TITLE PAGE

Division: Worldwide Development
Information Type: Worldwide Epidemiology Study Protocol

Title:	A prospective observational cohort study nested within the Hepatitis C Therapeutic Registry and Research Network (HCV-TARGET) 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, Thrombocytopenia, Cohort study
Author(s):	[redacted]

PASS information

Title	A prospective observational cohort study nested within the Hepatitis C Therapeutic Registry and Research Network (HCV-TARGET) to evalute 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	20-MAR-2014
EU PAS register number	To be registered after PRAC approval
Active substance	Eltrombopag
Medicinal product	Eltrombopag
Product reference	SB-497115-GR
Procedure number	Not applicable
Marketing authorisation holder(s)	GlaxoSmithKline Trading Services Limited 6900 Cork Airport Business Park Kinsdale Road, Cork Country: Ireland Telephone: [redacted]
Joint PASS	No
Research question and objectives	The primary objective of this study is to report the incidence of hepatic decompensation in a real-world setting in patients with chronic hepatitis C virus infection who receive eltrombopag therapy with interferon-based therapy that also includes direct acting anti-viral agents, a group not studied in the Phase III randomized clinical trials. Secondary objectives include reporting the real-world incidence of thromboembolic events and mortality and identifying risk factors for hepatic decompensation, thromboembolic events and mortality in this group of understudied patients. 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 patients treated with interferon-based therapy and direct acting agents, which has not yet been studied. The study will also examine effectiveness of eltrombopag to initiate and maintain HCV therapy and achieve EVR and SVR among patients specifically using direct-acting anti-virals with interferon-based therapy.
Country(-ies) of study	United States and Europe
Author	[redacted]

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]
MAH contact person	[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
GSK	GlaxoSmithKline
HCV	Hepatitis C Virus
HCV-TARGET	Hepatitis C Therapeutic Registry and Research Network
IFN	Interferon
DAA	Direct acting anti-virals
SAE	Serious adverse event
EVR	Early virologic response
SVR	Sustained virologic response
PI	Principal Investigator
RNA	Ribonucleic acid
TCP	Thrombocytopenia

Trademark Information

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PROMACTA / REVOLADE

Trademarks not owned by the GlaxoSmithKline group of companies
SAS

2. RESPONSIBLE PARTIES

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

Contact details and the list of all investigators are kept in a stand-alone document (listed in ANNEX 1) and be available upon request.

WWEpi Project Identifier: WEUSKOP7135

Sponsor Legal Registered Address:

GlaxoSmithKline Research & Development Limited
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Sponsor Contact Address:

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6900 Cork Airport Business Park
Kinsdale Road, Cork
Ireland
Telephone: [redacted]
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E-Mail:

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.

Sponsor Medical Monitor Contact Information: [redacted],MD
[redacted]

Sponsor Serious Adverse Events (SAE) Contact Information: Serious and non-serious adverse events related to eltrombopag use must be faxed to GSK Global Clinical Safety and Pharmacovigilance at [redacted] within 24 hours of becoming aware.

Regulatory Agency Identifying Number(s): Not applicable.

SPONSOR SIGNATORY:

[redacted] PhD
Primary Author/ Project officer

Aug 12, 2014
Date

[redacted] PhD
Therapy Area Leader

Aug 12, 2014
Date

[redacted]

[redacted]

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 Hepatitis C Therapeutic Registry and Research Network (HCV-TARGET) 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) 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 anti-viral agent (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 of interferon-based therapy in these patients.

Eltrombopag (Revolade™/Promacta™) is an oral second generation thrombopoietin receptor agonist which promotes megakaryocyte differentiation and proliferation. Eltrombopag (Promacta) was approved in the U.S. in November 2012 for chronic hepatitis C virus (HCV)-associated thrombocytopenia to allow for the initiation and maintenance of interferon-based therapy. Eltrombopag (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%). The incidence of hepatic decompensation and thromboembolic events has 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 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 in eltrombopag HCV patients undergoing interferon-based anti-HCV treatment with direct acting agents. 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, if approved by the HCV-

TARGET Publication Committee, results will be published in one or more peer-reviewed journal publications.

