Appendix 1 – Protocol and Protocol Amendments

Document	Version	Effective date
Final Protocol	Version 0.2	27 May 2014

No Protocol Amendments have been issued.

TITLE PAGE

Division: Worldwide Development

Information Type: Worldwide Epidemiology Study Protocol

Title:	**REVIEU** - A multinational, retrospective, observational drug utilisation study of **REV**OLADE™ (eltrombopag) **I**n selected countries in the **E**uropean **U**nion

Compound Number:	SB-497115-GR
Development Phase	IV
Effective Date:	27-MAY-2014
Subject:	Chronic Hepatitis C Virus, Immune Thrombocytopenia, Drug Utilisation Study
Author(s):	[redacted]

PASS information

Title	**REVIEU**- A multinational, retrospective, observational drug utilisation study of **REV**OLADE™ (eltrombopag) **I**n selected countries in the **E**uropean **U**nion
Protocol version identifier	0.2
Date of last version of protocol	NA
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Active substance	Eltrombopag
Medicinal product	Eltrombopag
Product reference	SB-497115-GR
Procedure number	EMEA/H/C/001110/X/012G
Marketing authorisation holder(s)	GlaxoSmithKline Trading Services Limited 6900 Cork Airport Business Park, Kinsdale Road, Cork Ireland Telephone Number: [redacted]
Joint PASS	No

Research question and objectives	The aim of this DUS is to provide real-world data on use and indications for use among REVOLADE users within several EU countries. The objectives of the study are: • To document REVOLADE utilisation patterns according to the medical conditions and the patient age categories for which REVOLADE is being prescribed in selected European countries • To characterize the patients who are prescribed REVOLADE in routine clinical practice.
Country(-ies) of study	Germany, Spain, France and other EU Member States as appropriate
Author	[redacted]

MARKETING AUTHORISATION HOLDER(S)

Marketing authorisation holder(s)	GlaxoSmithKline Trading Services Limited 6900 Cork Airport Business Park, Kinsdale Road, Cork Ireland Telephone Number: [redacted] Telefax Number: [redacted]
MAH contact person	[redacted] Email: [redacted]

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1. LIST OF ABBREVIATIONS

ADR	Adverse drug reaction
AE	Adverse event
ATC	Anatomical Therapeutic Chemical
CI	Confidence interval
CLL	Chronic Lymphocytic Leukemia
CRO	Contract Research Organisation
DMP	Data management plan
DUS	Drug utilisation study
eCRF	Electronic case report form
EDC	Electronic data capture
EMA	European Medicines Agency
ENABLE 1	Eltrombopag to INitiate and Maintain Interferon Antiviral Treatment to Benefit Subjects with Hepatitis C related Liver DiseasE
ENABLE 2	Eltrombopag to INitiate and Maintain Interferon Antiviral Treatment to Benefit Subjects with Hepatitis C related Liver DiseasE
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
EU PAS register	European Union electronic register of post-authorisation studies
GPP	Good Pharmacoepidemiology Practices
GVP	Good Pharmacovigilance Practices
HCV	Hepatitis C Virus
HD	Hodgkin's disease
ICF	Informed consent form
ICMJE	International Committee of Medical Journal Editors
IEC	Independent ethics committee
ISPE	International Society for Pharmacoepidemiology
ITP	Immune Thrombocytopenia
MA	Marketing Authorisation
MAH	Marketing Authorisation Holder
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
N	Number
NHL	non-Hodgkin's lymphomas
QA	Quality assurance
SADR	Serious adverse drug reaction
SAE	Serious adverse event
SAP	Statistical analysis plan

SOP	Standard operating procedure
STROBE	STrengthening the Reporting of OBservational studies in Epidemiology
WHO	World Health Organisation

TRADEMARK INFORMATION

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Pegasys
Pegintron
SAS

2. RESPONSIBLE PARTIES

The list of investigators will be available upon request.

The management of the study will be outsourced to a Contract Research Organisation (CRO), details of which will be available upon request.

SPONSOR SIGNATORY

[redacted] MD, MPH
Primary Author/ Project officer

27 May 2014
Date

[redacted] PhD
Therapy Area Leader

27 May 2014
Date

SPONSOR INFORMATION PAGE

WWEpi Project Identifier: WEUKBRE7133

Sponsor Legal Registered Address:

GlaxoSmithKline Trading Services Limited

6900 Cork Airport Business Park, Kinsdale Road, Cork

Ireland

Telephone Number: [redacted]

Telefax: [redacted]

Sponsor Contact Address:

GlaxoSmithKline Research & Development
1250 South Collegeville Road
Collegeville, PA 19426, USA
Telephone Number: [redacted]

Sponsor Medical Monitor Contact Information: Dr. [redacted] Medical Affairs Director

Telephone Number: [redacted]

Email: [redacted]

Sponsor Serious Adverse Events (SAE) Contact Information:

If, during the study, an adverse event (AE) or serious adverse event (SAE) is identified in the medical record as explicitly attributed to Revolade and/or any known GSK brand products [i.e., an adverse drug reaction (ADR) or a serious adverse drug reaction (SADR)], the investigator or site staff will be responsible for immediately reporting such events that meet the definition of an AE or SAE as per Safety Reporting Manual to the CRO. The CRO will then forward to GSK Case Management Group either by fax (to [redacted] or by email (to [redacted] within 24 hours from the time when the CRO receives the report from the investigator/site.

In some countries, the study sponsor may be the local GlaxoSmithKline affiliate company (or designee). Where applicable, the details of the Sponsor and contact person will be provided to the relevant regulatory authority as part of the study submission.

Regulatory Agency Identifying Number(s): Not Applicable

INVESTIGATOR PROTOCOL AGREEMENT PAGE

- I confirm agreement to conduct the study in compliance with the protocol.
- I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described clinical study.
- I agree to ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations. Mechanisms are in place to ensure that site staff receives the appropriate information throughout the study.

Investigator Name: _____

_____ _____

Investigator Signature Date

STUDY ADVISORY COMMITTEE

Not applicable.

3. ABSTRACT

Full Study Title:

REVIEU - A multinational, retrospective, observational drug utilisation study of **REV**OLADE™ (eltrombopag) **i**n selected countries in the **E**uropean **U**nion (EU).

Rationale and Background:

Chronic primary immune thrombocytopenia (ITP) is an acquired immune mediated disorder characterized by isolated thrombocytopenia, defined as a peripheral blood platelet count less than 100 x 10^9/L, lasting for more than 12 months, and the absence of any underlying cause (Rodeghiero, 2009).

In Europe, adult ITP has an incidence range of 1.6 to 3.9 cases per 100,000 person-years with increasing incidence with older age. Estimates of prevalence range widely from 9.5 to as high as 189.3 per 100,000 population; prevalence is similar amongst men and women, except in the mid-adult years (i.e., 30-60 years of age), when the disease is more prevalent in women (Deane, 2010).

In addition, in patients with chronic Hepatitis C virus (HCV), thrombocytopenia occurs most commonly in those with progressive liver disease and cirrhosis. In such patients, thrombocytopenia may render patients ineligible for antiviral treatment and require dose reductions or discontinuation and may also prevent patients from having liver biopsies and other invasive procedures, thereby hampering a physician's ability to stage and monitor the patient's liver condition. Until recently, the treatment options for thrombocytopenia in HCV affected patients were limited to intravenous immunoglobulins, corticosteroids, and cytokines, and in severe cases, splenectomy. It is estimated that the global prevalence of chronic HCV infection is 130–170 million with an annual incidence of 3–4 million (WHO, 2013).

REVOLADE (eltrombopag; GlaxoSmithKline, Research Triangle Park, NC, USA) is an oral, non-peptide, thrombopoietin receptor (TPO-R) agonist that interacts with the TPO-R and induces differentiation of hematopoietic stem and progenitor cells to megakaryocytes, and has been approved for the treatment of patients with chronic ITP and chronic HCV associated thrombocytopenia. It is intended that REVOLADE dosing requirements be individualised based on the patient's platelet count, with the objective of treatment not to normalize platelet counts but rather to maintain platelet counts above the level for hemorrhagic risk (> 50 x 10^9/L).

