TITLE PAGE

Division: Worldwide Development
Information Type: Worldwide Epidemiology Study Protocol

Title:	A prospective observational cohort study nested within the HCV Research UK National Registry to evaluate real world use of eltrombopag in adult patients with chronic hepatitis C virus infection who are unable to initiate or maintain optimal interferon-based therapy due to thrombocytopenia

Compound Number:	SB-497115
Development Phase	IV
Effective Date:	12-AUG-2014
Subject:	Hepatitis C Virus, Cohort study
Author(s):	[redacted]

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PASS information

Title	A prospective observational cohort study nested within the HCV Research UK National Registry to evaluate real world use of eltrombopag in adult patients with chronic hepatitis C virus infection who are unable to initiate or maintain optimal interferon-based therapy due to thrombocytopenia
Protocol version identifier	02
Date of last version of protocol	[17 March 2014]
EU PAS register number	Study not registered
Active substance	Eltrombopag
Medicinal product	Eltrombopag
Product reference	SB-497115-GR
Procedure number	[If applicable, Agency or national procedure number(s), e.g. EMA/X/X/XXX]
Marketing authorisation holder(s)	GlaxoSmithKline
Joint PASS	No

Research question and objectives	The primary objective of this study is to report the incidence of hepatic decompensation among eltrombopag users with chronic hepatitis C virus infection who are unable to initiate or maintain optimal interferon-based therapy due to thrombocytopenia. Many of these patients will receive eltrombopag with interferon-based therapy that also includes direct acting anti-viral agents. Because this group was not studied in the Phase III randomized clinical trials and only limited information subsequently exists, it is important to better understand hepatic decompensation rates and other events in patients being treated with eltrombopag and DAAs in a real-world setting. Secondary objectives include reporting incidence of thromboembolic events and mortality and identifying risk factors for hepatic decompensation, thromboembolic events and mortality among eltrombopag users in a real-world setting. The study will also report the 3-year incidence of hepatic decompensation and mortality, comparing patients who achieve sustained virologic response to patients who do not achieve SVR among eltrombopag users, a subset of which will be on interferon-based therapy and direct acting agents. The study will also examine effectiveness of eltrombopag to initiate and maintain HCV therapy and achieve EVR and SVR among eltrombopag users. A subset of these patients will be on direct acting agents as part of their interferon-based therapy. Secondary Objectives: • Determine incidence of thromboembolic events and mortality among patients receiving eltrombopag • Explore factors associated with risk of hepatic decompensation and of thromboembolic events among patients receiving eltrombopag • Determine the incidence rate ratio of hepatic decompensation and mortality at 3 years, comparing eltrombopag patients achieved sustained virologic response to eltrombopag patients who did not achieve SVR • Obtain information on treatment effectiveness among patients receiving eltrombopag with respect to initiating, maintaining and completing HCV therapy, and achieving EVR and SVR • Examine primary and secondary objectives stratified by use of direct acting anti-viral agents if sample size allows

Country(-ies) of study	United Kingdom
Author	[redacted], PhD, MSPH GlaxoSmithKline

MARKETING AUTHORISATION HOLDER(S)

Marketing authorisation holder(s)	GlaxoSmithKline Trading Services Limited 6900 Cork Airport Business Park, Kinsdale Road, Cork, Ireland Telephone: [redacted] Telefax: [redacted] E-Mail: [redacted]
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1. LIST OF ABBREVIATIONS

AE	Adverse Event
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
EVR	Early Virologic Response
GSK	GlaxoSmithKline
HCV	Hepatitis C Virus
HES	Hospital Episode Statistics
NHS	National Health Service
SVR	Sustained Virologic Response

Trademark Information

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REVOLADE/ PROMACTA

Trademarks not owned by the GlaxoSmithKline group of companies
SAS

2. RESPONSIBLE PARTIES

Responsible parties for this study can be found in ANNEX 1.

SPONSOR SIGNATORY:

[redacted] PhD, MSPH
Primary Author/ Project officer

Aug 12, 2014
Date

[redacted] PhD
Therapy Area Leader

Aug 12, 2014
Date

SPONSOR INFORMATION PAGE

WWEpi Project Identifier: WEUSKOP7134

Sponsor Legal Registered Address:

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In some countries, the clinical trial 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 clinical trial submission.

Sponsor Medical Monitor Contact Information: [redacted], Medical Affairs Director Phone: [redacted] Email: [redacted]

Sponsor Serious Adverse Events (SAE) Contact Information: The adverse event must be faxed to GSK Global Clinical Safety and Pharmacovigilance at [redacted] within 24 hours of receiving the information.

Regulatory Agency Identifying Number(s): NA

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.

Co-Investigator Name:
_____

_____ _____
Co-Investigator Signature Date

Co-Investigator Name:
_____

_____ _____
Co-Investigator Signature Date

3. ABSTRACT

***Title** A prospective observational cohort study nested within the HCV Research UK National Registry to evaluate real world use of eltrombopag in adult patients with chronic hepatitis C virus infection who are unable to initiate or maintain optimal interferon-based therapy due to thrombocytopenia

***Rationale and background** Hepatitis C Virus (HCV) infection is a leading cause of chronic liver disease worldwide. Treatment consists of combination therapy with peginterferon and ribavirin (double therapy) or where appropriate, interferon, ribavirin and a direct acting antiviral (triple therapy), although the treatment landscape is changing rapidly with new therapies. Thrombocytopenia as an interferon related adverse event or a complication of chronic liver disease often necessitates dose reduction and discontinuation in these patients. .

Eltrombopag (Revolade™/Promacta™) is an oral second generation thrombopoietin receptor agonist which impacts megakaryocyte differentiation and proliferation. 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). REVOLADE was approved by the European Commission in September 2013 for the treatment of 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. Eltrombopag allows patients who would otherwise have been poor candidates due to low platelet counts to undergo interferon-based therapy for HCV.