***Research question and Objective(s).** The primary objective of this study is to report the incidence of hepatic decompensation in patients with chronic hepatitis C virus infection who receive eltrombopag therapy with interferon-based therapy that also includes direct acting anti-viral agents, a group not studied in the Phase III randomized clinical trials. Secondary objectives include reporting the real-world incidence of thromboembolic events and mortality and identifying risk factors for hepatic decompensation, thromboembolic events and mortality in this group of understudied patients. 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 patients treated with interferon-based therapy and direct acting agents, which has not yet been studied. The study will also examine effectiveness of eltrombopag to initiate and maintain HCV therapy and achieve EVR and SVR among patients specifically using direct-acting anti-virals with interferon-based therapy.

***Study Design.** The study is nested within the on-going Hepatitis C Therapeutic Registry and Research Network. The HCV-TARGET study is a carefully maintained longitudinal observational research registry to prospectively enrol and follow HCV patients treated with anti-HCV regimens in a real-world setting in order to rapidly inform strategies for better management of populations underrepresented in clinical trials, identify and remediate gaps in treatment guidelines and adverse event management in order to optimize rates of SVR. It is comprised of patients that receive HCV therapy with direct acting antiviral agents. The planned enrolment is 5000 patients. The GSK study nested with the HCV-TARGET study will comprise all patients treated with eltrombopag. Patients will be followed for up to three years after eltrombopag initiation.

***Population.** All patients treated with eltrombopag who are participants of the HCV-TARGET will be included in the GSK study nested. Most patients will receive direct-acting antivirals as part of their HCV therapy.

***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, and ability to reach early and sustained virologic response. The main exposure variables include treatment with eltrombopag, peginterferon, ribavirin, direct acting anti-viral agents, and other antiviral therapy.

***Data sources**. Within HCV-TARGET, patients are enrolled prospectively at participating sites and treated per local standard of care. Source data is the original medical record. All original clinic notes, telephone notes, safety and efficacy labs collected during the treatment observation period are submitted to a central data repository. Patient data from submitted records is abstracted at the HCV-TARGET clinical coordinating center and entered into the registry database. Where possible, data can be mapped directly from electronic medical records for transfer into the registry database.

***Study size.** Of the 2707 patients enrolled to date into HCV-TARGET with data available on concominant medications, 58 patients received eltrombopag (2.1%). Based on the enrolment rate of 2.1%, it is estimated that 105 eltrombopag patients will comprise the nested HCV-TARGET cohort study. Almost all of these patients will be taking direct acting antivirals.

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

4. AMENDMENTS AND UPDATES

None.

5. MILESTONES

Milestone	Planned date
Start of data collection	TBD, after protocol approval
End of data collection	2018
Interim report 1	March 2016
Registration in the EU PAS register	TBD, after protocol approval
Generate tables for final analysis	March 2018
Final report of study results	2018

6. RATIONALE AND BACKGROUND

6.1. Background

Hepatitis C Virus (HCV) is a leading cause of chronic liver disease worldwide. Treatment consists of combination therapy with peginterferon and ribavirin (double therapy) or interferon, ribavirin and a direct acting anti-viral agent (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 (Promacta) was approved in the U.S. in Novemer 2012 for chronic hepatitis C virus (HCV)-associated thrombocytopenia to allow for the initiation and maintenance of interferon-based therapy. Eltrombopag (Revolade) was approved by the European Commission in September 2013 with indication as follows: *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 allows patients who would otherwise have been poor candidates due to low platelet counts to undergo interferon-based therapy for HCV.

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%) (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 has not been characterized 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 in eltrombopag HCV patients undergoing interferon-based anti-HCV treatment with direct acting agents. 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, if approved by the HCV-TARGET Publication Committee, results will be published in one or more peer-reviewed journal publications.

7. RESEARCH QUESTION AND OBJECTIVE(S)

The primary objective of this study is to report the incidence of hepatic decompensation in patients with chronic hepatitis C virus infection who receive eltrombopag therapy with interferon-based therapy that also includes direct acting anti-viral agents, a group not studied in the Phase III randomized clinical trials. Secondary objectives include reporting the real-world incidence of thromboembolic events and mortality and identifying risk factors for hepatic decompensation, thromboembolic events and mortality in this group of understudied patients. 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 patients treated with interferon-based therapy and direct acting agents, which has not yet been studied. The study will also examine effectiveness of eltrombopag to initiate and maintain HCV therapy and achieve EVR and SVR among patients specifically using direct-acting anti-virals with interferon-based therapy.

