses codes and their corresponding admission dates;

ii. Outpatients dataset contains the records of patients' appointments at outpatient clinics throughout the NHS; the reasons for the outpatient appointments are given as ICD-10 codes accompanied by the respective dates of these appointments;

iii. Accident & Emergency (A&E) dataset includes the reasons for attendances in A&E Departments and the dates of these attendances; this is provided in the form of A&E diagnosis codes (not ICD 10 codes) and the respective arrival dates in the A&E Departments;

iv. Critical Care dataset contains the types of critical care support provided and the dates these were started.

HES data linked to registry participants are available from 1997 through to the end 2014 and will primarily be used to identify hospitalisations events of study subjects. The registry population has an approximately 98% match to the HES dataset. Any eligible study subjects not linked will not be included in the study.

9.5 Study Size

This is a natural cohort of individuals where the precision of the estimates will be dictated by the sample size of the cohort available for investigation. The Romiplostim cohort was estimated to have at least 84 subjects during a crude count as a pre-protocol assessment. Given that the cohort has a minimum of 84 individuals at this stage, the 95% confidence intervals are likely to be wide. Those for stratified analysis by covariate levels are bound to be wider due to the lower numbers per stratum.

Estimates of the width of the confidence intervals for a rate in person-years and for proportions are provided below. The rates of events in person-years is dependent on the number of events (bleeding or hospitalisation) observed over the total person-years at risk. Table 1 provides estimates on the width of the confidence intervals (as derived using exact poisson method) based on a range of total person-years and frequency of events.

Table 1. Expected 95% confidence interval estimates for event rates

Number of event	Based of 1 person-year per subject				Based of 4 person-years per subject			
	total person-year	rate per 100 person years	95% CI		total person-year	rate per 100 person years	95% CI	
			Lower	upper			Lower	upper
10	84	11.9	5.7	21.9	336	3.0	1.4	5.5
20	84	23.8	14.5	36.8	336	6.0	3.6	9.2
30	84	35.7	24.1	51.0	336	8.9	6.0	12.7
40	84	47.6	34.0	64.8	336	11.9	8.5	16.2

50	84	59.5	44.2	78.5	336	14.9	11.0	19.6
60	84	71.4	54.5	91.9	336	17.9	13.6	23.0
70	84	83.3	65.0	105.3	336	20.8	16.2	26.3
80	84	95.2	75.5	118.5	336	23.8	18.9	29.6

The possible confidence intervals for the set of percentages below were estimated (using exact binomial method) based on a minimum overall cohort of 84 subjects and a possible sub-cohort (or stratum) of 42 subjects, respectively.

Table 2. Expected 95% confidence interval estimates for proportions

Number of event	Sample size	Percentage %	95% CI		Sample size	Percentage %	95% CI	
			Lower	Upper			Lower	Upper
10	84	11.9	5.9	20.8	42	23.8	12.1	39.5
20	84	23.8	15.2	34.3	42	47.6	32.0	63.6
30	84	35.7	25.6	46.9	42	71.4	55.4	84.3
40	84	47.6	36.6	58.8				
50	84	59.5	48.3	70.1				
60	84	71.4	60.5	80.8				
70	84	83.3	73.6	90.6				
80	84	95.2	88.3	98.7				

The planned exploratory objectives include examining a subset of the romiplostim cohort and stratifying primary and secondary endpoints by splenectomy status.As a result, the sample sizes will be smaller than the above and the subsequent confidence intervals will be even wider. The second exploratory objective will only be performed if the number of splenectomised patients is large enough to allow sufficient estimations.

9.6 Data Management

The UKITP Registry will use its data to carry out this study. The Registry uses the data linkage service from the HSCIC to link subject data to HES data to improve data quality, completeness and to reduce loss to follow up (e.g. due to population mobility from a region with a collaborating centre to another without a collaboration centre). Data linkage of registry data to HES data has been achieved after approval from the confidentiality advisory group (CAG) and those who consented for their records to be linked. These datasets were obtained at the beginning of 2015 and included NHS datasets (Accident & Emergency Departments, In-patient Services, Out-patient Services, and Critical Care Departments) for episodes which occurred from 1997 to 2014.

