POST-AUTHORISATION SAFETY STUDY (PASS)

Final Study Report

Title	A global, prospective cohort study to evaluate the 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
Version	1.0
Date of last version of the final study report	09 June 2017
EU PAS/ENCePP register number	EUPAS7201
Active substance	Eltrombopag
Medicinal product	[redacted]
Product reference	ETB115
Procedure number	Not applicable
Marketing authorization holder(s)	Novartis Europharm Limited
Joint PASS	No
Research question and objectives	The aim of this study was to assess the safety and effectiveness of eltrombopag in routine clinical practice in patients with Hepatitis C virus (HCV) who are unable to initiate, maintain, or restart optimal interferon-based therapy due to thrombocytopenia (TCP). The specific objectives of the study were to: • Assess and compare the incidence of hepatic decompensation and mortality at three years in patients who achieve sustained virologic response (SVR) with patients who do not achieve SVR • Assess the incidence of thromboembolic events (TEEs) among new users of eltrombopag • Assess treatment effectiveness among eltrombopag users with respect to initiating, maintaining and completing antiviral therapy and achieving SVR • Evaluate all-cause and cause-specific mortality risk and survival rates among eltrombopag users at six months, 12 months, 18 months, 24 months and 36 months after starting eltrombopag • Explore the factors independently related to the risk of hepatic decompensation and the risk of TEEs

	Due to changes in standard therapy approaches for HCV and lower than anticipated use of interferon-based antiviral therapy, there were many challenges in patient enrollment for this study. Therefore, the decision was made to terminate the study early, and analyses related to the main outcomes for the study were not conducted. The statistical analysis plan (SAP) was revised to include only objectives and analyses in accordance to a short, closeout clinical study report (CSR).
Country(-ies) of study	[redacted]
Author	[redacted] QuintilesIMS [redacted] QuintilesIMS

This study was conducted in accordance with all relevant regulatory requirements, including, where applicable, the Declaration of Helsinki (and its amendments), the Guideline on Good Pharmacovigilance Practices (GVP) Module VIII – Post-Authorisation Safety Studies, and the Guidelines for Good Pharmacoepidemiology Practice (GPP) (ISPE).

Marketing authorization holder(s)

Marketing authorization holder(s) (MAH)	Novartis Europharm Limited [redacted]

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1. Abstract

Title	A global, prospective cohort study to evaluate the 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
Keywords	hepatitis C virus, thrombocytopenia, eltrombopag
Rationale and background	Patients with hepatitis C virus (HCV) are at risk for thrombocytopenia (TCP) as a result of their disease and/or treatment. The presence of TCP, 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, decreasing their probability of successful HCV treatment. This is of concern, as patients who discontinue antiviral therapy or who have less-than-optimal treatment doses experience decreased sustained virologic response (SVR) rates (Borroni et al. 2008, McHutchison et al. 2002). [redacted] (eltrombopag) is a second generation oral thrombopoietin receptor agonist approved for the treatment of immune (idiopathic) thrombocytopenia (ITP) and HCV-associated TCP. In the Phase 3 trials, eltrombopag treatment was associated with improved SVR over placebo in subjects taking interferon-based therapy for HCV. However, eltrombopag-treated patients were more likely to experience hepatic decompensation events and thromboembolic events (TEEs). This study was conducted to assess short and long-term effectiveness and safety outcomes in the post-approval setting to better inform the use of eltrombopag in HCV patients who were unable to initiate, maintain, or restart optimal interferon-based therapy due to TCP. The study was terminated early based on consultation with the European Medicines Agency (EMA) EMEA/H/C/001110/II/0036/G (decision received on 13 October 2016) due to changes in treatment paradigm for HCV resulting in unanticipated difficulties in patient enrollment.
Research question and objectives	The aim of this study was to assess the safety and effectiveness of eltrombopag in routine clinical practice in patients with HCV who were unable to initiate, maintain, or restart optimal interferon-based therapy due to TCP. The planned primary objective of this study was to: • Assess and compare the incidence of hepatic decompensation and mortality at three years in patients using eltrombopag who achieved SVR to patients using eltrombopag who did not achieve SVR. Planned secondary objectives of the study included: • Assess the incidence of TEEs among new users of eltrombopag; • Assess treatment effectiveness among eltrombopag users with respect to initiating, maintaining and completing antiviral therapy and achieving SVR; • Evaluate all-cause and cause-specific mortality risk and survival rates among eltrombopag users at 6 months, 12 months, 18 months, 24 months and 36 months after starting eltrombopag; and • Explore the factors independently related to the risk of hepatic decompensation and the risk of TEEs among eltrombopag users. The statistical analysis plan (SAP) was revised to include only objectives and analyses in accordance to a short, closeout clinical study report (CSR).
Study design	This study was planned as a global, multi-center, prospective, observational study and conducted to evaluate clinical outcomes and treatment patterns in HCV patients treated with eltrombopag. Country selection depended on the regulatory approval and