In the randomized clinical trials program, there was an increased incidence of hepatic decompensation events that occurred in the eltrombopag arm vs. the placebo arm (10% vs 5%, respectively), an increased incidence of thromboembolic events (3% vs 1%), and a higher death event (3% vs 2%) (Afdhal, 2014). The incidence of hepatic decompensation and thromboembolic events have been adequately assessed in previous randomized double-blinded placebo controlled clinical trials that included more than 1,500 patients and the current label for eltrombopag contains a warning for hepatotoxicity and hepatic decompensation. However, the occurrence of hepatic decompensation and other adverse events have not been characterized in patients outside the clinical trial setting, nor have they been assessed in thrombocytopenic HCV patients who have received direct acting agents in combination with interferon-based therapy.

GSK will take a proactive pharmacovigilance approach in generating incidence of hepatic decompensation and other events through long-term follow-up of eltrombopag users. Results will be reported to the EMA and the FDA and other regulatory agencies. Information will be made available publically through the Clinical Trial Registry and through a publication in a peer-reviewed journal.

***Research question and Objective(s)** The primary objective of this study is to report the incidence of hepatic decompensation among eltrombopag users with

chronic hepatitis C virus infection who are unable to initiate or maintain optimal interferon-based therapy due to thrombocytopenia. Many of these patients will receive eltrombopag with interferon-based therapy that also includes direct acting anti-viral agents. Because this group was not studied in the Phase III randomized clinical trials and only limited information subsequently exists, it is important to better understand hepatic decompensation rates and other events in patients being treated with eltrombopag and DAAs in a real-world setting. Secondary objectives include reporting incidence of thromboembolic events and mortality and identifying risk factors for hepatic decompensation, thromboembolic events and mortality among eltrombopag users in a real-world setting. The study will also report the 3-year incidence of hepatic decompensation and mortality, comparing patients who achieve sustained virologic response to patients who do not achieve SVR among eltrombopag users, a subset of which will be on interferon-based therapy and direct acting agents. The study will also examine effectiveness of eltrombopag to initiate and maintain HCV therapy and achieve EVR and SVR among eltrombopag users. A subset of these patients will be on direct acting agents as part of their interferon-based therapy.

***Study Design** The study is a multicenter, prospective, observational study conducted nested within the HCV Research UK consortium. HCV Research UK is a consortium of HCV researchers in the UK whose principal objective is to build a national clinical research database and biorepository for promoting and executing research studies into HCV infection. The entity comprises a multidisciplinary infrastructure that links major UK liver research centres involved in management of HCV-infected patients to basic science centres of excellence. It has been funded by the Medical Research Foundation to establish a national cohort of up to 10,000 HCV-infected people. The clinical research database is created by providing linked-anonymised information on patients collected from the medical charts by the treating physicians. There are no inclusion or exclusion criteria for patient enrolment. For each patient, information is collected at baseline and then cumulative clinical data are abstracted every two years from date of recruitment, for a minimum of 10 years. In addition to medical chart review, the registry links to critical UK data sources using patient-specific NHS identifying numbers on an annual basis to provide more current outcome data and to ensure major events are captured irrespective of the hospital location where patients may be admitted for care. These linkages are with the Hospital Episode Statistics (HES) database for hospitalizations and the Health and Social Care Information Centre databases for death certificate data and cancer registration.

For the GSK nested study, the only criteria for inclusion into the study is that the patient is part of the HCV Research UK Consortium and is treated with eltrombopag. For each eltrombopag patient, information will be collected at baseline and over a three-year period after the initiation of eltrombopag. The major focus of the study is to quantify the incidence of hepatic decompensation and thromboembolic events, and to examine short term and long term treatment effectiveness among eltrombopag users. As with the HCV Research UK registry, the nested study will be observational and non-interventional.

***Population** HCV Research UK is a consortium of HCV researchers in the UK that links major UK liver research centres involved in management of HCV-infected patients to basic science centres of excellence. It is expected to enroll 10,000 HCV patients recruited at all stages of their clinical care pathway by the end of 2014. The consortium is recruiting at more than 40 liver centers across the UK and has consented more than 7250 patients into the registry as of January 2014. All users of eltrombopag identified in the HCV Research UK database will be included in the nested study.

***Variables** Outcome variables include: hepatic decompensation, thromboembolic events, overall and cause-specific mortality, ability to initiate interferon-based antiviral therapy, ability to maintain interferon-based antiviral therapy defined by number of dose reductions, and ability to reach early and/or sustained virologic response. The main exposure variables include treatment with eltrombopag, peginterferon alfa-2a or 2b, ribavirin, direct acting antivirals and other antiviral therapy.

***Data sources** The registry consortia comprises a multidisciplinary infrastructure that links major UK liver research centres involved in management of HCV-infected patients to basic science centres of excellence. At each participating site, patients are enrolled prospectively and treated per local standard of care. The clinical research database is created by providing linked-anonymised information on patients collected from the medical charts by the treating physicians. For each patient, information is collected at baseline and then cumulative clinical data are abstracted from medical charts every two years from date of recruitment, for a minimum of 10 years. In addition to medical chart review, the registry links to critical UK data sources using patient-specific NHS identifying numbers on an annual basis to provide more current outcome data and to ensure major events are captured irrespective of the hospital location where patients may be admitted for care. These linkages are with the Hospital Episode Statistics (HES) database for hospitalizations and the Health and Social Care Information Centre databases for death certificate data and cancer registration.

***Study size** The exact number of eltrombopag patients cannot be stated at this time since enrolment of HCV patients into the registry will be on-going until end of 2014. We estimate that between 0.5-2% of the Registry's 10,000 HCV patients will be using eltrombopag as supportive care, resulting in a potential sample size between 50 and 200 eltrombopag users.

***Data analysis**

Cumulative incidence rates and corresponding 95% confidence intervals as well as Kaplan-Meier rates and corresponding 95% confidence intervals will be calculated for the occurrence of hepatic decompensation, thromboembolic events, or mortality, as separate events, at multiple time points during and at the end of the 3-year follow-up period. Baseline factors potentially predictive of events will be identified through Kaplan-Meier survival estimates for patients with vs. without the factor and testing for statistical significance using the log-rank test. Cox proportional hazards models

will be constructed to evaluate the influence of these identified factors simultaneously.