Specific Study Aims

Primary: Determine the incidence of hepatic decompensation among patients receiving eltrombopag with interferon-based therapy and direct acting anti-viral agents,

Secondary:

- Determine the incidence of thromboembolic events and mortality among patients receiving eltrombopag with interferon-based therapy and direct acting anti-viral agents
- Explore factors associated with risk of hepatic decompensation and risk of thromboembolic events among patients receiving eltrombopag with interferon-based therapy and direct acting anti-viral agents
- Determine the incidence rate ratio of hepatic decompensation and mortality at 3 years, comparing eltrombopag patients achieving sustained virologic response to eltrombopag patients who did not achieve SVR in the setting of treatment with interferon-based therapy and direct acting anti-viral agents
- Obtain information on treatment effectiveness among patients receiving eltrombopag with interferon-based therapy and direct acting anti-virals with respect to initiating, maintaining and completing HCV therapy, and achieving EVR and SVR

8. RESEARCH METHODS

8.1. Study Design

The HCV-TARGET study is a carefully maintained longitudinal observational research registry to prospectively enrol and follow HCV patients treated with anti-HCV regimens in a real-world setting in order to rapidly inform strategies for better management of populations underrepresented in clinical trials, identify and remediate gaps in treatment

guidelines and adverse event management in order to optimize rates of SVR. It's comprised of patients that receive HCV therapy with direct acting antiviral agents. All adult patients (age 18 or older) who are prescribed HCV treatment with direct acting antiviral agents outside of a clinical trial are eligible for participation, provided they provide written informed consent and are not participating in any other registry or study where HCV treatment outcomes are reported, except where approved or conducted as an adjunct project of the HCV-TARGET registry.

This study is an eltrombopag cohort study nested within HCV-TARGET, comprising all patients treated with eltrombopag. Nesting the eltrombopag cohort study within the HCV-TARGET is an efficient way to identify and study eltrombopag users in a real-world setting. All patients treated with eltrombopag will be included in the nested cohort study. No patients who have not been exposed to eltrombopag will be included in the nested cohort study. Within the nested cohort study, patients will be followed for up to 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 events. The major effectiveness outcomes include ability to initiate anti-viral therapy, ability to maintain anti-viral therapy, early virologic response and sustained virologic response. The incidence of hepatic decompensation and of mortality at three years will be compared between eltrombopag users who achieve SVR and those users who do not achieve SVR. An interim analysis will be conducted in 2016 and the final analysis will be completed in 2018.

8.2. Setting

The Hepatitis C Therapeutic Registry and Research Network is a consortium of more than 103 academic and community investigators enrolling patients treated with i-HCV regimens with direct acting agents. The first patient was enrolled on November 11, 2011. As of January 2014, 2845 patients have been enrolled in 103 U.S. sites. There is one site in Puerto Rico. Germany will be activated for enrollment in mid February 2014 with 2 sites. Discussion is underway to include one center each in the UK, France, Israel, Spain, and Canada. A list of participating sites is available on the website at http://www.hcvtarget.org/index.php/about-us/hcv-target-investigators-and-sites. Centers are both academic (59 sites) and community (44 sites) and primarily are hepatology practices. The visit frequency is defined by local standard of care. Long term follow-up was added in a September 2013 protocol amendment and includes 3-year follow-up on patients that continue to return to the center as part of their local standard of care.

The data in the registry is of published high quality [Fried, 2013]. The Clinical Coordinating Center (CCC) resides at the University of Florida (PI: Nelson) and the Data Coordinating Center (DCC) resides at the University of North Carolina at Chapel Hill (PI: Fried).

HCV-TARGET utilizes a novel, standardized, centralized source data abstraction core to abstract data from de-identified clinical source records provided from participating sites. Demographic, clinical, adverse event, virological, and long-term post treatment follow-

up, including co-morbid conditions, complications related to liver disease, mortality, and AEs, are obtained and subsequently verified by a separate monitoring team housed at the Data Coordinating Centre. Members of the data abstraction team are highly trained and quality control practices, including the development of standardized chart data abstraction conventions pertinent to clinically-based, real-world records have been implemented to ensure data quality, consistency, and error reductions.

For the eltrombopag cohort study nested within HCV-TARGET, users of eltrombopag will be identified and included. The study will be observational and non-interventional.