	reimbursement status of eltrombopag for the HCV-associated TCP indication, but was expected to include several countries in [redacted] Patients were planned to be followed for a period of three years after initiating eltrombopag. Patients were assessed regularly during interferon-based therapy and then approximately every six months thereafter according to local standard practice. Patients who permanently discontinued eltrombopag were planned to be followed for clinical outcomes and survival, according to the protocol schedule, for up to 36 months post-enrollment. Due to early study termination, follow-up durations ranged from 7 to 17 months. All data were provided by the investigator via an electronic case report form (eCRF). Any assessments were intended to be performed at the time of a routine clinical encounter or by referencing the medical record. No clinic visits were required in order to participate in the study.
Setting	The study was designed to enroll patients from at least 40 sites over the course of an enrollment period of at least 18 months. Eligible patients were to be enrolled by gastroenterologists, hepatologists, and other physicians and health care providers experienced in the management of patients with HCV, consistent with local treatment practices. Due to the reasons for and execution of the early study termination, patients were enrolled from two sites [redacted]
Subjects and study size	Inclusion criteria: The following criteria must have been met in order to be enrolled in the study: • Age ≥ 18 years at enrolment • Diagnosis of HCV verified by the presence of detectable HCV ribonucleic acid (RNA) • Initiation of first-time treatment with eltrombopag no more than 3 months prior to study enrolment • Patient was unable to initiate, maintain, or restart optimal interferon-based therapy due to TCP prior to initiating eltrombopag • Patient currently undergoing interferon-based antiviral therapy or initiation or restart of interferon-based antiviral therapy planned • Patient (or appropriate representative) willing and able to provide written informed consent. Exclusion criteria: Patients meeting ANY of the following criteria were not eligible for participation: • Current participation in any interventional clinical trials in which treatment regimen and/or monitoring is dictated by a protocol. The target sample size for this study was 200 patients to account for the potential variance in the percentage of patients achieving SVR or experiencing hepatic decompensation, and to account for the potential of patients being lost to follow-up. Only nine patients from two sites in two countries were enrolled due to difficulties in patient recruitment.
Variables and data sources	The main planned safety outcome of this study was as follows: • Hepatic decompensation defined by the presence of one or more of the following events: o Ascites o Hepatic encephalopathy o Variceal hemorrhage o Spontaneous bacterial peritonitis

	This outcome was collected through eCRFs. Due to early study termination, the analysis corresponding to this outcome was not assessed.
	
	Other planned study outcomes included the following:
	• TEEs, which include:
	  o Acute myocardial infarction
	  o Ischemic stroke
	  o Portal vein thrombosis
	  o Deep vein thrombosis
	  o Pulmonary embolism
	  o Acute coronary syndrome
	  o Other arterial TEEs
	  o Other venous TEEs
	• Non-serious and serious adverse drug reactions (ADRs/SADRs)
	These study outcomes were collected through the eCRFs. However, due to early study termination, only analyses corresponding to the requirements for the short, closeout CSR were conducted.
	
	Analyses to determine the following outcomes were planned to be conducted:
	• All-cause and cause-specific mortality risk and survival rates among eltrombopag users at 6 months, 12 months, 18 months, 24 months and 36 months after starting eltrombopag
	• Treatment effectiveness was planned to be assessed based upon:
	  o Ability to initiate (or restart) interferon-based antiviral therapy
	  o Ability to maintain planned interferon-based antiviral therapy
	  o Achievement of SVR defined by HCV RNA negative 24 weeks after cessation of antiviral treatment
	  o Achievement of early virologic response (EVR) and SVR
	Analyses corresponding to all-cause and cause-specific mortality risk, survival rates, and most of the treatment effectiveness components were not conducted due to early study termination. Data collected through the eCRF regarding interferon-based antiviral therapy, including type of therapy, dose, and duration of therapy, as well as achievement of SVR defined by HCV RNA negative 24 weeks after cessation of antiviral treatment are included in the study analyses.
	