The information generated by this study will be for the benefit of the European Medicines Agency (EMA), the Sponsor's stakeholders as well as to contribute to the published literature.

Research Question and Objectives:

REVOLADE received marketing authorization from the EMA in March 2010 for the treatment of adult splenectomised chronic ITP patients who are refractory to other treatments (e.g., corticosteroids, immunoglobulins). As part of the indication, REVOLADE may also be considered as second line treatment for adult non-splenectomised patients where surgery is contraindicated. REVOLADE was approved by the European Commission in September 2013 as a treatment for thrombocytopenia in adult patients with HCV, where the degree of thrombocytopenia is the main factor preventing the initiation or limiting the ability to maintain optimal interferon-based therapy.

It is generally acknowledged that prescribing practices of any particular drug in real life clinical practice may differ from its use as defined in the authorized indications. This drug utilisation study (DUS) for REVOLADE will be conducted in several European countries to determine the indications for use and patient age ranges for which REVOLADE is currently being prescribed. This DUS will also explore patient characteristics in order to better understand the patient population receiving REVOLADE in routine clinical practice.

The aim of this DUS is to determine indications for use among REVOLADE users within several EU countries utilizing real-world data obtained in medical charts.

The objectives of the study are:

- To document REVOLADE utilisation patterns according to the medical conditions and the patient age categories for which REVOLADE is being prescribed in selected European countries.
- To characterize the patients who are prescribed REVOLADE in routine clinical practice.

Study design:

This is a multi-national, multi-center study involving the retrospective review of approximately 300 to 450 patient medical records from selected European countries including France, Germany, Spain and possibly other countries, with each country having approximately six or seven sites. It is estimated that 18 to 21 hospital or office based sites overall, where prescribers of REVOLADE have been identified and medication records exist, will be targeted for recruitment. The investigators will be queried to identify REVOLADE-treated patients during the periods of interest. To meet the recruitment goal, additional EU country(ies) and sites may be added based on multiple factors including use of REVOLADE (compared to use approximated by sales data), available prescription data, market uptake, and favorable regulatory environment to conduct observational studies.

Medical records of all consecutive patients treated with REVOLADE, irrespective of indication, dose, treatment duration or any patient characteristic will be reviewed from first prescription of REVOLADE. This study is retrospective and therefore involves no intervention and will not impact the usual medical care nor affect the treatment of patients. The study will thus reflect real world medical practice without the potential for prescriber response bias which may occur in prospective studies (i.e., the Hawthorne Effect) (Mangione-Smith, 2002).

Study population:

Inclusion criteria

- Documented past treatment with REVOLADE (i.e., dispensed at least once by the pharmacy and patient received at least one dose) for whatever reason
- Patient (or a legal representative) has provided a written informed consent to participate in the study

Exclusion criteria

- Patients who participated or are participating in a randomized REVOLADE clinical trial

Variables

The following data will be collected for all patients enroled:

- Date of informed consent

The following data will be collected from *the medical records* for all patients enroled:

- Demographics [age at time of first REVOLADE prescribed dose, gender, race/ethnicity (where allowed by local regulation)]
- Primary diagnosis
- Medical history for applicable conditions and current medical conditions
- Treatment(s) preceding REVOLADE prescription (type, date, dose and duration)
- Concomitant treatment(s) with REVOLADE (type, date, dose and duration)
- All platelet counts ($x10^9$/L) at the time of primary medical condition, at initiation of REVOLADE, and dates, and resulting in dose change, by dose
- REVOLADE exposure (start date, stop date, doses)
- If REVOLADE discontinued, date and reason for discontinuation

Data Sources

This study is a retrospective medical chart review. Local site staff will review the medical chart of each enroled patient and extract the data.

These data will be entered pseudonymised into the eCRF via a secure web-based EDC system.

Study Size:

300 to 450 patients, enroled by approximately 18-21 sites will be recruited for participation in this study. It is planned to recruit all patients who are willing to participate, from all certified physicians in centers in selected EU countries, and without a minimum designated for any country, based on the estimated availability of eligible patients from the medical records within the planned recruitment period. Samples greater than 400 patients enable the estimation of the proportion of off-label use with an acceptable degree of precision. A sample size of 400 patients will allow the detection of a rate of 5% of off-label use with a precision of 2.1%, that is, the estimated proportion will be between 2.9% and 7.1%.

Data Analysis:

A Statistical Analysis Plan (SAP) describing the detailed statistical methodology and analysis will be provided as a separate document.

Continuous variables will be reported as mean, standard deviation, median and range. Categorical variables will be summarised as number and proportion of the total study population (counting missing data as a class), and by subgroups, where appropriate. Confidence intervals (as 95% CI) will be calculated using the method outlined by Newcombe (Newcombe, 1998) for the key variables.

All computations and generation of tables, listings and figures will be performed using SAS 9.1.3 or higher (SAS Institute, Cary, NC, USA) statistical software.

Estimated Milestones

- Final protocol submitted to the PRAC: October 2013
- Protocol approved with PRAC comments received: January 2014
- Sign Off of the updated protocol: May 2014
- Submission to the EU-PAS register: June 2014
- Start of data collection: September 2014
- End of data collection: 8 months after start of abstraction, April- May 2015
- Final study report: October 2015, i.e., 6 months after end of abstraction/study collection

4. AMENDMENTS AND UPDATES

None (original protocol).

5. MILESTONES

Estimated Milestone	**Estimated Date**
Final protocol submitted to the PRAC:	October 2013
Protocol approved with PRAC comments received	January 2014
Sign Off of the updated protocol	May 2014
Submission to the EU-PAS register	June 2014
Start of data collection (first patient in)	September 2014
End of data collection (last patient out)	April- May 2015
Study progress reports	As requested
Final study report	October 2015

6. RATIONALE AND BACKGROUND

6.1. Background

Chronic primary immune thrombocytopenia (ITP)

Chronic primary ITP is an acquired immune mediated disorder characterized by isolated thrombocytopenia, defined as a peripheral blood platelet count less than 100 x 10^9/L, the absence of any underlying cause, and lasting for more than 12 months (Rodeghiero, 2009).

In Europe, adult ITP has an incidence range of 1.6 to 3.9 cases per 100,000 person-years with increasing incidence with older age. Estimates of prevalence range widely from 9.5 to as high as 189.3 per 100,000 population; prevalence is similar amongst men and women, except in the mid-adult years (i.e., 30-60 years of age), when the disease is more prevalent in women (Deane, 2010).

Diagnosis of ITP is one of exclusion, when the history, physical examination, complete blood count and examination of peripheral blood smear do not suggest other etiology for the thrombocytopenia. Physical examination is typically normal apart from signs of bleeding and the peripheral blood count reveals isolated thrombocytopenia and normal red cell and white cell indices. If significant bleeding occurs there may be anemia proportional to the degree of bleeding with possible iron deficiency. Peripheral blood smear typically shows platelets normal to large in size with no abnormalities seen in red and white cell morphology. Bone marrow examination is currently not routinely conducted in patients with typical ITP presentations, but reserved for selected cases such as those with an atypical presentation.

Guidelines and consensus documents generally recommend clinical intervention in adults when platelet counts are $<30 \times 10^9$/L (Provan, 2009); treatment is rarely indicated for patients with platelets $>30 \times 10^9$/L unless they are undergoing a procedure likely to induce blood loss including surgery, dental extraction or childbirth (British Committee for Standards in Haematology General Haematology Task Force, 2003). Thrombopoietic agents have been extensively studied in ITP, and are increasingly used in patients with thrombocytopenia related to other chronic diseases.

Chronic Hepatitis C Virus (HCV) Infection

The global prevalence of chronic HCV infection is 130–170 million with an annual incidence of three to four million (WHO, 2013). A majority of HCV infected patients develop chronic liver disease making it a leading cause of cirrhosis and hepatocellular carcinoma worldwide.

The goal of medical therapy in HCV is to achieve sustained virologic response (SVR) defined as prolonged clearance of HCV RNA. Until recently, treatment of HCV consisted of combination therapy of a weekly injection of a pegylated interferon and oral ribavirin.