8.3. Variables

Variables included in this study are summarized below:

8.3.1. Outcomes

The main outcomes of this study are:

- Hepatic decompensation, defined as new onset or worsening of baseline of any of the following:
  - Ascites
  - Hepatic encephalopathy
  - Variceal Bleeding

- Thromboembolic events
  - Myocardial infarction (MI)
  - Ischemic Stroke (IS)
  - Portal vein thrombosis (PVT)
  - Deep vein thrombosis (DVT)
  - Pulmonary embolism (PE)
- Mortality (all cause and cause-specific)

- 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 interferon dose reductions

  - 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 achieve SVR, defined by HCV RNA negative 24 weeks after cessation of treatment

  - Change in platelet counts before and during antiviral therapy among those able to initiate antiviral therapy

8.3.2. Exposure

- The main exposure variable is Treatment with eltrombopag, including dose, duration of treatment, drug discontinuation, In combination with peginterferon, ribavirin, and direct acting antiviral agents (triple therapy)

8.3.3. Other Covariates

Demographics: Age, Sex, Race/ethnicity

Co-morbidities: Diabetes mellitus, cardiovascular or cardiac disease/conditions, lipid disorders, neurological disorders, pulmonary diseases/conditions, substances that contribute to co-morbid conditions (current or historical smoking, alcohol and substance abuse), coagulation disorders, prior/current malignancies including hepatocellular carcinoma, chronic skin disease, including dermatologic extrahepatic manifestation of CHC, HIV or HBV coinfection, other forms of liver disease (i.e. hemochromatosis, NASH), pre-existing complications of liver disease if present or being treated at baseline (ascites, encephalopathy, esophageal varices).

Virology data

History of Cirrhosis: liver biopsy results and/or clinical/histological diagnosis of cirrhosis

Concomitant Medications

8.4. Data sources

In HCV-TARGET, patients are enrolled prospectively at participating sites and treated per local standard of care. HCV-TARGET does not define treatment regimens, dosing, or duration or safety management practices. Source data is the original medical record. All original clinic notes, telephone notes, safety and efficacy labs collected during treatment observation period are submitted to a central data repository. Patient data from submitted records is abstracted at the HCV-TARGET clinical coordinating centre. Where possible, data can be mapped directly from electronic medical records for transfer into the registry database. These data include:

- Baseline factors (HCV viral load, HCV genotype, cirrhosis determination, prior HCV treatment, medical history, co-morbid conditions, IL-28b genotypes)
- HCV treatment regimen and dose adjustments
- Adverse events associated with anti-HCV therapy
- Concomitant medications (baseline and on treatment)
- Long-term post treatment follow-up (co-morbid conditions, complications related to liver disease, and mortality)

The eltrombopag cohort study nested within HCV-TARGET will include all pertinent data from HCV-TARGET.

8.5. Study size

It is estimated that between 1-3% of the 5000 HCV-TARGET patients will receive eltrombopag and be eligible for the nested eltrombopag cohort study, for a sample size between 50 and 150 patients. Almost all of these patients will be taking direct acting antivirals. As of January 2014, approximately 2700 patients have been enrolled into HCV-TARGET; 2.1% of patients have used eltrombopag.

Since this is a descriptive study, 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% (Afdhal, 2014), , 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% (Afdhal, 2014) 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)**