Patient demographics and characteristics will be described at the time of initiation of eltrombopag. Virology, laboratory information, information on dose and duration of eltrombopag, early and sustained virologic response, anti-viral therapy and incidence of hepatic decompensation and thromboembolic events will be described at baseline and distinct follow-up time points. Continuous variables will be reported as mean, standard deviation, median, 25th and 75th quartiles, and range. Categorical variables will be summarized as number and proportion of subjects with observed (non-missing) data, with corresponding 95% confidence intervals (CI) by exact methods.

The number and percentage of patients who achieve early virologic response and sustained virologic response will be reported at distinct follow-up time points. The probability of attaining EVR and SVR by these time points will be presented as Kaplan-Meier estimates, along with median time to attaining virologic response.

***Milestones** Enrollment of HCV patients into the HCV Research UK Registry is on-going and is expected to be completed by the end of 2014. Recruitment has exceeded 7200 patients with between 300-450 newly consented patients being added per month. Therefore, the target date for completion of the registry is achievable. The numbers of eltrombopag users nested within the Registry will be assessed at the time of enrollment completion for HCV Research UK. An interim analysis will be generated in 2016. The final analysis will be conducted in 2018.

4. AMENDMENTS AND UPDATES

None.

5. MILESTONES

Milestone	**Planned dates: Note: Dates will be modified based on new date for protocol approval**
Start of data collection	TBD, after protocol approval
End of data collection	2018
Interim report 1	2016
Registration in the EU PAS register	TBD, after protocol approval
Final report of study results	2018

6. RATIONALE AND BACKGROUND

6.1. Background

HCV is a leading cause of chronic liver disease worldwide. The current mainstay of treatment is combination therapy with peginterferon and ribavirin (double therapy) or interferon, ribavirin and a direct acting antiviral (triple therapy). Thrombocytopenia as a treatment related adverse event or a complication of chronic liver disease often necessitates dose reduction and discontinuation in these patients.

Eltrombopag (Revolade™/Promacta™) is an oral second generation thrombopoietin receptor agonist which promotes megakaryocyte differentiation and proliferation. Two global, randomized, double-blinded Phase III trials evaluated the efficacy of eltrombopag in 1500 HCV patients with platelet counts of less than 75,000 using a primary endpoint of achieving sustained viral response. In ENABLE 1, 23% of the eltrombopag group achieved a sustained virologic response versus 14% of the placebo group (*P*=0.0064). In ENABLE 2, 19% of the eltrombopag group achieved SVR versus 13% of the placebo group (p=0.0202) (Afdhal, 2014).

Eltrombopag was approved in the U.S. in 2012 for chronic hepatitis C virus (HCV)-associated thrombocytopenia to allow for the initiation and maintenance of interferon-based therapy.

Eltrombopag was approved by the European Commission in September 2013 for the following indication:

> Revolade is indicated in adult patients with chronic hepatitis C virus (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

Eltrombopag is also approved for chronic immune thrombocytopenic purpura (ITP), and under development for paediatric chronic ITP, thrombocytopenia in myelodysplastic syndromes (MDS) and acute myeloid leukaemia (AML).

6.2. Rationale

In the randomized clinical trials program, there was an increased incidence of hepatic decompensation events that occurred in the eltrombopag arm vs. the placebo arm (10% vs 5%, respectively), an increased incidence of thromboembolic events (3% vs 1%), and a higher death event (3% vs 2%). The incidence of hepatic decompensation and thromboembolic events have been adequately assessed in previous randomized double-blinded placebo controlled clinical trials that included more than 1,500 patients and the current label for eltrombopag contains a warning for hepatotoxicity and hepatic decompensation. However, the occurrence of hepatic decompensation and other adverse events have not been characterized in patients outside the clinical trial setting, nor have they been assessed in thrombocytopenic HCV patients who have received direct acting agents in combination with interferon-based therapy.

GSK will take a proactive pharmacovigilance approach in generating incidence of hepatic decompensation and other events through long-term follow-up of eltrombopag users. Results will be reported to the EMA and the FDA and other regulatory agencies. Information will be made available publically through the Clinical Trial Registry and through a publication in a peer-reviewed journal.

7. RESEARCH QUESTION AND OBJECTIVE(S)

The primary objective of this study is to report the incidence of hepatic decompensation among eltrombopag users with chronic hepatitis C virus infection who are unable to initiate or maintain optimal interferon-based therapy due to thrombocytopenia. Many of these patients will receive eltrombopag with interferon-based therapy that also includes direct acting anti-viral agents. Because this group was not studied in the Phase III randomized clinical trials and only limited information subsequently exists, it is important to better understand hepatic decompensation rates and other events in patients being treated with eltrombopag and DAAs in a real-world setting. Secondary objectives include reporting incidence of thromboembolic events and mortality and identifying risk factors for hepatic decompensation, thromboembolic events and mortality among eltrombopag users in a real-world setting. The study will also report the 3-year incidence of hepatic decompensation and mortality, comparing patients who achieve sustained virologic response to patients who do not achieve SVR among eltrombopag users, a subset of which will be on interferon-based therapy and direct acting agents. The study will also examine effectiveness of eltrombopag to initiate and maintain HCV therapy and achieve EVR and SVR among eltrombopag users. A subset of these patients will be on direct acting agents as part of their interferon-based therapy.

Specific Study Aims

Primary: Report the incidence of hepatic decompensation in patients with chronic hepatitis C virus infection who are unable to initiate or maintain optimal interferon-based therapy due to thrombocytopenia.

Secondary:

- Determine incidence of thromboembolic events and mortality among patients receiving eltrombopag
- Explore factors associated with risk of hepatic decompensation and of thromboembolic events among patients receiving eltrombopag
- Determine the incidence rate ratio of hepatic decompensation and mortality at 3 years, comparing eltrombopag patients achieved sustained virologic response to eltrombopag patients who did not achieve SVR
- Obtain information on treatment effectiveness among patients receiving eltrombopag with respect to initiating, maintaining and completing HCV therapy, and achieving EVR and SVR
- Examine primary and secondary objectives stratified by use of direct acting anti-viral agents if sample size allows