There are six types of HCV genotype; the viral genotype is integral in determining appropriate treatment regimens, with genotype 1 being particularly difficult to treat successfully. Less than 50% of genotype 1 patients achieve a sustained viral response (SVR) with standard peginterferon-ribavirin. Boceprevir and telaprevir were the first HCV protease inhibitors to be approved for the treatment of HCV genotype 1. These drugs must be used in combination with pegylated interferon (triple therapy) plus ribavirin to maximize efficacy and prevent the emergence of resistance-associated variants (Ferenci, 2011).

Treatment related toxicity is the primary limiting factor in HCV interferon-based therapy with significant side effects necessitating dose reductions in almost half of treated patients and discontinuation in nearly a third of all patients (National Institutes of Health Consensus, 2002). Thrombocytopenia is a dose and/or therapy-limiting side effect in patients with HCV receiving interferon-based therapies. Thrombocytopenia may be a result of antiviral treatment, but may also develop as a complication of chronic HCV infection, unrelated to antiviral treatment.

In patients with HCV, thrombocytopenia occurs most commonly in those with advanced liver disease and cirrhosis. In such patients, thrombocytopenia render patients ineligible for antiviral treatment and requiring dose reductions or discontinuation and may also prevent patients from having liver biopsies and other invasive procedures, thereby hampering a physician's ability to stage and monitor the patient's liver condition. Until recently, the treatment options for thrombocytopenia in HCV affected patients were limited to intravenous immunoglobulins, corticosteroids, platelet transfusions, and cytokines, and in severe cases, splenectomy.

REVOLADE (eltrombopag)

REVOLADE (eltrombopag; GlaxoSmithKline, Research Triangle Park, NC, USA) is an oral, non-peptide, thrombopoietin receptor (TPO-R) agonist that interacts with the TPO-R and induces differentiation of hematopoietic stem and progenitor cells to megakaryocytes.

REVOLADE received marketing authorization from the European Medicines Agency (EMA) in March 2010 for the treatment of adult splenectomised chronic ITP patients who are refractory to other treatments (e.g., corticosteroids, immunoglobulins). As part of the indication, REVOLADE may also be considered as second line treatment for adult non-splenectomised patients where surgery is contraindicated.

The efficacy and safety of REVOLADE in adult patients with chronic ITP were evaluated in three randomized, double-blind, placebo-controlled trials and in an open-label extension trial. Trial 1 randomized 114 patients (2:1) to REVOLADE 50 mg or placebo. Trial 2 randomized 117 patients (1:1:1:1) among placebo or one of three dose regimens of REVOLADE, 30 mg, 50 mg, or 75 mg each administered daily. In the third trial, 197 patients were randomized (2:1) to receive either REVOLADE 50 mg once daily

(n = 135) or placebo (n = 62) for 6 months, during which time the dose of REVOLADE could be adjusted based on individual platelet counts. Patients were allowed to taper or discontinue concomitant ITP medications after being treated with REVOLADE for 6 weeks. Overall, during clinical development for the ITP indication, REVOLADE showed a dose-dependent increase in platelet counts and a decrease in bleeding events compared with placebo, and was generally safe and well tolerated.

In addition to the ITP indication, the efficacy and safety of REVOLADE for the treatment of adult patients with chronic hepatitis C who were unable to initiate or maintain optimal interferon-based therapy due to thrombocytopenia were evaluated in 2 randomized, double-blind, placebo-controlled trials. The ENABLE 1 (Eltrombopag to INitiate and Maintain Interferon Antiviral Treatment to Benefit Subjects with Hepatitis C related Liver DiseasE) trial utilized peginterferon alfa-2a (Pegasys) plus ribavirin for antiviral treatment and ENABLE 2 utilized peginterferon alfa-2b (Pegintron) plus ribavirin. These global, randomized, double-blinded Phase 3 trials evaluated the efficacy of REVOLADE in 1521 HCV patients with platelet counts of less than 75×10^9/L using a primary endpoint of achieving SVR and a secondary endpoint of early virologic response (EVR). In ENABLE 1, 66% of patients treated with REVOLADE plus Pegasys and ribavirin had an early virologic response, compared with 50% of patients who received Pegasys, ribavirin, and a placebo ($p<0.0001$). Additionally, 23% of the REVOLADE group achieved SVR versus 14% of the placebo group ($p=0.0064$) (Afdhal, 2012). In ENABLE 2, 62% of patients treated with REVOLADE plus Pegasys 2b and ribavirin had an early virologic response, compared with 41% of patients who received Pegasys, ribavirin, and a placebo ($p<0.0001$). Additionally, 19% of the REVOLADE group achieved SVR versus 13% of the placebo group ($p=0.0202$) (Dusheiko, 2012). REVOLADE was approved by the European Commission as a treatment for thrombocytopenia in adult patients with HCV, where the degree of thrombocytopenia is the main factor preventing the initiation or limiting the ability to maintain optimal interferon-based therapy in September 2013.

Regardless of indication, it is intended that REVOLADE dosing requirements be individualised based on the patient's platelet count, with the objective of treatment not to normalize platelet counts but rather to maintain platelet counts above a level that reduces the risk of bleeding ($> 50 \times 10^9$/L). The recommended starting dose for adults with chronic ITP is 50 mg once daily. For patients of East Asian ancestry, REVOLADE should be initiated at a reduced dose of 25 mg once daily. If after two to three weeks of therapy the platelet counts are below the clinically indicated levels (e.g., 50×10^9/L), the dose may be increased by 25 mg to a maximum of 75 mg once daily. A treatment therapy cannot exceed a dose of 75 mg daily for patients with chronic ITP. The standard REVOLADE dose adjustment, either decrease or increase, would be 25 mg once daily. Patient platelet counts are to be monitored with dose adjustments made based upon platelet count response. For patients with chronic HCV associated thrombocytopenia, initial REVOLADE dose is 25 mg once daily. No dosage adjustment is necessary for

HCV patients of East Asian ancestry or patients with mild hepatic impairment. The dose of REVOLADE should be adjusted in 25 mg increments every 2 weeks as necessary to achieve the target platelet count required to initiate anti-viral therapy. Platelet counts should be monitored every week prior to starting antiviral therapy. A treatment therapy cannot exceed a dose of 100 mg REVOLADE once daily for patients with chronic HCV associated thrombocytopenia.

6.2. Rationale

ITP comprises a heterogeneous group of disorders and may occur in the absence of an evident predisposing etiology (called primary ITP) or secondary to a growing list of associated conditions such as chronic lymphocytic leukemia (CLL), Hodgkin's disease (HD), and non-Hodgkin's lymphomas (NHL) (called secondary ITP).

It is generally well-known that prescribing practices of any particular drug in real life clinical practice may differ from its use as defined in the authorized indications; therefore, this drug utilisation study (DUS) for REVOLADE will be conducted in several European countries to determine the indications for use and patient age ranges for which REVOLADE is currently being prescribed. This DUS will also explore patient characteristics in order to better understand the patient population receiving REVOLADE in routine clinical practice.

Databases containing health medical records or administrative medical claims can represent the most appropriate tool for drug use studies under some circumstances, due to the recording of diagnosis and prescription data generally performed either for administrative reasons or as part of the computerized management of patients records, independently of any study purposes, and due to the large panel of prescribers and associated population coverage. However, some key missing information such as platelet counts or relevant diagnoses will not be accurate enough or are only partially available in such databases or indirectly by means of proxy measures. In addition, REVOLADE may be prescribed by different specialists who must be accounted for while selecting a particular database. As a result, it was determined that a multi-national, multi-center retrospective medical chart review study was preferred to document REVOLADE utilisation patterns in real world practice. Based on IMS prescription sales data, France, Germany and Spain are the three highest REVOLADE using countries in Europe at this time. To gain a national perspective to the extent possible, approximately six or seven sites per country among these three will be selected and other countries as needed.

7. RESEARCH QUESTION AND OBJECTIVES

The aim of this DUS is to determine indications for use among REVOLADE users within several EU countries utilizing real-world data obtained in medical records.