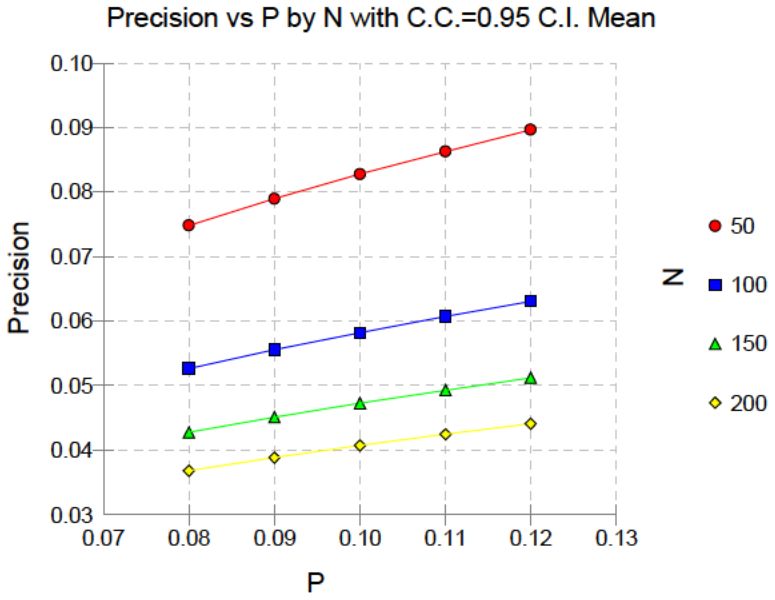
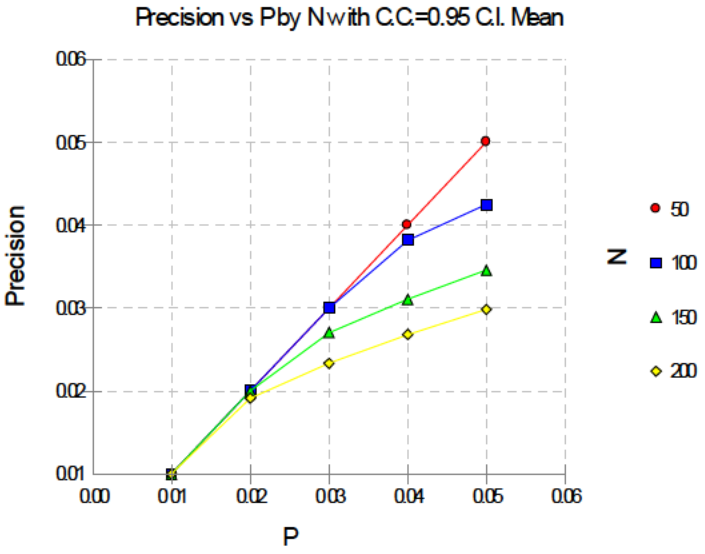


Figure 2 **Precision (y-axis) for event rates (x-axis) ranging from 1%-5% for the outcome of thromboembolic events for 4 potential sample sizes of eltrombopag users**



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 HCV-TARGET patients not using eltrombopag due to insufficiency of the sample size to draw statistical inferences. Based on the enrolment

rate of 2.1%, it is estimated that 105 eltrombopag patients will comprise the nested HCV-TARGET cohort study when all 5000 HCV-TARGET patients have been enrolled.

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 rate of 10% in the eltrombopag treated group and 5% in placebo patients is:

- 19% if there is propensity-score matching of eltrombopag users to non-users on a 1:1 basis
- 30% if matched 1:2
- 36% if matched 1:3
- 39% if matched 1:4
- 42% if matched 1:5
- 44% if matched 1:6.

This assumes that 5 patients of the 105 projected users can not be propensity-scored matched, which is conservative given that eltrombopag users compared to non-users could differ on important factors in addition to eltrombopag use, such as presence of thrombocytopenia, level of thrombocytopenia, MELD score, serum albumin, and site (representing physician preference or medical care standard).

Additionally, the study is not be powered to detect a difference in hepatic decompensation or in mortality comparing patients who achieve SVR to patients who do not achieve SVR. A separate research study is being conducted by GSK to address this question and it will enrol 200 patients (with approximately 150 patients needed for adequate power and 50 additional patients to be included to allow for potential overly liberal rate assumptions and for drop outs).

8.6. Data management

Data is transmitted to the Data Coordinating Center (DCC) at the University of North Carolina via a distributed web-based data entry system that is 21 CFR Part 11 validated and compliant. The DCC in conjunction with the Clinical Coordinating Center (CCC) at the University of Florida have established standardized systems and operational protocols to ensure data quality control.

In order to reduce chart data abstraction errors and inconsistencies and improve data quality, HCV-TARGET utilizes a specially trained Centralized Chart Data Abstraction team at the CCC as the method for chart abstraction. Participating sites provide de-identified copies of clinically available source data on enrolled participants to the CCC. This data includes ALL clinic notes, nursing/staff telephone notes, evaluations and lab results collected to monitor the HCV baseline condition, on-treatment safety and efficacy as well as long term health outcomes. The Centralized Chart Abstraction or respective country Abstraction Core team will abstract and enter the data from those provided participant de-identified medical records. Those records are maintained at the CCC or Abstraction Core to facilitate data monitoring as needed.

DCC personnel in conjunction with the CCC will closely monitor clinical center adherence to study protocol and data collection practices for complete and accurate research data. Monitoring is performed following an established Data Management and Clinical Monitoring Plan to facilitate the smooth conduct of the study. At the time of the on-site visit, DCC personnel will have access to all study and patient documents and to clinical center personnel. All patient and study documents will be kept confidential. Identifiers such as patient name and address can be viewed by the DCC or CCC to facilitate remote monitoring, but these identifiers will not be included on any datasets used for data analyses. For the purposes of Centralized Abstraction, sites will redact all protected health information (PHI) identifiers from records before transmitting to the CCC. In instances where a PHI identifier is present on a record received at the CCC, delegated CCC personnel will redact that information.