8. RESEARCH METHODS

8.1. Study Design

This is a prospective, multicenter, observational cohort study of HCV-infected patients who have been treated with eltrombopag because they were unable to initiate or maintain optimal interferon-based therapy due to thrombocytopenia.The study is nested within the existing HCV Research UK Registry, a consortium of HCV-infection researchers in the UK comprising a multidisciplinary infrastructure that links major UK liver research centres involved in management of HCV-infected patients to basic science centres of excellence. There are no inclusion or exclusion criteria for patient enrolment into HCV Research UK Registry. Nesting the eltrombopag-treated cohort study within the UK Registry is an efficient way to identify and study eltrombopag users in a real-world setting. All patients who have been treated with eltrombopag during the HCV Research UK study will be included in the nested cohort study. Within the eltrombopag prospective cohort study, patients will be followed for three years after eltrombopag initiation. The major safety outcome is hepatic decompensation. Incidence of thromboembolic events and mortality will also be determined. Thromboembolic events include myocardial infarction, ischemic stroke, pulmonary embolism, deep vein thrombosis, portal vein thrombosis, and other TEEs. The major effectiveness outcomes include ability to initiate anti-viral therapy, ability to prevent anti-viral therapy dose reductions due to thrombocytopenia, early virologic response and sustained virologic response, assessed at several time points during the follow-up period. The incidence of hepatic decompensation and of mortality at three years will be compared between eltrombopag users who reach SVR and those users who do not reach SVR.

An interim analysis will be conducted in 2016 and the final analysis will be completed in 2018.

8.2. Setting

HCV Research UK is a consortium of HCV researchers in the UK established to build a national clinical research database and biorepository for promoting and executing research studies. The entity comprises a multidisciplinary infrastructure that links major UK liver research centres involved in management of HCV-infected patients to basic science centres of excellence. It has been funded by the Medical Research Foundation to establish a national cohort of up to 10,000 HCV-infected people. Recruitment is ongoing at more than 40 liver centres across the UK. As of January 2014, there are 7200 patients in the registry, with recruitment achieving 300-450 patients per month. The estimated recruitment closure date is the end of 2014. To support research studies, HCV Research UK has set up a clinical research database that each investigator inputs into by providing linked-anonymised information on patients collected from the medical charts by the treating physicians. The database is structured by Events. Each participating site enters an Enrolment Event into the clinical database once a patient has been enrolled. If the patient has been treated for HCV in the past, a Treatment Event is entered or the site indicates the treatment data is unavailable. If the patient is on treatment at the time of enrolment, the site enters a Treatment Event to document treatment details. All treatment episodes post-enrolment are also entered as Treatment Events at the time the treatment commences or when the site enters the patient's Follow-up data. If the patient has undergone a liver biopsy, a Biopsy Event is entered into the clinical database. If the patient has died, a Death Event is entered. Any subsequent changes in liver disease status or treatment status are recorded in a Follow-up Event. Laboratory data are stored with Lab Events. Imaging data (fibroscan results) are also stored with Lab Events.

Patient demographics, risk factors, social history, and co-morbid disease are obtained at enrolment. HCV diagnosis, such as date of first positive test, HCV RNA status, genotype and status of infections in parents is collected at enrolment. Physical characteristics are collected at enrolment, at onset of treatment, and at every follow-up point. Co-medications are collected at enrolment, onset of treatment, and follow-up. Liver disease status and treatment status are collected at enrolment, onset of treatment, and follow-up, including information on biopsy, cirrhosis, portal hypertension, decompensation date and method of diagnosis, hepatic cellular carcinoma, liver transplantation, previous treatment episodes and treatment status. Cause of death is obtained when a patient dies. HCV treatments including start and stop dates, adherence, and outcome (rapid, early and sustained response and viral load) are collected at pre-enrolment, at enrolment, and post enrolment. Biopsy data are collected at each follow-up point.

In addition to medical chart review and entering Events records into the database, the Registry will link to several critical UK data sources using patient-specific NHS identifying numbers. The linkage will be conducted on an annual basis. This will provide the Registry with more contemporary patient data to complement medical chart review and additionally, it will ensure that thromboembolic events and deaths are captured irrespective of the hospital location where patients may be admitted for care. One linkage will be to the Hospital Episode Statistics (HES) database. HES is a data

warehouse containing details of all admissions, outpatient appointments and A&E attendances at NHS trusts in England, including acute hospitals, primary care trusts and mental health trusts. The other linkages will be to the Health and Social Care Information Centre. This will provide access to death certificate data and cancer registration for all patients in the cohort.

For the GSK observational study nested within the HCV Research UK Registry, all users of eltrombopag will be identified in the registry. Information will be collected at baseline and through 3 years post-eltrombopag initiation.

8.3. Variables

Variables included in this study are summarized below:

8.3.1. Outcomes

1. Hepatic decompensation in users of eltrombopag, obtained from the Follow-up Event record, defined as any one of:
    - Ascites
    - Total bilirubin > 50 μmol/L
    - Hepatic encephalopathy
    - Variceal hemorrhage

2. Thromboembolic events in users of eltrombopag, identified in the HES database using ICD10 codes, which have been included in ANNEX 3
    - Myocardial infarction
    - Ischemic Stroke
    - Portal vein thrombosis
    - Deep vein thrombosis
    - Pulmonary embolism
    - Other arterial thromboembolic events
    - Other venous thromboembolic events

3. Mortality (all cause and cause-specific), obtained from the Death Event record and linkages to the NHS data sources

4. Treatment effectiveness among eltrombopag users, assessed as

    - Percentage of eltrombopag users able to initiate antiviral therapy

    - Percentage of eltrombopag users requiring no, one, two, three, or four or more dose reductions due to TCP

    - Percentage of eltrombopag users reaching early virologic response, defined as clinically significant reduction in HCV RNA (≥2 log10 drop or

undetectable) after 12 weeks of antiviral treatment

- Percentage of eltrombopag users reach SVR, defined by HCV RNA negative 24 weeks after cessation of treatment

8.3.2. Exposure definitions

The main exposure variable is treatment with eltrombopag:

- In combination with peginterferon and ribavirin (double therapy), or
- In combination with (peginterferon, ribavirin, and direct acting antiviral (triple therapy)

Modalities of treatment will contain information on dose, duration and discontinuation from the Treatment Event Record

Anti-viral information, including dose, duration, and discontinuation, will also be obtained from the Treatment Event Record.