The objectives of the study are:

- To document REVOLADE utilisation patterns, classified according to the medical conditions and the patient age categories for which REVOLADE is being prescribed in selected European countries
- To characterize the patients who are prescribed REVOLADE in routine clinical practice.

8. RESEARCH METHODS

8.1. Study Design

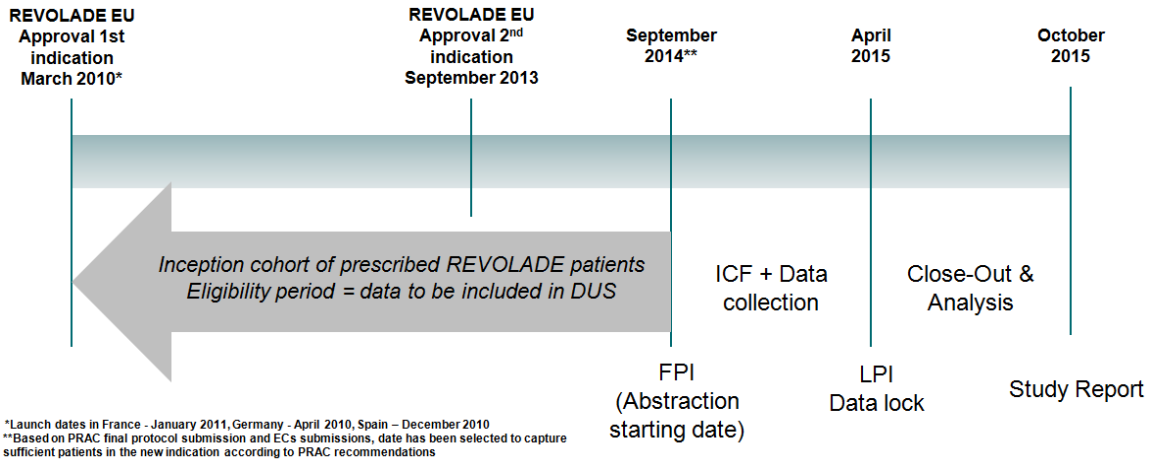
This is a multi-national, multi-center study involving the retrospective review of approximately 300 to 450 patient medical records from selected European countries including France, Germany, Spain, and other relevant selected European Union (EU) Member States (see Section 8.2) with each country contributing approximately six or seven sites. It is estimated that 18 to 21 hospital or office based sites overall where prescribers of REVOLADE have been identified and medication records exist, will be targeted for recruitment. The investigators will be queried to identify REVOLADE treated patients during the periods of interest. To the extent possible, a selection of sites representative of the country prescription volumes will be enroled.

Medical records of all consecutive patients treated with REVOLADE, irrespective of indication, dose, treatment duration or any patient characteristic will be retrospectively reviewed to confirm eligibility.

Medical records will be reviewed for data from REVOLADE first prescription. This study involves no intervention, and will not impact the usual medical care or affect the treatment of patients. Thus, the study will reflect a real world medical practice without the potential for prescriber response bias, which may occur in prospective studies (i.e., the Hawthorne Effect) (Mangione-Smith, 2002).

The study overview is provided in the figure below:

Figure 1 REVIEU Study Overview



In Figure 1 EU approval for first indication (March 2010) refers to the approval of REVOLADE: "Revolade is indicated for adult chronic immune (idiopathic) thrombocytopenic purpura (ITP) splenectomised patients who are refractory to other treatments (e.g. corticosteroids, immunoglobulins). Revolade may be considered as

second line treatment for adult non-splenectomised patients where surgery is contraindicated."

EU approval for second indication refers to "Revolade is indicated in adult patients with chronic HCV infection for the treatment of thrombocytopenia, where the degree of thrombocytopenia is the main factor preventing the initiation or limiting the ability to maintain optimal interferon-based therapy."

8.2. Setting

The REVOLADE DUS will include approximately 300 to 450 patients being treated with REVOLADE at approximately 18-21 hospital/ward or office based sites in selected EU Member States. France, Germany and Spain are the primary targeted countries, based on the most frequent REVOLADE use approximated from IMS prescription sales data. To meet the recruitment goal, additional EU country(ies) and sites may be added based on multiple factors including use of REVOLADE (compared to use approximated by sales data), available prescription data, and favourable regulatory environment to conduct observational studies.

To avoid overrepresentation of any individual sites or countries, recruitment may be capped during the study at site or country level.

8.2.1. Inclusion Criteria

To be enroled into the study, patients must meet the following criteria:

- Documented past treatment with REVOLADE between the period immediately after first approval/launch and September 2014 (i.e., dispensed at least once by the pharmacy and patient received at least one dose) for whatever reason
- Patient (or a legal representative) has provided a written informed consent to participate in the study

8.2.2. Exclusion Criteria

- Patients who participated or are participating in a randomized REVOLADE clinical trial

8.2.3. Study Duration

The eligibility period begins within the period immediately after REVOLADE has been launched in a given country (for instance, REVOLADE launch dates for the chronic ITP indication are in Germany, France and Spain, April 2010, January 2011, and December 2010, respectively) until the index date chosen as the start date of data abstraction i.e., September 2014 (Figure 1).

The observational period for each patient is the interval between the first dose of REVOLADE and the last dose if discontinued before September 2014. If a patient stops and re-starts REVOLADE during the observation period, all repeated treatment intervals will be captured. Also, if the patient is still on REVOLADE at the end of the study period, September 2014, then the observation period is between first dose and September 2014.

The planned duration of the study is approximately 14 months after the inclusion of the first patient. This period takes into account 8 months of data collection and study start-up and a 6 month period between last patient in and final study report.

GSK will closely monitor inclusion rates. If projected recruitment rates indicate that patient targets may not be achieved in the planned recruitment period, consideration will be given to extending the recruitment period, initiating additional sites within the three existing countries, and/or expanding the study into additional EU countries.

8.2.4. Site Selection

The study will be implemented at approximately 18- 21 sites in selected countries in the EU (six or seven sites per country) by selecting sites that are geographically dispersed to best represent different practices across regions/provinces within the selected EU Member States. Also, selection of study sites will be determined at the country level in order to obtain a representative sample of sites reflective of the treatment patterns within each country. Site qualification and selection criteria will include: type of physician/hospital, geographic location (e.g., rural, urban), practice setting (clinics, academic setting, and reference centre), capture area, estimated eligible patient availability, number of patients seen in previous year, availability and number of eltrombopag pharmacy records), and staffing availability.

The Study will target a representative sample of physicians who prescribe REVOLADE, irrespective of the indication. These include hematologists, oncologists, virologists, hepatologists, internal medicine and other specialists from the hospital or office based setting. The data collected in the Study will be used to determine the characteristics of patients for whom REVOLADE is prescribed and to understand if it is being prescribed in accordance with the product labelling.

The site and investigator identification, selection and recruitment process will be detailed in the Site Recruitment Plan document, which will be developed at study start-up. This document will describe the process for site identification, site recruitment process with flow chart, site qualification process via the study specific site qualification questionnaire. In addition, this document will describe the process how to contact and conduct follow-up activities of identified sites and investigators. Potential risks to the plan will be identified early in its development to ensure that proper risk mitigation measures are put in place to ensure achievement of site enrolment objectives.

Given the prescription rates of REVOLADE in EU Member States, a multi-faceted approach will be taken to identify potential sites and investigators. This approach will include the review of the CRO internal database, and the collaboration with GSK local operating companies on most suitable sites and market research of prescription data. A Site Qualification Survey will be administered to all identified potential sites requesting information on their location, practice (specialty, type), patients treated with REVOLADE within their practice (past and current number, treating duration) and dispensing system (not specifically related to the main objective of the DUS).

Based on responses from the Site Qualification Survey, a probability sample of REVOLADE prescribers will be selected, using a stratified unbiased random approach to produce a representative set of sites. This will ensure both representativeness and comprehensiveness of the sample in terms of types of REVOLADE prescribers. The general aim of this approach is to minimize biases such as for instance the recruitment of prescribers from academic versus community hospitals.