The DCC resides in the Biomedical Informatics Core of the UNC- Chapel Hill CTSA-funded TraCS Institute. The database is housed within a secure server environment of the data center on the UNC campus, and is governed by the standard University of School of Medicine information security guidelines.

The REDCap based data management system implemented for the HCV-TARGET registry is being adapted to the specified FDA recommendations, and annual internal audits will be performed to ensure compliance is achieved.

8.6.1. Timings of Assessment during follow-up

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

8.7. Data analysis

The eltrombopag cohort study nested within HCV-TARGET is 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 are treated with direct acting anti-viral agents as part of their interferon-based regimen, a group of patients 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 the study 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. 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 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 SVR by these time points will be presented as Kaplan-Meier estimates, along with median time to attaining SVR.

For the long term outcomes of hepatic decompensation or mortality at 3 years (as separate events), incidence rate ratios comparing eltrombopag 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]. For eltrombopag patients with less than three years of follow-up, survival analyses will be used to take censoring into account. 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 multivariate Cox proportional hazards model along with SVR to determine independence of SVR as a predictor variable.

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 HCV-TARGET registry team commissions qualified resources to conduct monitoring of the data. Clinical site visits and data monitoring will be performed in accordance with the Clinical Monitoring Plan (CMP) Monitors will inspect the operations to ensure that:

- The protocol is followed and implemented in compliance with Good Clinical Practices;
- Accurate and complete records are maintained;
- Staff are trained, certified, and are performing the agreed-upon activities and not delegated to other unspecified staff.

All monitoring activities are completed with a formal, written report. The report will summarize the findings and highlight all recommendations and action items.

Designated CCC and Abstraction Core staff receives detailed protocol, REDCap database and disease specific training as well as gain familiarity with the Study Reference Manual prior to being authorized for access to the HCV-TARGET data management system. The

HCV-TARGET training session(s) must be completed successfully before a CDAS will be considered certified and authorized to abstract data from submitted records. Further to this specific analysis, the abstraction staff will receive specialized training for eltrombopag specific data forms and related data abstraction from the medical records.

The DCC monitors the centrally abstracted chart data from the data provided by all clinical sites through standard reporting and methods. Real-time data integrity instruments are written into the database utilizing skip logic techniques to prevent collection of erroneous interdependent data and maximize the use of pre-defined selection options and calculated values to reduce capture of inaccurate data due to human error. Data elements are pre-coded for statistical analysis as a part of the data collection instrument design and implementation. These coded data are immediately available within the database for reporting and extraction by the Data Manager and Biostatistics faculty and staff.

To help minimize the frequency of errors, the Data Manager will conduct regular conference calls with the Clinical Monitoring and Abstraction Core staff to discuss any consistently observed deficiencies in the use of the data management system. The CRA will maintain regular contact with the CDAS staff and will address identified deficiencies. Also, provision of timely data quality reports will be an important aspect of the Data Management function. In addition to documenting exemplary performance, these reports will provide a basis for setting goals for high-quality data collection, and for tracking progress towards achieving those goals. Data queries will be generated by the Data Manager or CRA in order to identify problems on an on-going basis. Such data checks will include, but are not limited to:

- Frequencies on selected variables by CDAS, to identify differences in the application or interpretation of study protocol or abstraction conventions;
- Tabulations and listings of incomplete or inconsistent responses on data collection forms; tabulations and listings of expected forms not received in a timely manner; and tabulations of clinical center error rates in data entry;
- Analyses of digit preferences for clinical measurements (e.g., blood pressure, weight, height) and other evidence suggesting inadequate or erroneous data entry; and
- The collection of repeated measures for quality control purposes as selectively implemented.