8.3.3. Other variables

Demographics: Age, Sex, Race/ethnicity

HCV risk/clinical factors: Probable infection route, Year of infection (if able to estimate) Date of first positive HCV test, HCV RNA Status, HCV genotype subtype, Alcohol use, Smoking history, Injected drug use

Comorbidities: Diabetes mellitus, renal failure, depression, coagulation bleeding disorder, HIV co-infection, cancer

Laboratory values: Haemoglobin concentration (g/dL), Creatinine clearance (mL/minute), Platelet count (Gi/L), Total bilirubin (μmol/L), Albumin (g/L), Prothrombin (INR)

Other variables: Virology data, Liver biopsy results, Specific disease outcomes of liver elasticity (fibroscan), Clinical/histological diagnosis of cirrhosis

8.4. Data sources

Patients are enrolled prospectively at participating sites and treated according to local standard of care. The clinical research database is created by providing linked-anonymised information on patients collected from the medical charts by the treating physicians. For each patient, information is collected at baseline by interview at the time of consent and from medical records. Subsequently, cumulative clinical data are abstracted from medical charts every two years from date of recruitment, for a minimum of 10 years. In addition, laboratory data is downloaded from hospital IT systems for entry into the registry. As well as medical chart review, the registry links to critical UK data sources using patient-specific NHS identifying numbers on an annual basis to

provide more current outcome data and to ensure major events are captured irrespective of the hospital location where patients may be admitted for care. These linkages are with the Hospital Episode Statistics (HES) database for hospitalizations and the Health and Social Care Information Centre databases for death certificate data and cancer registration.

8.5. Study size

The exact number of patients that will come from the existing registry cannot be defined *a priori*. We estimate that between 0.5-2% of the expected 10,000 patients will be eligible, and that a sample size between 50 and 200 patients can be achieved.

Since the study is descriptive, sample size informs the degree of precision around point estimates for the events of hepatic decompensation and thromboembolic events.

The event rate of hepatic decompensation in this specific population is unknown. The rate that occurred among eltrombopag users in the combined ENABLE trials, which was 10%, is used as an estimate and for sample size calculation; this rate is varied from 8% to 12%.

Figure 1 below depicts the precision around potential event rates. Number of assumed eltrombopag users is marked by different colored lines and symbols. The x-axis notes the percentage of patients with an event. The y-axis is the precision for each specific event rate, which can be added and subtracted to the point estimate to obtain a 95% confidence interval. For example, if 10% of patients experience a hepatic decompensation event, the half width varies across sample size as follows:

Sample Size	Half Width
50	0.083
100	0.058
150	0.047
200	0.041

A similar figure is presented for the event rate for thromboembolic events, using the ENABLE trials event rate of 3% as the mid-point and varying the rate from 1% to 5% (Figure 2).

Figure 1 **Precision (y-axis) for event rates (x-axis) ranging from 8%-12% for the outcome of hepatic decompensation for 4 potential sample sizes of eltrombopag users (different colored lines)**

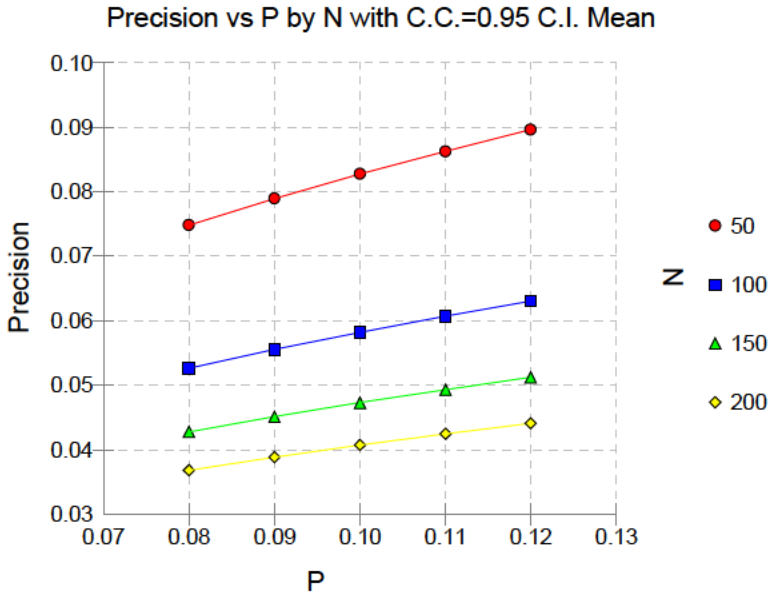
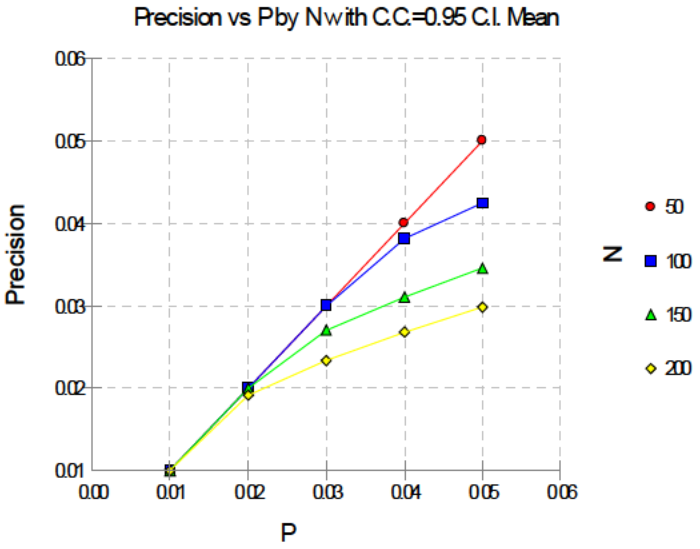


Figure 2 **Precision (y-axis) for event rates (x-axis) ranging from 1%-5% for the outcome of thromboembolic events for 4 potential sample sizes of eltrombopag users (different colored lines)**



Calculations and graphs have been derived using the NPASS software [Hintze, 2006]

The study is not designed to compare hepatic decompensation rates in eltrombopag users with rates in a control group of patients not using eltrombopag due to insufficiency of the sample size to draw statistical inferences.