In order to ensure adequate numbers of participating sites, the Potential Prescriber List will include three times the number of sites required for the study. Depending on the participation rate and enrolment rates for the Study, the Back-up Potential Prescriber List of study sites may be contacted. To maximize representativeness at the study level, quota sampling of the remaining sites from the list will be performed.

The dispensing system of REVOLADE in the selected Member States is fully described in the ANNEX 2.

8.2.5. Patient Enrolment

Since the purpose of this study is to evaluate routine clinical use of REVOLADE, patients will be identified based on the prescription of REVOLADE rather than on a specific diagnosis or condition.

The study population will consist of patients who have been prescribed REVOLADE for whatever reason according to the data retrieved in the medical records, provided they gave informed consent, had not or were not currently participating in a REVOLADE clinical trial, and used REVOLADE within the time period defined below. The medical records of all patients treated with REVOLADE in a participating centre will be reviewed for inclusion in this retrospective study, until the overall target number of at least 300 patients has been reached, irrespective of indication, medical condition, dose and treatment duration.

Patients are eligible for inclusion in study if their first prescription of REVOLADE was given between the period immediately after REVOLADE launch date and the start date for data abstraction i.e., September 2014. Patients who have been first prescribed REVOLADE after September 2014 will not be included in the study in order to ensure that study procedures do not influence prescribing practices. Informed consent will be

obtained as per country-specific regulations. Assuming the country-based first launched dates of REVOLADE in its initial chronic ITP indication (see Figure 1), the eligibility periods in the three selected countries thus span between January 2011 and September 2014 for France, April 2010 and September 2014 for Germany and December 2010 and September 2014 for Spain.

The earliest launch date for the chronic HCV-associated thrombocytopenia indication in these countries can be no sooner than September 2013, corresponding to the date it was approved by the European Commission. Considering that approval of HCV-associated thrombocytopenia indication was just recently, the number of expected HCV-associated thrombocytopenia patients therefore will be very small.

It is expected that approximately six or seven sites will be identified per country, and that up to 50 medical records will be abstracted at each site accounting for a total of 300 to 450 patients for the study.

To assess the representativeness of the sampled patient population, a screening log of all patients treated with REVOLADE will be maintained by the site, including birth year, gender and whether the patient participated in the DUS or not during the eligibility period. For patients who did not participate in the DUS, the reasons for non-participation will be documented on the screening log.

8.2.6. Patient Withdrawal

Patients may withdraw consent and discontinue participation from the DUS at any time, with no effect on their medical care or access to treatment. If a patient is withdrawn prior to completing the study, any known reason for withdrawal should be documented in the electronic case report form (eCRF). All information already collected as part of the study will be retained for analysis; however, no further efforts will be made to obtain or record additional information regarding the patient.

8.3. Variables

An eCRF will be used to collect study data.

8.3.1. Site Questionnaire

The following data will be collected regarding the site and prescribing physician:

- Type of setting (Community hospital, Academic/medical center, office based, etc)
- Physician specialty prescribing REVOLADE (hematologist, oncologist, etc)

8.3.2. REVOLADE General Information

The following data will be collected for all patients enroled:

- Date of informed consent.

The following data will be collected from the medical records for all patients enroled:

- Demographics:
  - age at time of first REVOLADE prescribing dose
  - gender
  - race/ethnicity (where allowed by local regulation)
- Diagnosis of chronic ITP and date (if medical record data available, will record the disease phase as 'acute' or 'chronic' ITP specifically or just 'ITP', duration of ITP if available)
- Diagnosis of HCV and date; information on previous treatment with antiviral therapy
- Diagnosis of other conditions and date
  - Hematologic malignancies (AML, MDS, other leukemia, lymphoma, etc)
  - Aplastic anemia and bone marrow failure
  - Other
- Medical history for applicable conditions and current medical conditions
  - Surgery (i.e., splenectomized or not)
  - Comorbidities that may be contraindications for surgery (anemia, hyperbilirubinemia, neutropenia, leukopenia, pancytopenia, pneumonia, and others)
  - Pregnancy status
  - Non haematological malignancy and type
  - Comorbidities:
    - Cardiovascular diseases
    - Pulmonary Arterial Hypertension
    - Hypertension
    - Diabetes
- Treatment(s) preceding REVOLADE prescription:
  - Type (corticosteroids, immunoglobulins, cytokines, ribavirin, peginterferon, etc.)
  - Date of treatment initiation
  - Dose and duration
- Concomitant treatment(s) initiated with REVOLADE:
  - Type (corticosteroids, immunoglobulins, cytokines, ribavirin, peginterferon, etc.)
  - Date of treatment initiation
  - Dose and duration
- All platelet counts ($x10^9$/L) at the time of primary medical condition, at initiation of REVOLADE, and dates, and resulting in dose change, by dose

8.3.3. REVOLADE Exposure during Observational Period

- REVOLADE exposure
  - Start date
  - Stop date if recorded
  - Hospital discharge date (if hospitalized)
  - Doses administered (including all changes in dose)
- Indication for REVOLADE
- If REVOLADE discontinued, date and reason for discontinuation

8.3.4. On label and off label definitions

If information on splenectomy, prior medication use, and contraindications for surgery is available, then use of eltrombopag for a patient will be categorized into the following groups:

- On-label use:
  - patient is an adult, has a diagnosis of chronic ITP, has been splenectomized or has a contraindication for surgery, and has received prior corticosteroids, immunoglobulins therapy; or
  - patient is an adult, has a diagnosis of chronic HCV, has clinically meaningful thrombocytopenia limiting interferon-based therapy, and date of eltrombopag is after REVOLADE approval date (September 2013).
- Off-label use:
  - patient is an adult, has chronic ITP, but has not received prior corticosteroids, immunoglobulins therapy or has not been splenectomized and does not have a contraindication for surgery;
  - patient is an adult, has HCV, but does not have clinically meaningful thrombocytopenia limiting interferon-based therapy or the date of REVOLADE is prior to REVOLADE approval date;
  - patient is an adult, but does not have ITP or HCV;
  - patient is < 18 years of age

If there is no information on splenectomy, prior medication use, and contraindications for surgery, then classification will be more general:

- On-label use:
  - patient is an adult and has a diagnosis of chronic ITP; or
  - patient is an adult and has a diagnosis of HCV with clinically meaningful thrombocytopenia limiting interferon-based therapy, and date of eltrombopag after REVOLADE approval date
- Off-label use:
  - patient is an adult, but has acute rather than chronic ITP;

- patient is an adult, but does not have ITP and does not have HCV with clinically meaningful thrombocytopenia or has clinically meaningful thrombocytopenia limiting interferon-based therapy but date of eltrombopag is prior to REVOLADE approval date;
- patient is an adult, but does not have ITP or HCV; or
- patient is < 18 years of age

8.4. Data Sources

This study is a retrospective medical chart review. Local site staff will review the medical chart of each enroled patient and extract the data.

These data will be entered pseudonymised into the eCRF via secure web-based EDC system.

8.5. Study Size

8.5.1. Sample Size for the DUS

300 to 450 patients, enroled by approximately 18-21 sites will be recruited for participation in this study. It is planned to recruit all patients who are willing to participate, from all certified physicians in certified centers in all participating EU countries, and without a minimum designated for any country based on the estimated availability of eligible patients from the medical records within the planned recruitment period.

We provide hereafter the level of precision i.e., width of the 95% confidence interval (CI) for various sample sizes and proportions. Table 1 presents the precision in the estimate of the tentative proportion of use of REVOLADE out of the labelled indication for tentative proportions of 2, 3, 4 and 5% and different sample sizes.