8.9. Strenghts and limitations of the research methods

A strength of this study is that it will report the incidence of hepatic decompensation and other events among eltrombopag-users in the group of HCV patients receiving direct acting anti-viral agents as part of their interferon-based therapy, a group that was not part of the randomized clinical trial program because DAAs were not available at the time of RCT start. Very little information is available for this group of patients. HCV-TARGET is comprised almost entirely of patients receiving DAAs. A second strength is that selection bias will be miminized because all patients in HCV-TARGET who receive

eltrombopag will be included in the nested cohort study. Thirdly, there are multiple centers (over 103) participanting in the study to provide patient diversity. . A fourth stength is that information on outcomes, exposures and covariates are abstracted directly from the medical record, ensuring high detection rates for major events.

A major limitation of the study is the small sample size. Becasue of the small sample size and the low event rates of interest, it is not feasible to implement a study design that successfully uses a control group of non-eltrombopag users upon which to test if rates are higher than expected. For the event of hepatic decompensation, its estimated that power to detect differences comparing eltrombopag users to non-users would be only 19% if propensity score matching is performed on a 1:1 bases and 44% if matching is on a 1:6 basis, based on the projected number of eltrombopag users.

9. PROTECTION OF HUMAN SUBJECTS

9.1. Ethical approval and subject consent

The HCV-TARGET protocol and informed consent documents received approval by the local site IRB prior to initiation of the study at each site. Consent for participation in HCV-TARGET includes permission 1) to submit de-identified historical medical records related to patient demographics, medical/co-morbid condition history, prior HCV therapy and evaluation of liver disease, 2) to submit prospective de-identified medical records related to HCV treatment response, safety, side effects, side effect management and safety/efficacy outcomes of antiviral therapy; 3) for collection of biospecimens including genomic DNA to be archived for future studies (optional); and 4) to be followed for HCV co-morbid conditions and mortality for up to 3 years after treatment outcome is determined.

Written informed consent must be obtained before any data collection and may be given by patients after being prescribed HCV treatment up to 4 weeks after treatment initiation. The method of obtaining and documenting the informed consent and the contents of the consent complies with ICH GCP guidelines and all applicable laws and regulations.

9.2. Subject confidentiality

Study sites and the CCC Chart Data Abstraction team is responsible for the confidentiality of the data associated with participants in HCV-TARGET in the same manner they are responsible for the confidentiality of any patient information within their spheres of responsibility. All forms used for the study data are only identified by coded identifiers to maintain subject confidentiality. All records are kept in locked files at study sites and CCC with access limited to HCV-TARGET study staff. All study staff will identify patients by the patient identifier number generated at the study site. Clinical information will not be released without written permission of the participant, except as necessary for monitoring by the IRB or DCC and centralized abstraction at the CCC. Participants grant permission to share research data with these entities in the consent document. Federal regulations govern the protection of patient's rights relative to data confidentiality and use of research data. Consent procedures and forms, and the

communication, transmission and storage of patient data comply with individual site IRB and federal requirements for compliance with HIPPA.

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 the Americas should be sent to: us.naps@gsk.com or fax 919-483-5404

Cases from Rest of World should be sent to: oax37649@gsk.com or fax +44 208 754 7822

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

The results of this study are to provide data for 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 GSK about long-term safety 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 to coincide with twice-annual cleaning. 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, FDA, and other regulatory agencies. Information will be made available publically through the Clinical Trial Registry, and the intent is to work with the HCV-TARGET Publications committee to submit manuscripts to peer-reviewed journals.

12. REFERENCES

Afdhal N, Dusheiko G, Giannini E, Chen P,Han K, Mohsin A, Rodriguez-Torres M, Rugina S, Bakulin I , Lawitz E, Shiffman M, Tayyab G, Poordad F, Kamel Y, Brainsky A, Geib J, Vasey S, Patwardhan R, Campbell F, Theodore D. Eltrombopag increases platelet numbers in thrombocytopenic patients with HCV infections and cirrhosis, allowing for effective antiviral therapy. Gastroenterology 2014; 146 (2): 442-452.

Dobson AJ, Kuulasmaa K, Eberle E, Scherer J. Confidence intervals for weighted sums of Poisson parameters. Stat Med 1991; 10(3):457-462.

Fried MW, Reddy KR, Di Bisceglie AM, et al. HCV-TARGET: A longitudinal, observational study of North America patients with chronic hepatitis C (HCV) treated with boceprevir or telaprevir. EASL 48th Annual Meeting April 24th - 28th 2013, Amsterdam, the Netherlands. Journal of Hepatology. Volume 58, Supplement 1 , Page S335, April 2013.