For hepatic decompensation, the power to detect a doubling in event rates comparing users to non-users in HCV-TARGET, assuming the ENABLE clinical trial rates of 10% in the eltrombopag treated group and 5% in placebo patients is as follows:

- **Power if 50 eltrombopag patients are enrolled**:
  - 6% if propensity-score matching of eltrombopag users to non-users is made on a 1:1 basis
  - 13% if matched 1:2
  - 16% if matched 1:3
  - 17% if matched 1:4
  - 20% if matched 1:5
  - 20% if matched 1:6
- **Power if 200 eltrombopag patients are enrolled**:
  - 40% if propensity-score matching of eltrombopag users to non-users is made on a 1:1 basis
  - 56% if matched 1:2
  - 61% if matched 1:3
  - 64% if matched 1:4
  - 67% if matched 1:5
  - 68% if matched 1:6

Successfully propensity score matching multiple controls (e.g., non-users) to one eltrombopag user is problematic considering that eltrombopag users compared to non-users could differ on very important factors in addition to eltrombopag use, such as presence of thrombocytopenia, level of thrombocytopenia, MELD score, serum albumin, site (representing physician preference or medical care standard), and other factors. It is expected that some eltrombopag users will not have an appropriately-matched control.

Even though this is a descriptive study, if the number of eltrombopag users within the HCV Research UK Registry turns out to be very small, arbitrarily and preliminarily defined as < 50 patients, then the full study may not go forward. The decision to go forward based on at least a minimum number of patients will ensure that findings from the study will be robust.

8.6. Data management

Nottingham University Hospitals NHS Trust, the sponsor for the registry, will preserve the confidentiality of participants taking part in the study and the registry is registered under the Data Protection Act.

On Enrolment, each patient is assigned a unique study number and all data and biological samples are recorded against that number. The code for study numbers is held securely, locally in each clinic. Access to the clinical data held in the database is restricted to members of the HCV Research UK management group.

Site Investigators and their delegates have password-protected access to the database for the purpose of recording and maintaining data. They are only able to access the data from

patients at their own centre for editing purposes. Access will only be granted once adequate training has been completed.

All blood-derived samples are anonymised with a unique barcode consisting of a primary number and sub-number. The primary number links the sample to the patient study number, their clinical details and date of sample acquisition. Sub-numbers define aliquots, nature of the sample, volume, date of processing and storage location. All subsequent sub-divisions of the sample are allocated a new unique barcode. Linking of clinical data to the Tissue bank will be possible by the use of unique patient study numbers.

8.6.1. Timings of Assessment during follow-up

The number of patients within the HCV Research UK Registry will be assessed at the prescribed end of enrolment, projected to be end of 2014. The data will also be assessed for an interim analysis in 2016 and at the scheduled end of follow-up of the nested study, projected to be in 2018.

8.7. Data analysis

The analysis plan, including complete analytical specifications, tables and listings, will be fully described in a written SAP and approved prior to database lock for any analysis.

The eltrombopag cohort study nested within HCV Research UK is a descriptive study conducted to provide primarily incidence of hepatic decompensation and secondarily other important outcomes such as thromboembolic events and mortality in HCV patients who use eltrombopag in a real world setting. A subset of these patients will be treated with direct acting anti-viral agents as part of their interferon-based regimen; this subset was not previously studied in the randomized clinical trials. Cumulative incidence rates will be calculated for the occurrence of hepatic decompensation, thromboembolic events, or mortality, as separate events, at multiple time points during and at the end of the 3-year follow-up period. The 95% CIs for cumulative incidence will be calculated using the method outlined by Newcombe et al [Newcombe, 1998]. Baseline factors potentially related to each event will be identified during exploratory analyses by comparing Kaplan-Meier survival estimates for patients with vs. without the factor and testing for statistical significance using the log-rank test, after assuring that the assumption of proportionality holds. Cox proportional hazards models will be constructed to evaluate the influence of these identified factors simultaneously.

Kaplan-Meier survival estimates will be calculated for the outcomes of hepatic decompensation, thromboembolic events, and all-cause mortality. Thromboembolic events will be presented as a single category as well as grouped by venous or arterial origin, and by individual event types. Confidence intervals for survival rates will be calculated using the method outlined by Simon et al [Simon, 1986]

Patient demographics and characteristics will be described at the time of initiation of eltrombopag. Virology, laboratory information, information on dose and duration of eltrombopag, early and sustained virologic response, anti-viral therapy and incidence of hepatic decompensation and thromboembolic events will be described at baseline and at 6

months, 12 months, 18 months, 2 years and 3 years of follow-up. Information will be presented for all patients and if a sufficiently large sample size, for subgroups of interest, specifically, by modality of anti-viral therapy, and by attained SVR status. Continuous variables will be reported as mean, standard deviation, median, 25th and 75th quartiles, and range. Categorical variables will be summarized as number and proportion of subjects with observed (non-missing) data, with corresponding 95% confidence intervals (CI) by exact methods.

The number and percentage of patients who achieve early virologic response and sustained virologic response will be reported. The probability of attaining SVR by distinct time points will be presented as Kaplan-Meier estimates, along with median time to attaining EVR and SVR.

For the long term outcomes of hepatic decompensation or mortality at 3 years (as separate events), incidence rate ratios comparing patients who did vs. did not attain SVR will be calculated, along with 95% confidence intervals using the method outlined by Dobson et al [Dobson, 1991]. Kaplan-Meier survival graphs will be plotted and the log rank test will be used to determine statistical significance of SVR (after assuming proportionality assumptions). Factors determined to be related to hepatic decompensation (or to all-cause mortality in a separate analysis) from the earlier exploratory work will be included in a Cox proportional hazards model along with SVR.

For those patients who are lost to follow-up, or who drop out of the study, the analyses will include all data up to the point of their last data collection.

