The study listed may include approved and non-approved uses, formulations or treatment regimens. The results reported in any single study may not reflect the overall results obtained on studies of a product. Before prescribing any product mentioned in this Register, healthcare professionals should consult prescribing information for the product approved in their country.

GSK Medicine: Eltrombopag
Study Number: 201109
Title: WEUSKOP7134: PASS HCV Research UK: Prospective observational cohort study to explore the safety and effectiveness of eltrombopag in a real-world setting in adult patients with chronic hepatitis C virus infection who are unable to initiate or maintain optimal interferon-based therapy due to thrombocytopenia nested within the HCV Research UK National Registry
Rationale: Thrombocytopenia (TCP) is a common complication of chronic hepatitis C virus (HCV) infection that can be caused by the disease itself and/or treatment. The presence of thrombocytopenia, and the consequent risk of bleeding complications, may render patients ineligible for interferon-based antiviral treatment. Patients who are treated with interferon may receive a reduced dose or need to discontinue treatment if their platelet count drops even further, which decreases their probability of successful HCV treatment. Discontinuation and nonadherence due to treatment-related adverse events associated with antiviral therapy are of concern as patients who discontinue therapy or have less-than-optimal treatment doses experience decreased sustained virologic response (SVR) rates. Eltrombopag is an second generation oral thrombopoeitin receptor agonist developed by GlaxoSmithKline (GSK) and approved for the treatment of chronic immune (idiopathic) thrombocytopenia (ITP), hepatitis C associated thrombocytopenia, and severe aplastic anemia that has had insufficient response to immunosuppressive therapy. This study represents a proactive pharmacovigilance approach in generating real-world safety data, along with short and long-term effectiveness and other outcomes in the post-approval setting to better inform the use of eltrombopag in HCV patients who are unable to initiate or maintain optimal interferon-based therapy due to TCP.
Study Period: 01-Aug-2014 to 01-Feb-2015
Objectives: The aim 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. 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 early virologic response (EVR) and SVR among eltrombopag users. A subset of these patients will be on direct acting agents as part of their interferon-based therapy.
Indication: Thrombocytopenia in HCV patients who are unable to initiate or maintain optimal interferon-based therapy.
Study Investigators/Centers: HCV Research UK
Research Methods: 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. Because the study “passively” enrols eltrombopag users, there is no aprior information available to know exactly how many users will be participants of the HCV Research UK Registry. The protocol was written to specify that 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.

Data Source: 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.

Study Design: Prospective cohort study of eltrombopag users nested within the HCV Research UK Registry

Study Population: The HCV Research UK National Registry finished its enrolment in December 2014, reaching its enrolment target of 10,000 patients. There were only 6 eltrombopag users in the registry. These six eltrombopag users comprised 1.1% of patients with severe HCV, or 0.7% of patients on triple therapy. At the time of the GSK study design (Apr 2013), GSK estimated that among the 10,000 patients expected to be enrolled into the HCV Research UK National Registry, between 0.5-2.0% of them would receive eltrombopag, resulting in between 50 and 200 patients in the GSK study nested within the HCV Research UK National Registry. The wide range was used to offset lack of knowing:

- how many patients were already enrolled into the National Registry prior to the official beginning of the GSK study in July 2014;
- how many patients were enrolled who had already completed their interferon-based therapy at the time of enrolling; and
- how many patients were enrolled into the Registry who were unable to initiate or maintain optimal interferon-based therapy due to thrombocytopenia

The most important factor in the low number of eltrombopag users in HCV Research UK is the major treatment paradigm shift away from pegylated interferon-ribavirin with or without first generation direct acting agents (telaprevir and boceprevir) toward treatment with new second generation directing acting agents, which have afforded shortened treatment times, fewer adverse reactions, and improved achievement of SVR. Most notably, these benefits could be achieved in some patients with favorable HCV genotypes without the burden of interferon. Both sofosburir and simeprevir were approved prior to the July 2014 approval of the GSK study (January and May, 2014, respectively) and daclatasvir was approved one month after approval of the GSK study. The ledipasvir / sofosbuvir combination was approved in Nov 2014. Moreover, in many instances, physicians treating HCV patients strategically withheld treatment in anticipation of approval of the second generation direct acting agents, where clinically appropriate, in order to gain the advantages in shorter treatment duration and higher SVR afforded by these new medicines. What began as all oral HCV treatment for the minority of patients with favorable HCV genotypes quickly paved the way for interferon-free treatment regimens for the majority of HCV patients. The low number of eltrombopag users reflects the new reality of interferon-free HCV therapy for the vast majority of HCV patients.

GSK proposed to terminate the GSK study nested within the HCV Research UK National Registry because the low number of patients (n=6) available for study would not yield robust findings.

Terminating the study was consistent with the original as well as revised protocols that stated:
"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."

Study Exposures, Outcomes: Had the study continued, the following study exposures and outcomes would have been included:

Exposure - Eltrombopag users with hepatic decompensation - Users of eltrombopag with chronic hepatitis C virus infection who are unable to initiate or maintain optimal interferon-based therapy due to thrombocytopenia and experience hepatic decompensation and thromboembolic events

Primary Outcome - 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.
Time Frame: 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

Secondary Outcomes

Mortality

Time Frame: Kaplan-Meier survival estimates will be calculated for 6 month, 12 month, 18 month, 24 month and 36 month observation periods for all-cause and liver-specific mortality.

Thromboembolic events.

Time Frame: The incidence of thromboembolic events will be described at baseline and at 6 months, 12 months, 18 months, 24 months and 36 months.

Data Analysis Methods:Had the study continued, the following statistical analyses would have been conducted: 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 followup 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 modelswill 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.

Limitations:

As outlined in the protocol - 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.

As observed – Only 6 patients in the HCV Research UK Registry were eltrombopag users at the time the Registry completed it's final enrolment of 10,000 patients.

Study Results:

The HCV Research UK National Registry finished its enrolment in December 2014, reaching its enrolment target of 10,000 patients. There were only 6 eltrombopag users in the registry. This was too few patients to continue with the study. As proposed in the protocol, if too few eltrombopag users were participants of the Registry, the study would terminate.

There are no study results.

Demographics/Baseline Characteristics		Study Group	Comparison Group
Total N		6	0
Age		Not determined. Study did not go past counting number of patients prior to its termination.	Na
Gender		Not determined. Study did not go past counting number of patients prior to its termination.	na
Major risk factors or other key characteristics		Not determined. Study did not go past counting number of patients prior to its termination.	Na
Primary and Secondary Outcome(s)	**Study Group**	**Comparison Group**	**Evaluation of Study Outcome**
	Not determined. Study did not go past counting number of patients prior to its termination.Not determined. Study did not go past counting number of patients prior to its termination. not determined, no data shared with GSK not determined, no data shared with GSK	na	There was no evaluation. Only a count of the number of patients was provided prior to study's termination.

Conclusion:
The study concluded that when the HCV Research UK National Registry finished its enrolment in December 2014, among the enrolled 10,000 patients, only 6 eltrombopag users were participants in the registry. These six eltrombopag users comprised 1.1% of patients with severe HCV, or 0.7% of patients on triple therapy. As per protocol, at the end of the enrolment period when the number of eltrombopag users was deemed too small to go forward (protocol specified decision making criterion of < 50 patients), the study was terminated and no data analysis of these six patients was performed.