	Variables collected at enrollment included patient demographics, HCV genotype, HCV treatment history, other relevant medical history, Child Pugh score, Model for End-Stage Liver Disease (MELD) score, liver status, TCP history, eltrombopag exposure, concomitant medications, and recent laboratory values, including platelet count. Additional variables collected during follow-up included updated eltrombopag exposure, antiviral treatment, concomitant medications, and laboratory values (if performed as part of routine care).

Results	The mean age among study patients was 46 years (range: 29 to 62 years). Eight of the nine patients were male. [redacted]. All patients had a history of TCP at study enrollment, and no patient reported a TEE occurrence in the last six months prior to enrollment. Eight of nine patients maintained a 12.5 mg daily dose of eltrombopag during the study, while [redacted] All nine patients permanently discontinued eltrombopag during the study, and seven patients did so within 40 days of eltrombopag initiation. Reasons for stopping eltrombopag were mostly due to an achieved increased platelet count (n=7) or due to the completion of antiviral treatment (n=2).

	HCV antiviral treatment administered to the patients included the following: double therapy (interferon and ribavirin), n=7, and triple therapy (interferon, ribavirin, and direct-acting antiviral agent [DAA]), n=2. Two patients had dose changes in their antiviral treatments during the study. [redacted] Eight patients completed their antiviral treatments during the study while one patient reported ongoing antiviral treatment. Three patients achieved SVR between 204 to 280 days after initiating eltrombopag, and one patient did not achieve SVR. In four patients, SVR was not achievable due to the study ending less than 24 weeks after cessation of the treatment. SVR status was unknown for one patient. Among the nine study patients, three patients (33.3%) reported adverse events (AEs) which were all under the system organ class (SOC) blood and lymphatic system disorders. [redacted]. No patients were withdrawn from the study due to an AE, and there were no serious adverse events (SAEs) including deaths. No patients reported an ADR or SADR related to eltrombopag. [redacted]
Discussion	The results of this study are limited in providing a comprehensive picture of safety outcomes for HCV patients treated with antivirals and eltrombopag in the post-approval setting. Due to early study termination, the main objectives of the study, i.e., to assess the incidence of hepatic decompensation, TEEs, and mortality at three years and associated risk factors, were not assessed. Although there is some evidence to show that eltrombopag use may have enabled treatment with interferon-based antiviral therapy for study patients, results should be interpreted with caution due to the small sample size and lack of comprehensive effectiveness and safety data.
Marketing authorization holder (MAH)	Novartis Europharm Limited [redacted]

2. List of abbreviations

ADR	Adverse drug reaction
AE	Adverse event
BMI	Body mass index
CRF	Case report form
CSR	Clinical study report
DAA	Direct-acting antiviral agent
eCRF	Electronic case report form
EDC	Electronic data capture
EMA	European Medicines Agency
ENABLE	Eltrombopag to INitiate and Maintain Interferon Antiviral Treatment to Benefit Subjects with Hepatitis C related Liver DiseasE
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
EVR	Early virologic response
FPFV	First patient first visit
GPP	Good Pharmacoepidemiology Practice
GSK	GlaxoSmithKline
GVP	Good Pharmacovigilance Practices
HCV	Hepatitis C virus
Hgb	Hemoglobin
ICF	Informed consent form
IEC	Independent ethics committee
INR	International normalized ratio
IRB	Institutional review board
ISPE	International Society for Pharmacoepidemiology
ITP	Immune (idiopathic) thrombocytopenia
LPFV	Last patient first visit
LPLV	Last patient last visit
MAH	Marketing authorization holder
MedDRA	Medical Dictionary for Regulatory Activities
MELD	Model for End-Stage Liver Disease
PAS	Post-authorisation study
PASS	Post-authorisation safety study
PT	Preferred term
Q1	25th quartile
Q3	75th quartile
RNA	Ribonucleic acid
SADR	Serious adverse drug reaction
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SOC	System organ class

SVR	Sustained virologic response
TCP	Thrombocytopenia
TEE	Thromboembolic event
U.S.	United States

3. Investigators

[redacted] enrolled patients into the study. Contact details are provided in Section 14, Appendix 4.

4. Other responsible parties

This study was performed by QuintilesIMS, a contract research organization, with guidance, input, review, and approval of GlaxoSmithKline (GSK) Trading Services Limited and Novartis Europharm Limited, including development of materials, recruitment, training and management of sites, electronic data capture (EDC) and data management and analysis.