8.8. Quality control

The reliability of HES diagnostic data has been assessed in several studies. Kirkman et al validated ICD-10 hospital discharge codes for stroke against chart review for 2147 patients admitted between 2002 and 2007 and documented a positive predictive value of 96% [Kirkman, 2009]. Wright et al conducted a validation study for vascular disease, cerebrovascular disease, and venous thromboembolism in women comparing the NHS HES to comprehensive medical records held by general practitioners and found overall agreement in the range 93-97% for the 3 events [Wright, 2012]. Discharge data from the NHS HES is considered complete and of high quality in the UK, and has been used as the gold standard to validate outcomes obtained from other data sources [Britton, 2012]

8.9. Strengths and limitations of the research methods

This study will be one of the first prospective observational cohort studies to assess the use of eltrombopag in HCV patients unable to initiate or maintain optimal interferon-based therapy due to thrombocytopenia. A subset of patients under study will receive direct acting anti-viral agents as part of their backbone of interferon treatment and this set of patients was not studied in the randomized clinical trial setting because DAAs were not available at the initiation of the clinical trial program. The prospective observational study will evaluate the use of eltrombopag in a real-world setting in the United Kingdom.

This study may be limited by its size. Eltrombopag for HCV-associated thrombocytopenia was approved by the CHMP in July 2013 and obtained full approval by the EMA in September 2013. Assuming that data collection within HCV Research UK will complete at the end of 2014, it is possible that the number of eltrombopag patients enrolled in the Registry will be small. If the number is too small, defined arbitrarily and preliminarily as fewer than 50 patients, to provide robust findings for the event of hepatic decompensation, then the full cohort study nested within the Registry may not continue. The study may still have too few patients to be able to stratify by modality of anti-viral therapy (double vs. triple therapy). Further, because of limited sample size, the study cannot effectively include and use a control group to successfully test whether rates occurring in the eltrombopag group are statistically higher than expected.

8.9.1. Study closure/uninterpretability of results

As described in the Limitations section above, if the number of eltrombopag users is too small to provide robust findings for the event of hepatic decompensation, where the threshold for sample size is arbitrarily and preliminarily set at fewer than 50 patients, then the full cohort study may not continue.

9. PROTECTION OF HUMAN SUBJECTS

9.1. Ethical approval and subject consent

The study falls within the principal research objective of the HCV Research UK Registry and does not require separate ethics approval. Approval for the HCV Research UK Registry was obtained from the Derby 1 Research Ethics Committee Copies of the Site Specific Assessment approval letter at each participating NHS Trust were obtained before accepting participants into the study. The HCV Research UK study is conducted in accordance with the recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki 1964 and later revisions.

9.2. Subject confidentiality

Nottingham University Hospitals NHS Trust, the sponsor for the registry, preserves the confidentiality of participants taking part in the study and the registry is registered under the Data Protection Act.

On Enrolment, each patient is assigned a unique study number and all data and biological samples are recorded against that number. The code for study numbers are held securely, locally in each clinic. Access to the clinical data held in the database is restricted.

Site Investigators and their delegates have password-protected access to the database for the purpose of recording and maintaining data. They are only able to access the data from patients at their own centre. Access is granted once adequate training has been completed.

All blood derived samples is anonymised with a unique barcode consisting of a primary number and sub-number. The primary number links the sample to the patient study

number, their clinical details and date of sample acquisition. Sub-numbers define aliquots, nature of the sample, volume, date of processing and storage location. All subsequent sub-divisions of the sample are allocated a new unique barcode. Linking of clinical data to the Tissue bank is possible by the use of unique patient study numbers.

10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

If, during the study, an adverse event (serious or non serious) is identified as explicitly attributed to any GSK product (including products not covered in the specific study objective), this will be reported to GSK Global Clinical Safety and Pharmacovigilance.

These adverse events must be faxed by the site to GSK Global Clinical Safety and Pharmacovigilance within 24 hours of becoming aware of the information. Cases from UK should be sent to: [redacted] or fax [redacted]

Additional details regarding definitions and reporting procedures will be provided in the Safety Reporting Manual.

Regarding the reporting of adverse events to regulatory authorities, GSK will provide information on relevant adverse events according to Good Pharmacovigilance Practices Module VI.

11. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

11.1. Target Audience

This is a Post-authorisation Safety Study (PASS) study requested by the European Medicines Agency (EMA). The results from this study will help inform the EMA and the eltrombopag study team about long-term safety and effectiveness data among HCV patients receiving eltrombopag in a real-world setting.

11.2. Study reporting and publications

An interim analysis will be conducted in 2016 and the final analysis will be completed in 2018. Study reports from both the interim and final analyses will be completed and submitted to the EMA. Manuscripts based on the results from this study will be prepared and submitted to peer-reviewed journals.

12. REFERENCES

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Wright FL, Green J, Canoy D, Cairns B, Balkwill A, Beral V. Vascular disease in women: comparison of diagnoses in hospital episode statistics and general practice records in England. BMC Medical Research Methodology 2012;12:161-170.

ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

No.	Document Reference No	Date	Title
1.	<No>	30 September 2013	List of Responsible Parties

ANNEX 2.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)	☒	☐	☐	17
1.1.2 The objectives of the study?	☒	☐	☐	17-18
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)	☒	☐	☐	18
1.2.2 Which formal hypothesis(-es) is (are) to be tested?	☒	☐	☐	25
1.2.3 if applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

Section 2: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
2.1 Is the source population described?	☒	☐	☐	19-20
2.2 Is the planned study population defined in terms of:				
2.2.1 Study time period?	☒	☐	☐	19-20
2.2.2 Age and sex?	☒	☐	☐	19-20

Section 2: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
2.2.3 Country of origin?	☒	☐	☐	19-20
2.2.4 Disease/indication?	☒	☐	☐	19-20
2.2.5 Co-morbidity?	☒	☐	☐	19-20
2.2.6 Seasonality?	☐	☐	☒	
2.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	19-20

Comments:

This is an all comers study, where all patients on eltrombopag will be captured. We are not definint the cohort based on having a comorbidity. So while we collect comorbidities, we aren't defining our population based on them.