9.7 Data Analysis

This analysis is descriptive in nature and no formal hypothesis will be tested. To describe the cohort's characteristics, univariate analysis will be adopted using frequencies and percentages for categorical variables and the mean (standard deviation)

and median (interquartile range, minimum and maximum value) for continuous variables. For measuring rate of events of interest in person-time, the number of events during the time at risk will be divided by the total person-time at risk. Rates for bleeding, hospitalisation and rescue medications will also be calculated and plotted at intervals over time before and after index date. Primary and secondary endpoints may also be stratified by other clinically relevant variables including but not limited to platelet count at index date. A 95% confidence interval (Poisson) will be generated for each estimate. Random effects models will be employed to account for the within-patient correlation, induced by multiple platelet counts per patient.

9.7.1 Analysis Sets

Two analysis sets will be identified:

- The overall romiplostim cohort;
- The sub-cohort of romiplostim and rituximab subjects defined as subjects who have received at least one dose of romiplostim and at least one dose of rituximab.

9.7.2 Subgroups

Primary and secondary outcomes, where appropriate, will also be stratified by the splenectomy status of patients Analysis for this sub cohort will be considered only if the number of splenectomised patients is large enough to allow sufficient estimations.

9.8 Quality Control

Data from the participating centres are uploaded onto the secure Registry online database. Data checks are carried out at regular intervals by the Registry team and checked for errors and missing data. Any queries are referred to the relevant centres for corrections and clarifications. Since this study draws its data primarily from medical records, the information contained in the medical record is considered to be reliable, especially the data relating to diagnosis and treatment. Where the data present in the medical record is partially complete (such as only the year that an event occurred is present), and in the event of missing data (such as dates an event occurred or event that occurred sometime before), this will be verified against the available HES data for the subjects concerned.

Prior to any analyses, the data collected undergo a rigorous data checking process where outliers, missing data and potential erroneous entries are identified and rechecked against original sources. This requires coordination with all the centres throughout the UK. Remaining ones are checked against the data contained in the HES datasets and amended accordingly.

9.9 Limitations of the Research Methods

9.9.1 Internal Validity of Study Design

9.9.1.1 Measurement Error(s)/Misclassification(s) and Information Bias

A small proportion of secondary ITP cases may be misdiagnosed as having primary ITP. Should this become evident the individuals concerned will not be enrolled into further studies on primary ITP. Data on biological markers come from different centres and laboratories and may vary in accuracy due to different equipment and methods used in their measurements. As for all administrative databases, such as HES, there is a degree of miscoding which can lead to systematic errors.

There are several sources of misclassification:

- At clinical history taking due to recall bias by patients about their conditions, treatment and specific dates of clinically meaningful events;
- During extraction due to data entry errors (minimised by double entry: first onto a paper form and then in the electronic database; also, providing ranges to check against before entering into the database);
- Illegible entries on clinical notes difficult for data extractors to interpret;
- Coding errors, especially with HES data, is a possibility.
- The registry database contains a mixture of retrospectively and prospectively collected data. Rompiplostim is largely used in chronic ITP patients and as such may have many years of data available. The quality of clinical data collected may differ if collected more recently or if collected prospectively.

Reducing missclassification and measurement error is a high priority activity by the Registry team and checks are made against different data sources to minismise it, e.g HES data. It is anticipated that any any misclassification or measurement error due to miscoding or data entry erros is unlikely to differ between sub categories in the protocol. Romiplostim was only available in the UK from October 2009 so information bias is minimised by describing key endpoints after romiplostim initiation and only up to 6 months before. Descriptions of ITP medications prior to index date and since diagnosis are kept to simple summaries.The proportion of patients with prospectively collected data since index date will also be described.