The Marketing Authorization was transferred from GSK Trading Services Limited to Novartis Europharm Limited on 06 May 2015, while the study was being conducted.

5. Milestones

Table 1 Study Milestones

Milestone	Planned date	Actual date	Comments
Date of first IEC/IRB approval	N/A	22 December 2014	N/A
Date of last IEC/IRB approval	N/A	25 January 2016	N/A
Start of data collection	November 2014	18 June 2015	N/A
End of data collection	April 2019	30 December 2016	N/A
Registration in the EU PAS register	N/A	06 August 2014	N/A
Study progress reports	Annually following first patient enrolled	N/A	Not developed due to early study termination.
Interim report 1	December 2016	N/A	Not developed due to early study termination.
Interim report 2	June 2017	N/A	Not developed due to early study termination.
Interim report 3	December 2017	N/A	Not developed due to early study termination.
Final report of study results	November 2019	09 June 2017	N/A

EU = European Union; PAS = post-authorisation study; IEC = independent ethics committee; IRB = institutional review board; N/A = not applicable

6. Rationale and background

6.1 Background

This is the final study report for the post-authorisation safety study (PASS) "A global, prospective cohort study to evaluate the 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", as specified in Art 36 to 38 and Art 40 of the Commission Implementing Regulation (European Union [EU]) No 520/2012.

Thrombocytopenia (TCP) is a common complication of chronic hepatitis C virus (HCV) infection resulting from the disease itself and/or treatment. Data regarding the prevalence of TCP in HCV patients in the current literature is very limited and variable. A review of the literature revealed a prevalence of TCP ranging broadly from 0.2% to 45% in HCV patients, with more than half of the studies reporting a TCP prevalence of at least 24% (Louie et al. 2011). The presence of TCP 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, decreasing their probability of successful HCV treatment. In a cohort study by Roomer et al., 42% of the 321 patients treated with peginterferon alfa and ribavirin experienced a drop in platelet count during treatment; 30 patients (9.3%) had platelet counts below 50×10^9/L, and 2 patients (0.6%) had a platelet count below 20×10^9/L (Roomer et al. 2010).

Many of the treatment-related adverse events (AEs) associated with peginterferon and ribavirin combination therapy have been well-established in clinical trials and in the post-marketing setting. Interferon therapy, and in particular peginterferons are known to cause a substantial drop in platelet count associated with their bone marrow suppressing effects. Discontinuation and non-adherence due to treatment-related AEs associated with antiviral therapy are of concern as, not unexpectedly, patients who discontinue therapy or who have less-than-optimal treatment doses experience unfavorable sustained virologic response (SVR) rates (Borroni et al. 2008, McHutchison et al. 2002). Achievement of SVR is associated with a 99% chance of being HCV ribonucleic acid (RNA) negative during long-term follow-up (Swain et al. 2010), and has been associated with decreases in all-cause mortality, liver-related deaths, the need for liver transplantation, hepatocellular carcinoma rates, and liver-related complications (Backus et al. 2011, Veldt et al. 2007).

6.2 Rationale

[redacted] (eltrombopag) is a second generation oral thrombopoietin receptor agonist developed by GSK and approved for the treatment of chronic immune (idiopathic)

thrombocytopenia (ITP) and HCV-associated TCP in [redacted] in [redacted] and in [redacted] in [redacted] to allow for the initiation and maintenance of interferon-based therapy. It is intended to raise platelet counts to a level sufficient to reduce the risk of bleeding (i.e., $\geq 50 \times 10^9$/L), but is not intended to completely normalize the platelet count.

Two randomized, double-blind, placebo-controlled Phase 3 trials evaluated the efficacy and safety of eltrombopag for the treatment of TCP in 1521 adult HCV patients with platelet counts of less than 75×10^9/L with the primary endpoint defined as achieving SVR (Afdhal et al. 2014). The ENABLE 1 (Eltrombopag to INitiate and Maintain Interferon Antiviral Treatment to Benefit Subjects with Hepatitis C related Liver DiseasE) trial utilized peginterferon alfa-2a ([redacted]) plus ribavirin for antiviral treatment, and ENABLE 2 utilized peginterferon alfa-2b ([redacted]) plus ribavirin. The majority of patients (95% in ENABLE 1 and 97% in ENABLE 2) achieved platelet count increases to $\geq 90 \times 10^9$/L within four weeks of initiating eltrombopag. In ENABLE 1, more subjects treated with eltrombopag (compared with placebo) achieved an early virologic response (EVR) (66% vs. 50%, $p < 0.0001$) and SVR (23% vs. 14%, $p = 0.0064$) (Afdhal et al. 2014). Similar efficacious results were found for the eltrombopag-treated group over placebo in the ENABLE 2 trial (Afdhal et al. 2014).