Table 1 Precision of estimation for proportions of 2, 3, 4 and 5% of off-label use and increasing sample size

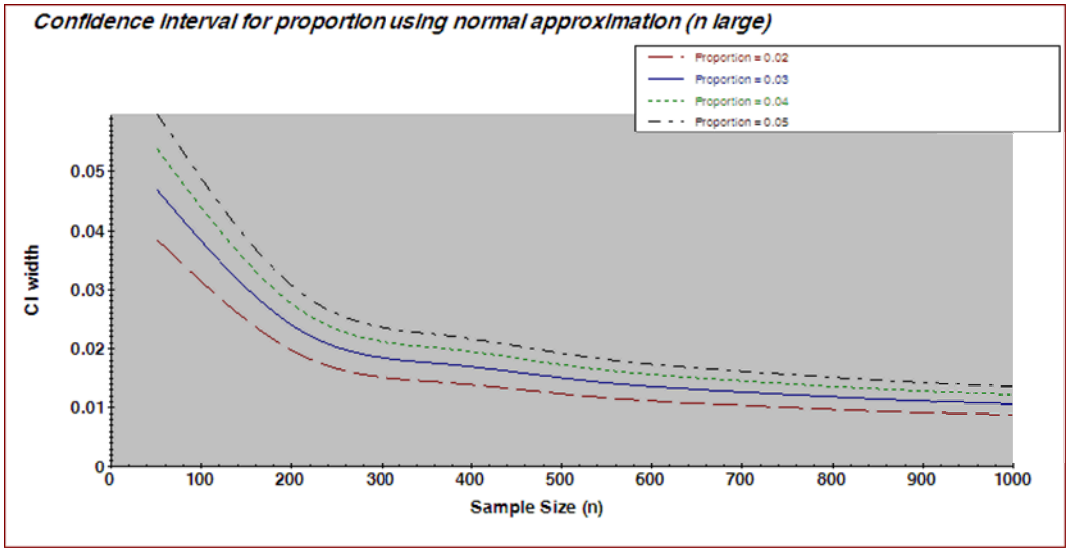
	Tentative proportions of REVOLADE off-label use											
	0.02			0.03			0.04			0.05		
Sample Size Patients	CI Width	L95%	U95%	CI Width	L95%	U95%	CI Width	L95%	U95%	CI Width	L95%	U95%
200	0.019	0.001	0.039	0.024	0.006	0.054	0.027	0.013	0.067	0.03	0.02	0.08
400	0.014	0.006	0.034	0.017	0.013	0.047	0.019	0.021	0.059	0.021	0.029	0.071
600	0.011	0.009	0.031	0.014	0.016	0.044	0.016	0.024	0.056	0.017	0.033	0.067

CI: 95% confidence interval; L: lower bound; U: upper bound.

Table 1 and Figure 2 show that the width of the 95% CI decreases as sample size increases; samples greater than 500 patients enable the estimation of the proportion of off-label use with an acceptable degree of precision. Increasing the sample size beyond 600 patients has minimal effect on the width of the 95% CI.

A sample size of 400 patients will allow the detection of a rate of 5% of off-label use with a precision of 2.1%, that is, the estimated proportion will be between 2.9% and 7.1%.

Figure 2 Confidence interval for tentative proportions of 2, 3, 4 and 5% and increasing sample size



8.6. Data Management

A data management plan (DMP) will be created and will describe all functions, processes, and specifications for data collection, cleaning and validation for the DUS. High data quality standards will be maintained and processes and procedures utilized to repeatedly ensure that the data are as clean and accurate as possible when presented for analysis. Data quality will be enhanced through a series of programmed data quality checks that automatically detect out-of-range or anomalous data at the time of data entry.

8.6.1. Data Entry for DUS / Electronic Data Capture

Each patient will be uniquely identified in the study by a patient identification number.

All data captured at sites will be collected and entered directly by physician (or designee) into the secure internet-based eCRF. All sites will be fully trained on using the eCRF. The eCRF users will be able to access their account with a personalised username and password. All eCRFs should be reviewed, electronically signed, and dated by the investigator (or designee). An adequate explanation should be documented for all

changes or corrections to eCRFs. Each site will only have access to the patient data entered by the individual site through the eCRF.

8.6.2. Source Documents

In most cases, the source documents will be contained in the patient's medical record and data collected in the eCRF must match the data in the medical records. All original source documentation is expected to be stored at the site for the longest possible time as required by local applicable regulations or as specified in the contract, whichever is longer. The site will be instructed to notify GSK before any destruction of medical records of study participants.

8.6.3. File Retention and Archiving

To enable audits from regulatory authorities or GSK, the investigator must agree to keep records, including the identity of all participating patients, all original signed informed consent forms (ICFs), patient screening logs, copies of all eCRFs (which will be provided by sponsor at study end), source documents and adequate documentation of relevant correspondence. The records should be retained by the investigator. The records must be available for review in the event the site is selected for monitoring, audits, or inspections and must be safely archived following the study conclusion, according to local regulations or as specified in the contract, whichever is longer. In the event that archiving of the file is no longer possible at the site, the site will be instructed to notify GSK.

8.7. Data Analysis

8.7.1. DUS Analyses

This is a multinational, retrospective, observational, medical chart review study. A Statistical Analysis Plan (SAP) describing the detailed statistical methodology and analysis will be provided as a separate document.

Continuous variables will be reported as mean, standard deviation, median and range. Categorical variables will be summarised as number and proportion of the total study population (counting missing data as a class), and by subgroups if and where appropriate. Confidence intervals (as 95% CI) will be calculated using the method outlined by Newcombe (Newcombe, 1998) for the key variables.

Participating physicians

Number of participating physician, and practice setting, will be summarized descriptively.

Patient demographics and disease characteristics

Descriptive statistics will be given for the variables below:

- Age at time of initial REVOLADE prescribing dose
- Gender
- Race/Ethnicity
- Relevant medical history for applicable conditions

REVOLADE Patient characteristics

Number and percentage of the following categories will be described and stratified if number permits according to the dates of new indication approval:

- Adult chronic ITP patients
- Adult patients with HCV and clinically meaningful thrombocytopenia
- Patients < 18 years with chronic ITP
- Patients < 18 years with HCV (with and without thrombocytopenia)
- Patients < 18 years without chronic ITP or HCV but with another disease type, by specific disease type
- Adult patients with cancer, by cancer type
- Adult patients with myelodysplastic syndrome/AML
- Adult patients receiving surgery during the observation period
- Adult patients in any other disease groups, by specific disease type

REVOLADE Utilisation characteristics

Descriptive statistics will be given for the variables below:

- Duration of REVOLADE treatment, stratified by the categories described above (if numbers permit)
- Initial dose (25 mg, 50 mg or other)
- Dose changes
- Rationale for dose changes
- Reason for temporary or permanent discontinuation

Platelet count characteristics

Descriptive statistics will be given for the variables below:

- Platelet count ($x10^9$/L) at the time of primary medical condition, at initiation of REVOLADE, overall and by indication and by initial starting dose
- Platelet count resulting in dose change, by dose

8.7.2. Handling of Missing Data

In general, missing data will not be imputed and will be analyzed as they are recorded in the study CRF.

The proportion of missing data will be reported for each measured variable in the study.

8.7.3. General Considerations

All computations and generation of tables, listings and figures will be performed using SAS 9.1.3 or higher (SAS Institute, Cary, NC, USA) statistical software.

The analysis methods will be fully described in a SAP written and finalised before database lock. Data will be presented for the whole study population and per country (as appropriate).

8.8. Quality Control

This study will be outsourced to a CRO, selected in accordance with GSK standard operating procedures (SOPs). The study will be performed by the CRO, with guidance, input, review and approval of GSK, including development of materials, recruitment, training and management of sites, site monitoring, electronic data capture (EDC) and data management and analysis.

8.8.1. Site Monitoring

During the site initiation visit, the monitor will provide training on the conduct of the study to the investigator, and all site staff involved in the study. In order to ensure the integrity of the data, sites will be monitored. A risk based monitoring approach will be conducted during the study with remote and ad hoc on site monitoring that will be performed to examine compliance with the protocol and adherence to the data collection procedures, to assess the accuracy and completeness of submitted data, and to verify that records and documents are being properly maintained for the duration of the study. The monitor will perform source data verification by review of original patient records. The investigator will allow the monitor to have direct access to appropriate parts of patients' medical records relating to their participation in this study, for the purpose of verifying the data submitted by the site.

The monitor will close out each site after the last patient's data collection is completed, all data have been entered and all outstanding monitoring issues have been resolved or addressed.