9.9.1.2 Selection Bias

The UKITP Registry recruits its regional centres and subjects as a result of voluntary collaboration and consent of participating haematologists and patients. For this reason, it is possible that the Registry is biased towards enrolling individuals who are in persistent, chronic or severe phases of the disorder and may be under-representing patients with a less severe form of the disorder or those who recover spontaneously. There is also a selection bias towards centres which have the resources (staff and funding) required to contribute data into the Registry.

The RLH is the largest secondary and tertiary centre for ITP care and jointly hosts the core UKITP Registry team with Barts and The London School of Medicine and Dentistry, Queen Mary University London. Subjects who are not local residents to the RLH's

catchment area but came to the hospital as tertiary referrals from distant hospitals are more likely to have severe or refractory primary ITP. By recruiting from other centres, the Registry will also capture less severe cases. Nevertheless, primary ITP seen at all the centres and RLH are generally those who are persistent, chronic and severe cases of ITP. However, this study aims to include patients who have received romiplostim who do tend to be the more severe and chronic cases of ITP.

The registry has a network of 56 participating centres; however, it is not known how many ITP centres exist in the UK. It is likely, however, that the largest centres have been included in the registry population and missing centres are likely to be small clinics with few patients. Therefore, we expect the registry to adequately represent the ITP population in the UK.

9.9.1.3 Confounding

The aim of this study is not to make causal inference or comparisons but seeks to describe clinical characteristics, romiplostim and rituximab use, bleeding rates and hospitalisation in patients who have received romiplostim in the UK. However, ITP is a complex condition in which the disease course and treatment pathway is likely to be individualised for each patient. Certain outcomes are being stratified by prior to and post-romiplostim initiation (Index Date) including medication use, platelet counts, bleeding and hospitalisation events. ITP is a progressive disease and severity is likely to increase over time from diagnosis and is likely to be related to the timing of romiplostim initiation (Index Date). Due to this complexity and individualsed treatment, however, it is difficult to adequately address all confounding factors that may be involved even with a large sample size of patients. Factors that may affect the key enpoints over time not only include disease severity and response to romiplostim but any pre-existing conditions or the development of new conditions, other ITP medications including rescue therapy or surgeries. The effect of romiplostim is not immediate and may last beyond the last dose. Patients may achieve a period of remission in which doses of romiplostim may not be required and the duration of these periods may vary or even allow discontinuation. This study aims to describe the pattern and duration of romiplostim courses as well as the key outcomes such as bleeding, platelet counts, hsopitalisation and rescue medication over time post romiplostim initation. Due to this variation, the outcomes across different time periods should not be compared. Additionally, unmeasured confounding is likely to be present in the study as clinical events can be a result of the disease, influenced by past medical condition or prior medications. Therefore, no inferences on the causality of endpoints will be made.

9.9.2 External Validity of Study Design

The Registry has one of the largest samples of individuals with primary ITP in Europe or other parts of the world. It has 56 centres throughout the UK, including at least one centre in Scotland, Northern Ireland and Wales. It is likely to be representative of practices in the UK but there are at times differences in availability of treatments in some parts. This is expected to have a minimal impact on this study.

9.9.3 Analysis Limitations

The Registry collects real life data and is therefore limited to what is contained within medical records and HES. There is a possibility that platelet counts or other similar markers may be unavailable following exposure to specific treatments. In these instances certain subjects cannot be followed throughout the follow up period. To provide an estimate of platelet count when these are missing for certain subjects, the mean and median platelet count based on the available counts from other subjects within time periods will be presented. For certain events, their dates of occurrence may be missing and this cannot be checked against HES. Therefore, it will not be possible to use the records for these subjects in analysis which are required in describing the occurrence of these events with reference to a point in time (e.g. whether a bleeding event occurred before or after treatment).

A key limitation of the analysis is the sample size of the full study population and the occurrence of possible small cell sizes during the descriptive analyses. ITP is a rare condition and only a small proportion of patients may end up being administered romiplostim, therefore, for a single country study the number of patients is actually quite reasonable.However, in a statistical sense, there are still limitations and the team will aim to use appropriate categorisations based on the numbers available and include descriptions of the denominator for rates to aid interpretation, where possible.