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?	☒	☐	☐	20-21
3.2 Is the study design described? (e.g. cohort, case-control, randomised controlled trial, new or alternative design)	☒	☐	☐	18
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)	☒	☐	☐	20-21;25
3.4 Is sample size considered?	☒	☐	☐	23
3.5 Is statistical power calculated?	☒	☐	☐	25

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, general practice prescribing, claims data, self-report, face-to-face interview, etc)	☒	☐	☐	21
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)	☒	☐	☐	20-21
4.1.3 Covariates?	☒	☐	☐	21-22
4.2 Does the protocol describe the information available from the data source(s) on:				

Section 4: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
4.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	20
4.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	20
4.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☒	☐	☐	20
4.3 Is the coding system described for:				
4.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10)	☒	☐	☐	40-43
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)	☒	☐	☐	22

Comments:

Exposure to eltrombopag will be captured via CRFs

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)	☒	☐	☐	18
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)	☒	☐	☐	18
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?	☒	☐	☐	20-21
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)	☒	☐	☐	27

Comments:

Section 7: Biases and Effect modifiers	**Yes**	**No**	**N/A**	**Page Number(s)**
7.1 Does the protocol address: 7.1.1 Selection biases? 7.1.2 Information biases? (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)	☒	☐	☐	
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?	☒	☐	☐	27

Comments:

Section 8: Analysis plan	**Yes**	**No**	**N/A**	**Page Number(s)**
8.1 Does the plan include measurement of absolute effects?	☒	☐	☐	18
8.2 Is the choice of statistical techniques described?	☒	☐	☐	25-26
8.3 Are descriptive analyses included?	☒	☐	☐	25-26
8.4 Are stratified analyses included?	☒	☐	☐	18, if sample size allows

Section 8: Analysis plan	**Yes**	**No**	**N/A**	**Page Number(s)**
8.5 Does the plan describe the methods for identifying: 8.5.1 Confounders? 8.5.2 Effect modifiers?	☒ ☐	☐ ☐	☐ ☒	26
8.6 Does the plan describe how the analysis will address: 8.6.1 Confounding? 8.6.2 Effect modification?	☒ ☐	☐ ☐	☐ ☒	26

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)	☒	☐	☐	25
9.2 Are methods of quality assurance described?	☒	☐	☐	27
9.3 Does the protocol describe quality issues related to the data source(s)?	☒	☐	☐	27
9.4 Does the protocol discuss study feasibility? (e.g. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	22

Section 9: Quality assurance, feasibility and reporting	**Yes**	**No**	**N/A**	**Page Number(s)**
9.5 Does the protocol specify timelines for				
9.5.1 Start of data collection?	☒	☐	☐	16
9.5.2 Any progress report?	☒	☐	☐	16
9.5.3 End of data collection?	☒	☐	☐	16
9.5.4 Reporting? (i.e. interim reports, final study report)	☒	☐	☐	16
9.6 Does the protocol include a section to document future amendments and deviations?	☒	☐	☐	16
9.7 Are communication methods to disseminate results described?	☒	☐	☐	29
9.8 Is there a system in place for independent review of study results?	☒	☐	☐	29

Comments:

Section 10: Ethical issues	**Yes**	**No**	**N/A**	**Page Number(s)**
10.1 Have requirements of Ethics Committee/Institutional Review Board approval been described?	☒	☐	☐	28
10.2 Has any outcome of an ethical review procedure been addressed?	☒	☐	☐	28
10.3 Have data protection requirements been described?	☒	☐	☐	28

Comments:

Name of main author of study protocol: [redacted]

Date:14/10/2013

Signature: _____

ANNEX 3. ADDITIONAL INFORMATION

ICD-10 codes for Myocardial Infarction:

Code Variable	Description
I220	subsequent myocardial infarction of anterior wall
I221	subsequent myocardial infarction of inferior wall
I228	subsequent myocardial infarction of other sites
I229	subsequent myocardial infarction of unspecified site
I230	haemopericardium as curr comp folow acut myocard infarct
I231	atral sept defect as curr comp folow acut myocardal infarct
I232	ventric sep defect as curr comp fol acut myocardal infarc
I233	rup cardac wal withou haemopercard as cur comp fol ac mi
I234	rup chordae tendinae as curr comp fol acut myocard infarct
I235	rup papilary muscle as curr comp fol acute myocard infarct
I236	thromb atrium/auric append/vent as curr comp foll acute mi
I238	oth current comp following acute myocardial infarction

ICD-10 codes for Stroke:

Code Variable	Description
I630	cerebral infarct due to thrombosis of precerebral arteries
I631	cerebral infarction due to embolism of precerebral arteries
I632	cereb infarct due unsp occlusion or stenos precerebrl arts
I633	cerebral infarction due to thrombosis of cerebral arteries
I634	cerebral infarction due to embolism of cerebral arteries
I635	cerebrl infarct due unspec occlusion or stenos cerebrl arts
I636	cereb infarct due cerebral venous thrombosis, nonpyogenic
I638	other cerebral infarction
I639	cerebral infarction, unspecified

ICD-10 codes for portal venous thrombosis:

Code Variable	Description
I81	Portal vein thrombosis
I810	Portal vein thrombosis
I81x	Portal vein thrombosis

ICD-10 codes for Deep Vein Thrombosis:

Code Variable	Description
I801	Phlebitis and thrombophlebitis of femoral vein
I802	Phlebitis/thrombophlebitis oth deep vessels low extremties

ICD-10 codes for Pulmonary Embolism:

Code Variable	Description
I26	Pulmonary embolism
I260	Pulmonary embolism with mention of acute cor pulmonale
I269	Pulmonary embolism without mention of acute cor pulmonale

ICD-10 codes for Other Venous Thromboembolism:

Code Variable	Description
G08	Intracranial and intraspinal phlebitis and thrombophlebitis
G080	Intracranial and intraspinal phlebitis and thrombophlebitis
G08X	Intracranial and intraspinal phlebitis and thrombophlebitis
I636	Cereb infarct due cerebral venous thrombosis, nonpyogenic

I80	Phlebitis and thrombophlebitis
I800	Phlebitis/thrombophlebitis superfic vessels low extremties
I803	Phlebitis and thrombophlebitis of lower extremities, unspec
I808	Phlebitis and thrombophlebitis of other sites
I809	Phlebitis and thrombophlebitis of unspecified site
I82	Other venous embolism and thrombosis
I820	Budd-Chiari syndrome
I821	Thrombophlebitis migrans
I822	Embolism and thrombosis of vena cava
I823	Embolism and thrombosis of renal vein
I828	Embolism and thrombosis of other specified veins
I829	Embolism and thrombosis of unspecified vein
O222	Superficial thrombophlebitis in pregnancy
O870	Superficial thrombophlebitis in the puerperium
O873	Cerebral venous thrombosis in the puerperium