Representatives of GSK and Competent Authorities must be permitted to inspect all study-related documents and other materials at the site, including the Investigator (Investigator) Site File, the completed eCRFs and the patients' original medical records. Inspections may be conducted at any time during or after the study to ensure the validity and integrity of the study data.

8.8.2. Data Quality and Monitoring

In addition, the eCRF will include programmable edits to obtain immediate feedback if data are missing, out of range, illogical or potentially erroneous. Ad hoc queries will be generated within the eCRF and followed up for resolution.

High data quality standards will be maintained and processes and procedures utilised to repeatedly ensure that the data are as clean and accurate as possible when presented for analysis. Data quality will be enhanced through a series of programmed data quality checks that automatically detect out-of-range or anomalous data.

8.9. Limitations of the Research Methods

Potential limitations of the study design and measures proposed to address them include enrolment bias. To address this, sites will be expected to consecutively enrol eligible subjects and to maintain screening logs of all subjects meeting eligibility criteria, along with reasons for non-enrolment.

The Marketing Authorization Holder will closely monitor the enrolment rates. If projected enrolment rates indicate that patient targets may not be achieved within the planned enrolment period, consideration will be given to initiate additional sites within the participating countries, and/or to expand the study into additional EU countries.

Data collection will be initiated following the study-defined abstraction starting date. Initiation of selection of patient records meeting study selection criteria will commence on or following this date- September 2014. Data on drug utilisation will be censored from then and not considered in the analyses. This approach will ensure that study procedures do not influence prescribing practices.

A number of measures will also be implemented to ensure the completion of the drug utilisation questionnaire is conducted in a systematic, professional, and unbiased manner:

- Programming of the EDC version of the questionnaire (eCRF) will be reviewed by a quality control process and simulation prior to implementing the questionnaire
- Standard scripts will provide consistent instruction on completion of the questionnaire All individuals performing abstraction of data from medical records will be trained on appropriate data abstraction techniques

8.9.1. Study closure/uninterpretability of results

The planned study closure is October 2015, time of the final report. Medical records will be abstracted until April 2015 unless patients discontinue or withdraw from the study. It is foreseen that study enrolment will stop upon reaching circa 300-450 patients or at the end of abstraction whichever comes first.

The study can be terminated at any time for any reason by GSK. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. The investigator will be responsible for informing IECs of the early termination of the study. The early termination of the study is considered a major amendment; therefore, the relevant competent authorities will be notified before a final decision is made and approval for termination is granted.

8.10. Other Aspects: Changes to the Protocol

Changes to the protocol will be documented in written protocol amendments. Major (i.e., substantial, significant) amendments will be approved by the relevant competent authorities (as applicable) and will usually require submission or notification to the relevant independent ethics committees (IECs) for approval or favourable opinion, if applicable. In such cases, the amendment will be implemented at the site only after approval or favourable opinion has been obtained.

Minor (non-substantial) protocol amendments, including administrative changes will be submitted to the relevant IECs or regulatory authorities where required by pertinent regulations. Any amendment that could have an impact on the patient's agreement to participate in the study requires the patient's informed consent prior to continued participation in the study.

9. PROTECTION OF HUMAN SUBJECTS

To ensure the quality and integrity of research, this study will be conducted under the Guidelines for Good Pharmacovigilance Practices (GVP) and Good Pharmacoepidemiology Practices (GPP) issued by the International Society for Pharmacoepidemiology (ISPE), the Declaration of Helsinki and its amendments, and any applicable national guidelines.

In applicable countries, the protocol and the proposed ICF must be reviewed and approved by a properly constituted IEC before study start. Prior to study start, the investigator (investigator) is required to sign a signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to monitors, auditors, Quality Assurance (QA) representatives, or designated agents of GSK, IECs and Competent Authorities as required.

9.1. Patient Information and Informed Consent

Patients treated with REVOLADE in EU hospitals/wards including office based participating in this study will be identified after being discharged from the hospitalization involving treatment with REVOLADE by periodic query of medication records. At the national or local level, ICFs will be sent to each of these patients (or to next of kin for those patients who are deceased), and only consenting patients will be enroled in the study.

Informed consents must be obtained before conducting any study-specific procedures (i.e. all of the procedures described in the protocol). The process of obtaining informed consent, including the identity of the person who conducted the consenting process, should be documented in the patient medical records. The date when a patient's informed consent was actually obtained will be captured in the eCRF.

Each patient (or legal representative if applicable) must sign the ICF(s) before any data is collected. A copy of each signed ICF must be provided to the patient or the patient's legally authorised representative. All signed and dated ICFs must remain in each patient's study file and must be available for verification by study monitors at any time.

The ICF(s) should be revised whenever there are changes to procedures outlined in the informed consent or when new information becomes available that may affect the willingness of the patient to participate. For any updated or revised ICF(s), the medical record for each patient should document the ICF process and that written informed consent was obtained for the updated/revised ICF(s) for continued participation in the study.

9.2. Patient Confidentiality

In order to maintain patient confidentiality, each patient will be assigned a patient identification number upon study enrolment. This patient number will be used in place of patient name for the purpose of data analysis and reporting. Medical record number or other local reference identifiers are not collected as part of the study database. All parties will ensure protection of patient personal data and will not include patient names on any study forms, reports, publications, or in any other disclosures, except where required by law. In accordance with local regulations in each of the study countries, patients will be informed in the ICF about data handling procedures. Data protection and privacy regulations will be observed in capturing, forwarding, processing, and storing patient data.

All patient information will be handled in accordance with national data protection standards and the EU Directive 2002/58/EC (July 12, 2002) on the processing of personal data and the protection of privacy in the electronic communication sector. Every effort will be made to protect participant confidentiality according to the Directive 95/46/EC on the protection of individuals with regard to the processing of personal data.

9.3. Independent Ethics Committee

Consistent with local regulations and prior to enrolment of patients at a given site, the study protocol will be submitted together with its associated documents (e.g., ICF(s)) to the responsible IEC for its review. Patient enrolment will not start at any site before GSK has obtained written confirmation of a favourable opinion/approval from the relevant central or local IEC. The IEC will be asked to provide documentation of the date of the meeting at which the favourable opinion/approval was given that clearly identifies the study, the protocol version, and the ICF version reviewed.

Before implementation of any substantial changes to the protocol, protocol amendments will also be submitted to the relevant IEC in a manner consistent with local regulations. Pertinent safety information will be submitted to the relevant IECs during the course of the study in accordance with local regulations and requirements. It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, ICFs, and other relevant documents, if applicable, from their local IRB/IEC and provide documentation of approval to GSK. All correspondence with the IRB/IEC should be retained in the Investigator Site File.

Should the study be terminated early for any unanticipated reason, the investigator will be responsible for informing the local IRB/IEC of the early termination.

10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

According to the Module VI of the Good Pharmacovigilance Practices (European Medicines Agency, 2012), for non-interventional study designs which are based on secondary use of data (i.e. medical records are used as source of information of the study), adverse reactions reporting is not required to competent authorities.

If, during the study, an adverse event (AE) or serious adverse event (SAE) is identified in the medical record as explicitly attributed to any known GSK brand products [i.e., an adverse drug reaction (ADR) or a serious adverse drug reaction (SADR)], the investigator or site staff will be responsible for immediately reporting such events that meet the definition of an AE or SAE as per Safety Reporting Manual to the CRO conducting the DUS. The CRO will then forward the ADR/SADR to GSK Case Management Group either by fax (to [redacted] or by email (to [redacted] within 24 hours from the time when the CRO receives the report from the investigator/site.

All additional details regarding definitions and reporting procedures are provided in the Safety Reporting Manual.

11. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

11.1. Target Audience

The information generated by this study will be for the benefit of the EMA, the Sponsor's stakeholders as well as to contribute to the published literature. The results may be disseminated externally via manuscripts or presentations (see Section 11.2).

11.2. Study reporting and publications

A final study report will be generated after all data collection is complete for the DUS and will be submitted to the competent authority(ies) within 6 months upon study completion.

Any publication of the results from this study must be consistent with GSK' publication policy and guided by the Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication of the International Committee of Medical Journal Editors (ICMJE), updated April 2010. The rights of the investigator (investigator) and of GSK with regard to publication of the results of this study will be described in the relevant contract e.g. investigator (investigator) contract.