9.9.4 Limitations Due to Missing Data and/or Incomplete Data

Prospective data collected after a study is designed tend to be of better quality than historical data. Missing or incomplete data, especially those predating the Registry's start, are issues that the Registry is addressing by regular data checks and corrections by the centres. In some circumstances the data cannot be improved by the centres because they do not have the complete data. In this situation, the Registry draws on HES data to confirm occurrence of an event and its date. HES data only goes back to 1997 and therefore these checks are limited to this date. Missing and incomplete data is expected in this study and will become known during the analysis stage, but their occurrences have been minimised with measures described above and elsewhere in this protocol.

9.10 Other Aspects

9.10.1 Protocol Amendments and Study Termination

Amgen may amend the protocol at any time. If Amgen amends the protocol, written agreement from the collaborator must be obtained where applicable per local governing law and/or regulations.

Amgen reserves the right to terminate the study at any time. Both Amgen and the collaborator reserve the right to terminate the collaborator's participation in the study according to the contractual agreement.

10. Protection of Human Subjects

10.1 Informed Consent

The subjects have provided their informed consent to be part of the Registry and its studies. They have the right to remove their participations at any time without having to provide any reasons. Approval for the Registry to collect data under informed consent was obtained from the London Research Ethic Committee (07/H0718/57).

10.2 Institutional Review Board/Independent Ethics Committee

The Registry's activities and studies are reviewed by the Joint Research Management Office for Queen Mary University London and also approved by the London Research Ethics Committee in 2002 and 2007, including all its subsequent amendments. Regional centres do not need to seek additional local REC approvals but require their local Research and Development's administrative office to approve that it can participate in the Registry's studies**.**

10.3 Confidentiality

All data collected on the subjects are kept strictly confidential and within secure network and physical spaces. Any data used for analysis and reporting are de-identified. No person-identifiable information will be provided to Amgen.

11. Management and Reporting of Adverse Events/Adverse Reactions

Individual event collection and reporting is not applicable to this study.

12. Plans for Disseminating and Communicating Study Results

The results of this study will be published. Authorship of any publications resulting from this study will be determined on the basis of the Uniform Requirement for Manuscripts Submitted to Biomedical Journals (International Committee of Medical Journal Editors), which states:

- Authorship credit should be based on (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; (3) final approval of the version to be published; and (4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Authors should meet conditions 1, 2, 3, and 4.
- When a large, multicenter group has conducted the work, the group should identify the individuals who accept direct responsibility for the manuscript. These individuals should fully meet the criteria for authorship defined above.
- Acquisition of funding, collection of data, or general supervision of the research group, alone, does not justify authorship.
- All persons designated as authors should qualify for authorship, and all those who qualify should be listed.
- Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content.

All publications (eg, manuscripts, abstracts, oral/slide presentations, book chapters) based on this study must be submitted to Amgen for review. The contractual agreement between the institution, Investigator, and Amgen will detail the procedures for, and timing of, Amgen's review of publications.