Hintze, J. (2006). NCSS, PASS, and GESS. NCSS. Kaysville, Utah. www.nccs.com

Newcombe RG. Two-sided confidence intervals for the single proportion: comparison of seven methods. Stat Med 1998; 17(8):857-872.

Simon R. Confidence intervals for reporting results of clinical trials. Ann Intern Med 1986; 105(3):429-435.

ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

No.	Document Reference No	Date	Title
1.	1.0	TBD	Contact details of responsible parties and all investigtors

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)	☒	☐	☐	11, 15
1.1.2 The objectives of the study?	☒	☐	☐	12, 15
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)	☒	☐	☐	12,15,26
1.2.2 Which formal hypothesis(-es) is (are) to be tested?	☒	☐	☐	23, 24
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?	☒	☐	☐	12, 16, 17
2.2 Is the planned study population defined in terms of:				
2.2.1 Study time period?	☒	☐	☐	12, 16
2.2.2 Age and sex?	☒	☐	☐	12, 16

Section 2: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
2.2.3 Country of origin?	☒	☐	☐	12, 17
2.2.4 Disease/indication?	☒	☐	☐	12, 15
2.2.5 Co-morbidity?	☒	☐	☐	12, 16
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)	☒	☐	☐	12, 13, 16

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?	☒	☐	☐	12, 15, 16
3.2 Is the study design described? (e.g. cohort, case-control, randomised controlled trial, new or alternative design)	☒	☐	☐	12, 16
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)	☒	☐	☐	23
3.4 Is sample size considered?	☒	☐	☐	19-21
3.5 Is statistical power calculated?	☒	☐	☐	21

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)				
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)	☒	☐	☐	19
4.1.3 Covariates?	☒	☐	☐	19
	☒	☐	☐	19
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)				
4.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	18
4.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☒	☐	☐	17
	☒	☐	☐	18, 19
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	☐	☐	☒	

Section 4: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
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)	☐	☐	☒	

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)	☒	☐	☐	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)	☒	☐	☐	17, 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?	☒	☐	☐	17, 18
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:				
7.1.1 Selection biases?	☒	☐	☐	26
7.1.2 Information biases?	☒	☐	☐	26
(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)	☒	☐	☐	18,19,23,24
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?	☒	☐	☐	26

Comments:

Section 8: Analysis plan	**Yes**	**No**	**N/A**	**Page Number(s)**
8.1 Does the plan include measurement of absolute effects?	☒	☐	☐	23, 24
8.2 Is the choice of statistical techniques described?	☒	☐	☐	23, 24
8.3 Are descriptive analyses included?	☒	☐	☐	23, 24
8.4 Are stratified analyses included?	☒	☐	☐	23, 24
8.5 Does the plan describe the methods for identifying: 8.5.1 Confounders? 8.5.2 Effect modifiers?	☒ ☐	☐ ☒	☐ ☐	23, 24
8.6 Does the plan describe how the analysis will address: 8.6.1 Confounding? 8.6.2 Effect modification?	☒ ☐	☐ ☒	☐ ☐	23, 24

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)	☒	☐	☐	22
9.2 Are methods of quality assurance described?	☒	☐	☐	22, 24

Section 9: Quality assurance, feasibility and reporting	**Yes**	**No**	**N/A**	**Page Number(s)**
9.3 Does the protocol describe quality issues related to the data source(s)?	☒	☐	☐	22, 24
9.4 Does the protocol discuss study feasibility? (e.g. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	19
9.5 Does the protocol specify timelines for				
9.5.1 Start of data collection?	☒	☐	☐	14
9.5.2 Any progress report?	☒	☐	☐	14, 23
9.5.3 End of data collection?	☒	☐	☐	14, 23
9.5.4 Reporting? (i.e. interim reports, final study report)	☒	☐	☐	14, 23
9.6 Does the protocol include a section to document future amendments and deviations?	☒	☐	☐	14
9.7 Are communication methods to disseminate results described?	☒	☐	☐	27
9.8 Is there a system in place for independent review of study results?	☒	☐	☐	27

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?	☒	☐	☐	26
10.2 Has any outcome of an ethical review	☒	☐	☐	26

Section 10: Ethical issues	**Yes**	**No**	**N/A**	**Page Number(s)**
procedure been addressed?				
10.3 Have data protection requirements been described?	☒	☐	☐	26, 27

Comments:

Name of main author of study protocol: [redacted], PhD

Date: / /

Signature: _____

ANNEX 3. ADDITIONAL INFORMATION

None