All reporting will be consistent with the STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) Initiative checklist for cohort studies (STROBE, 2008).

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ANNEX 1. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Section 1: Research question	**Yes**	**No**	**N/A**	**Page Number(s)**
1.1 Does the formulation of the research question clearly explain:				
1.1.1 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)	☒	☐	☐	21-24
1.1.2 The objectives of the study?	☒	☐	☐	25
1.2 Does the formulation of the research question specify:				
1.2.1 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	22-23
1.2.2 Which formal hypothesis(-es) is (are) to be tested?	☐	☐	☒	
1.2.3 if applicable, that there is no *a priori* hypothesis?	☒	☐	☐	24

Comments:

Section 2: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
2.1 Is the source population described?	☒	☐	☐	26-27
2.2 Is the planned study population defined in terms of:				
2.2.1 Study time period?	☒	☐	☐	26-27
2.2.2 Age and sex?	☒	☐	☐	26
2.2.3 Country of origin?	☒	☐	☐	28
2.2.4 Disease/indication?	☒	☐	☐	26
2.2.5 Co-morbidity?	☒	☐	☐	26
2.2.6 Seasonality?	☐	☒	☐	

Section 2: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
2.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	27

Comments:

Section 3: Study design	**Yes**	**No**	**N/A**	**Page Number(s)**
3.1 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	☒	☐	☐	30-32
3.2 Is the study design described? (e.g. cohort, case-control, randomised controlled trial, new or alternative design)	☒	☐	☐	26
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)	☐	☐	☒	
3.4 Is sample size considered?	☒	☐	☐	33
3.5 Is statistical power calculated?	☒	☐	☐	33-35

Comments:

Section 4: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
4.1 Does the protocol describe the data source(s) used in the study for the ascertainment of: 4.1.1 Exposure? (e.g. pharmacy dispensing,				

Section 4: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
general practice prescribing, claims data, self-report, face-to-face interview, etc)				
4.1.2 Endpoints? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics, etc)	☒	☐	☐	29
4.1.3 Covariates?	☒	☐	☐	30-32
	☒	☐	☐	30-32
4.2 Does the protocol describe the information available from the data source(s) on:				
4.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	32
4.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	32
4.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☒	☐	☐	32
4.3 Is the coding system described for:				
4.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10)	☐	☒	☐	
4.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory Activities(MedDRA) for adverse events)	☐	☒	☐	
4.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System)	☐	☒	☐	
4.4 Is the linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	35

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)	☒	☐	☐	32
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)	☐	☒	☐	
5.4 Is exposure classified based on biological mechanism of action?	☐	☒	☐	
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?	☒	☐	☐	30-32
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: Biases and Effect modifiers	**Yes**	**No**	**N/A**	**Page Number(s)**
7.1 Does the protocol address:				

Section 7: Biases and Effect modifiers	**Yes**	**No**	**N/A**	**Page Number(s)**
7.1.1 Selection biases?	☒	☐	☐	39
7.1.2 Information biases?	☒	☐	☐	39
(e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)				
7.2 Does the protocol address known confounders? (e.g. collection of data on known confounders, methods of controlling for known confounders)	☒	☐	☐	39
7.3 Does the protocol address known effect modifiers? (e.g. collection of data on known effect modifiers, anticipated direction of effect)	☐	☐	☒	
7.4 Does the protocol address other limitations?	☒	☐	☐	39

Comments:

Section 8: Analysis plan	**Yes**	**No**	**N/A**	**Page Number(s)**
8.1 Does the plan include measurement of absolute effects?	☐	☐	☒	
8.2 Is the choice of statistical techniques described?	☒	☐	☐	36-37
8.3 Are descriptive analyses included?	☒	☐	☐	36-37
8.4 Are stratified analyses included?	☒	☐	☐	36-37
8.5 Does the plan describe the methods for identifying:	☐	☐	☒	
8.5.1 Confounders?	☐	☐	☒	
8.5.2 Effect modifiers?				
8.6 Does the plan describe how the analysis will address:	☐	☐	☒	
8.6.1 Confounding?	☐	☐	☒	
8.6.2 Effect modification?				

Comments:

Section 9: Quality assurance, feasibility and reporting	**Yes**	**No**	**N/A**	**Page Number(s)**
9.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	38
9.2 Are methods of quality assurance described?	☒	☐	☐	38
9.3 Does the protocol describe quality issues related to the data source(s)?	☒	☐	☐	39
9.4 Does the protocol discuss study feasibility? (e.g. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	33
9.5 Does the protocol specify timelines for				
9.5.1 Start of data collection?	☒	☐	☐	20
9.5.2 Any progress report?	☒	☐	☐	20
9.5.3 End of data collection?	☒	☐	☐	20
9.5.4 Reporting? (i.e. interim reports, final study report)	☒	☐	☐	20
9.6 Does the protocol include a section to document future amendments and deviations?	☒	☐	☐	20
9.7 Are communication methods to disseminate results described?	☒	☐	☐	44
9.8 Is there a system in place for independent review of study results?	☐	☒	☐	

Comments:

Section 10: Ethical issues	**Yes**	**No**	**N/A**	**Page Number(s)**
10.1 Have requirements of Ethics	☒	☐	☐	41-42

Section 10: Ethical issues	**Yes**	**No**	**N/A**	**Page Number(s)**
Committee/Institutional Review Board approval been described?				
10.2 Has any outcome of an ethical review procedure been addressed?	☒	☐	☐	41-42
10.3 Have data protection requirements been described?	☒	☐	☐	41-42

Comments:

ANNEX 2. DISPENSING SYSTEMS IN SELECTED EU MEMBER STATES

Distribution of REVOLADE in Germany

There are two channels of REVOLADE distribution in Germany- 1) a hospital based channel and 2) a retail based channel.

1. In the first hospital based channel, doctors that work in a hospital can prescribe REVOLADE and then patients can fill a prescription either at a hospital based pharmacy (in-patient) or public pharmacy including pharmacy specialized in oncology field (out-patient). In this channel, an order placement for REVOLADE and product delivery occurs directly between the GSK order center and hospital based pharmacies or hospital supplying pharmacies in this case.
2. In the second retail pharmacy channel, an office based hematologists and oncologists can prescribe REVOLADE and then patients can fill a prescription through public pharmacies or pharmacies specialized in oncology. In this second channel, an order placement for REVOLADE and product delivery occurs through a wholesaler, which then can deliver REVOLADE to public pharmacies and pharmacies specialized in oncology.

It is critical to point out that doctors or Institutions can't order REVOLADE directly from the GSK order center. They must place an order through a pharmacist. More importantly, considering the German data privacy law, pharmicists are not allowed to disclose any information including the physician's or patient's name to anybody. Therefore, patients prescribed Revolade through both of these channels will be identified for the study.

Distribution of REVOLADE in Spain

Currently, there is a single channel of REVOLADE distribution in Spain and this is a hospital based channel. Doctors including hematologists, oncologists and hepatologists that work in a hospital can prescribe REVOLADE and then patients can fill a prescription at a hospital based pharmacy. An order placement for REVOLADE and product delivery can occur directly between the GSK order center and hospital based pharmacies. In addition, the pharmacists records can identify prescribers of REVOLADE in the entire hospital, not only hematology/oncology or gastroenterology and hepatology department. Therefore, patients who received REVOLADE will be identified through the hospital based physicians and hospital based pharmacists.

Distribution of REVOLADE in France

In France, the distribution of Revolade occurs through a hospital and private pharmacy based channel. Doctors including hematologists, oncologists, hepatologists, gastroenterologists and internal medicine physicians based at university hospitals, public hospitals, and private hospitals can prescribe Revolade and then patients can fill a prescription at a hospital and private pharmacy. It is critical to point out that considering the French privacy rules, pharmacists are not allowed to disclose any information

including the physician's or patient's name to anybody. Therefore, medical records of patients received Revolade through university hospital or public or private based hospital will be used for review in the study.

Name of main author of study protocol: [redacted]

Date: 23/05/2014

Signature: _____