13. References

1. Semple JW, Provan D. The immunopathogenesis of immune thrombocytopenia: T cells still take center-stage. Current opinion in hematology. 2012;19(5):357-62.
2. Abrahamson PE, Hall SA, Feudjo-Tepie M, Mitrani-Gold FS, Logie J. The incidence of idiopathic thrombocytopenic purpura among adults: a population-based study and literature review. European journal of haematology. 2009;83(2):83-9.
3. Bennett D, Hodgson ME, Shukla A, Logie JW. Prevalence of diagnosed adult immune thrombocytopenia in the United Kingdom. Advances in therapy. 2011;28(12):1096-104.
4. Fogarty PF, Segal JB. The epidemiology of immune thrombocytopenic purpura. Current opinion in hematology. 2007;14(5):515-9.
5. Schoonen WM, Kucera G, Coalson J, Li L, Rutstein M, Mowat F, et al. Epidemiology of immune thrombocytopenic purpura in the General Practice Research Database. British journal of haematology. 2009;145(2):235-44.
6. Provan D, Stasi R, Newland AC, Blanchette VS, Bolton-Maggs P, Bussel JB, et al. International consensus report on the investigation and management of primary immune thrombocytopenia. Blood. 2010;115(2):168-86.
7. Neylon AJ, Saunders PW, Howard MR, Proctor SJ, Taylor PR, Northern Region Haematology G. Clinically significant newly presenting autoimmune thrombocytopenic purpura in adults: a prospective study of a population-based cohort of 245 patients. British journal of haematology. 2003;122(6):966-74.
8. Stasi R, Stipa E, Masi M, Cecconi M, Scimo MT, Oliva F, et al. Long-term observation of 208 adults with chronic idiopathic thrombocytopenic purpura. The American journal of medicine. 1995;98(5):436-42.
9. Frederiksen H, Maegbaek ML, Norgaard M. Twenty-year mortality of adult patients with primary immune thrombocytopenia: a Danish population-based cohort study. British journal of haematology. 2014;166(2):260-7.
10. Norgaard M, Jensen AO, Engebjerg MC, Farkas DK, Thomsen RW, Cha S, et al. Long-term clinical outcomes of patients with primary chronic immune thrombocytopenia: a Danish population-based cohort study. Blood. 2011;117(13):3514-20.
11. Neunert C, Lim W, Crowther M, Cohen A, Solberg L, Jr., Crowther MA, et al. The American Society of Hematology 2011 evidence-based practice guideline for immune thrombocytopenia. Blood. 2011;117(16):4190-207.
12. Romiplostim for the treatment of chronic immune (idiopathic) thrombocytopenic purpura IAlmM.
13. Satia J AJ, Hollowell J, Rutstein, Descriptive epidemiology of immune thrombocytopenic purpura in three European countries. The 11th Congress of the European Hematology Association. Amsterdam: [poster presentation]; 2006.
14. Feudjo-Tepie MA, Le Roux G, Beach KJ, Bennett D, Robinson NJ. Comorbidities of idiopathic thrombocytopenic purpura: a population-based study. Advances in hematology. 2009;2009:963506.
15. Sarpatwari A, Bennett D, Logie JW, Shukla A, Beach KJ, Newland AC, et al. Thromboembolic events among adult patients with primary immune thrombocytopenia in the United Kingdom General Practice Research Database. Haematologica. 2010;95(7):1167-75.
16. Kuter DJ, Bussel JB, Lyons RM, Pullarkat V, Gernsheimer TB, Senecal FM, et al. Efficacy of romiplostim in patients with chronic immune thrombocytopenic purpura: a double-blind randomised controlled trial. Lancet. 2008;371(9610):395-403.

14. Annexes

Annex 1. ENCePP Checklist for Study Protocols

Doc.Ref. EMA/540136/2009

ENCePP Checklist for Study Protocols (Revision 2, amended)

Adopted by the ENCePP Steering Group on 14/01/2013

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the page number(s) of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). Note, the Checklist is a supporting document and does not replace the format of the protocol for PASS as recommended in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title:
Primary Immune Thrombocytopenia Treated with Romiplostim in Routine Clinical Practice: A Retrospective Study from the United Kingdom Immune Thrombocytopenia Registry

Study reference number:
20140451

Section 1: Milestones	**Yes**	**No**	**N/A**	**Page Number(s)**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	10
1.1.2 End of data collection[2]	☒	☐	☐	10
1.1.3 Study progress report(s)	☐	☐	☒	

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.

[2] Date from which the analytical dataset is completely available.

Section 1: Milestones	**Yes**	**No**	**N/A**	**Page Number(s)**
1.1.4 Interim progress report(s)	☐	☐	☒	
1.1.5 Registration in the EU PAS register	☐	☐	☒	
1.1.6 Final report of study results.	☒	☐	☐	10

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Page Number(s)**
2.1 Does the formulation of the research question and objectives clearly explain:				
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	11
2.1.2 The objective(s) of the study?	☒	☐	☐	12
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	13
2.1.4 Which formal hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

Section 3: Study design	**Yes**	**No**	**N/A**	**Page Number(s)**
3.1 Is the study design described? (e.g. cohort, case-control, randomised controlled trial, new or alternative design)	☒	☐	☐	12
3.2 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	☒	☐	☐	14
3.3 Does the protocol describe the measure(s) of effect? (e.g. relative risk, odds ratio, deaths per 1000 person-years, absolute risk, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☒	☐	☐	14

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
4.1 Is the source population described?	☒	☐	☐	15
4.2 Is the planned study population defined in terms of:				13

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
4.2.1 Study time period?	☒	☐	☐	
4.2.2 Age and sex?	☐	☐	☒	13
4.2.3 Country of origin?	☒	☐	☐	13
4.2.4 Disease/indication?	☒	☐	☐	
4.2.5 Co-morbidity?	☐	☐	☒	
4.2.6 Seasonality?	☐	☐	☒	
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	13

Comments:

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
5.1 Does the protocol describe how exposure is defined and measured? (e.g. operational details for defining and categorising exposure)	☒	☐	☐	14
5.2 Does the protocol discuss the validity of exposure measurement? (e.g. precision, accuracy, prospective ascertainment, exposure information recorded before the outcome occurred, use of validation sub-study)	☐	☒	☐	
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☒	☐	☐	14
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	
5.5 Does the protocol specify whether a dose-dependent or duration-dependent response is measured?	☐	☐	☒	

Comments:

Section 6: Endpoint definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
6.1 Does the protocol describe how the endpoints are defined and measured?	☒	☐	☐	14
6.2 Does the protocol discuss the validity of endpoint measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☐	☒	☐	

Comments:

Section 7: Confounders and effect modifiers	**Yes**	**No**	**N/A**	**Page Number(s)**
7.1 Does the protocol address known confounders? (e.g. collection of data on known confounders, methods of controlling for known confounders)	☒	☐	☐	14
7.2 Does the protocol address known effect modifiers? (e.g. collection of data on known effect modifiers, anticipated direction of effect)	☐	☐	☒	

Comments:

Section 8: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
8.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
8.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc.)	☒	☐	☐	15
8.1.2 Endpoints? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics, etc.)	☒	☐	☐	15
8.1.3 Covariates?	☒	☐	☐	15
8.2 Does the protocol describe the information available from the data source(s) on:				
8.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	14
8.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	14
8.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☒	☐	☐	14
8.3 Is a coding system described for:				
8.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10)	☐	☐	☒	
8.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory Activities (MedDRA) for adverse events)	☐	☐	☒	
8.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System)	☐	☐	☒	
8.4 Is the linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	15

Comments:

Section 9: Study size and power	**Yes**	**No**	**N/A**	**Page Number(s)**
9.1 Is sample size and/or statistical power	☒	☐	☐	16

Section 9: Study size and power	**Yes**	**No**	**N/A**	**Page Number(s)**
calculated?				

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Page Number(s)**
10.1 Does the plan include measurement of excess risks?	☐	☐	☒	
10.2 Is the choice of statistical techniques described?	☒	☐	☐	17
10.3 Are descriptive analyses included?	☒	☐	☐	17
10.4 Are stratified analyses included?	☒	☐	☐	18
10.5 Does the plan describe methods for adjusting for confounding?	☐	☐	☒	
10.6 Does the plan describe methods addressing effect modification?	☐	☐	☒	

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Page Number(s)**
11.1 Is information provided on the management of missing data?	☒	☐	☐	18
11.2 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☐	☒	☐	
11.3 Are methods of quality assurance described?	☒	☐	☐	18
11.4 Does the protocol describe possible quality issues related to the data source(s)?	☒	☐	☐	19
11.5 Is there a system in place for independent review of study results?	☐	☒	☐	

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Page Number(s)**
12.1 Does the protocol discuss:				
12.1.1 Selection biases?	☒	☐	☐	19
12.1.2 Information biases? (e.g. anticipated direction and magnitude of such biases,	☒	☐	☐	19

Section 12: Limitations	**Yes**	**No**	**N/A**	**Page Number(s)**
validation sub-study, use of validation and external data, analytical methods)				
12.2 Does the protocol discuss study feasibility? (e.g. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	16
12.3 Does the protocol address other limitations?	☒	☐	☐	19-21

Comments:

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Page Number(s)**
13.1 Have requirements of Ethics Committee/Institutional Review Board approval been described?	☒	☐	☐	22
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	22

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Page Number(s)**
14.1 Does the protocol include a section to document future amendments and deviations?	☒	☐	☐	10

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Page Number(s)**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☐	☒	☐	
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	22

Comments:

Name of the main author of the protocol: _____

Date: / /

Signature: _____

Annex 2. UKITP Registry centers

Royal London Hospital
Manchester Royal Infirmary
Bradford Royal Infirmary
Colchester General Hospital
Harrogate & District Hospital
East Kent Hospitals University NHS Foundation Trust
St. James' University Hospital
Royal Devon & Exeter
Sunderland Royal Infirmary
Poole Hospital
Glan Clywd Hospital
Ysbyty Gwynedd Hospital
Luton & Dunstable Hospital
Queen's Hospital, Burton
Milton Keynes Hospital
Scunthorpe General Hospital
Ealing Hospital
Dorset County Hospital
Queen Elizabeth Hospital, Kings Lynn
St Richards Hospital
West Suffolk Hospital
Northumbria Hospital
Coventry and Warwickshire
Mid Yorkshire Hospitals
The James Cook University Hospital
South Eastern Health and Social Care Trust
Guy's and St Thomas Hospital
Castle Hill Hospital
Glasgow Royal Infirmary
Peterborough and Stamford Hospitals
Newham University Hospital
West Middlesex University Hospital
Norfolk & Norwich University Hospitals
Scarborough Hospital
Queen Elizabeth Hospital, Birmingham
Heatherwood & Wexham Park Hospitals Foundation Trust
Diana Princess of Wales Hospital
Cardiff and Vale University Health Board
Royal Victoria Infirmary, Newcastle
Royal Liverpool University Hospital
Royal United Hospital, Bath
Worcester Royal Hospital
Barking,Havering and Redbridge University Hospitals NHS Trust
University College London Hospitals NHS Foundation Trust
John Radcliffe Hospital
Great Western Hospital
Torbay District General Hospital
Bedford Hospital
Leicester Royal Infirmary
Southend University Hospital
Hinchingbrooke Hospital
Pilgrim Hospital
Grantham Hospital
Royal Bournemouth Hospital
Plymouth Hospitals NHS Trust
Hammersmith Hospital

Annex 3. Fields collected by the Registry that are relevant for this study

Demographic and clinical characteristics

Date of birth
Ethnicity
Gender
Patient weight (kg) (at ITP diagnosis)
Comorbidities
ITP registration date and site
ITP treatment pattern (e.g., date of diagnosis, date treatment, dose)
Bleeding events, site and date
Hospitalization and date

ITP Related Treatments	Comorbidities
Anti-D	Autoimmune Disease
Azathioprine	Candida Infection
Cyclophosphamide	Cataracts
Cyclosporine	Chronic Liver Disease
Danazol	Cushing's Syndrome
Dapsone	Depression/Anxiety
Dexamethasone	H. Pylori Infection
Eltrombopag	Hypercholesterolaemia/Dyslipidaemia
H. Pylori Treatment	Hypertension
IVIg	Malignancy (Solid / Haematological)
Methylprednisolone	Miscarriage
Mycophenolate	Osteoarthritis
Prednisolone	Peptic Ulcers
Rituximab	Photoxicity
Vinca Alkaloids	Pneumonia
	Splenomegaly
	Thyroid Disease
	Thromboembolism (Venous / Arterial)
	Diabetes (Type 1 / 2)

Haematological markers

Platelets