There is some evidence from the ENABLE studies that treatment with eltrombopag may lead to higher occurrence of certain events over treatment with placebo. Hepatic decompensation (in particular, ascites and hepatic encephalopathy) was more common in the eltrombopag arm compared to the placebo arm in the ENABLE studies (Afdhal et al. 2014). In addition, there was an increased incidence of thromboembolic events (TEEs) (e.g., portal vein thrombosis and deep vein thrombosis) observed in the eltrombopag arm versus the placebo arm (Afdhal et al. 2014).

The safety and efficacy of eltrombopag use in HCV patients with TCP has not been evaluated in combination with protease inhibitors (boceprevir- or telaprevir-containing regimens), commonly used to treat HCV. Similarly, it has not been determined in a real-world setting whether the ability to achieve SVR confers long-term benefit in advanced HCV patients with significant TCP, who have been treated with eltrombopag in combination with interferon-based therapy. In order to better evaluate the use of eltrombopag in HCV patients who were unable to initiate, maintain, or restart optimal interferon-based therapy due to TCP, this study was conducted to generate safety data along with short and long-term effectiveness in the post-approval setting.

7. Research questions and objectives

The aim of this study was to assess the safety and effectiveness of eltrombopag in routine clinical practice in patients with HCV who were unable to initiate, maintain, or restart optimal interferon-based therapy due to TCP.

The primary objective of this study was to:

- Assess and compare the incidence of hepatic decompensation and mortality at three years in patients using eltrombopag who achieve SVR to patients using eltrombopag who do not achieve SVR.

Due to early study termination (see Section 8 for details), this report does not include analyses to address the primary objective.

Secondary objectives of the study included the following:

- Assess the incidence of TEEs among new users of eltrombopag;
- Assess treatment effectiveness among eltrombopag users with respect to initiating, maintaining and completing antiviral therapy and achieving SVR;
- Evaluate all-cause and cause-specific mortality risk and survival rates among eltrombopag users at 6 months, 12 months, 18 months, 24 months, and 36 months after staring eltrombopag; and
- Explore the factors independently related to the risk of hepatic decompensation and the risk of TEEs among eltrombopag users.

Due to changes in standard therapy approaches for HCV and lower than anticipated use of interferon-based antiviral therapy, there were many challenges in patient enrollment for this study. Therefore, the decision was made to terminate the study early, and analyses related to the main outcomes for the study were not conducted. The statistical analysis plan (SAP) was revised to include only objectives and analyses in accordance to a short, closeout clinical study report (CSR).

8. Amendments and updates

The Marketing Authorization was transferred from GSK Trading Services Limited to Novartis Europharm Limited on 06 May 2015, while the study was being conducted.

Novartis decided to terminate the study based on consultation with the European Medicines Agency (EMA) EMEA/H/C/001110/II/0036/G (decision received on 13 October 2016) due to changes in treatment paradigm for HCV resulting in unanticipated difficulties in patient enrollment.

The challenge in enrolling patients into this study was a consequence of the new availability of second generation direct-acting antiviral agent (DAA) therapies for HCV, which are largely interferon-sparing. Although the protocol for this study was initially submitted to the EMA Pharmacovigilance Risk Assessment Committee in October 2013, it was not approved until

July 2014. In the interim, two DAAs were approved (January and May 2014). An additional DAA was approved in August 2014, and a combination DAA therapy was approved in November 2014. These DAAs became the new standard of care, which in turn, heavily impacted country and site selection, and enrollment of patients into this study. Despite the continuous efforts from both GSK/Novartis and QuintilesIMS to identify suitable countries and sites that were treating HCV patients with interferon-based therapies, the number of physicians/sites needed to obtain the targeted number of patients into the study within the agreed timelines were not reached.

Due to the early study termination, the SAP was revised and finalized on 31 March 2017 to include the analyses corresponding to the requirements for a short, closeout CSR. As such, the analyses described in Section 8.7.1 of the study protocol were not performed. Analyses involving patient disposition, demographics, treatment exposure, and AEs were retained for this CSR. However, all available patient data were listed.

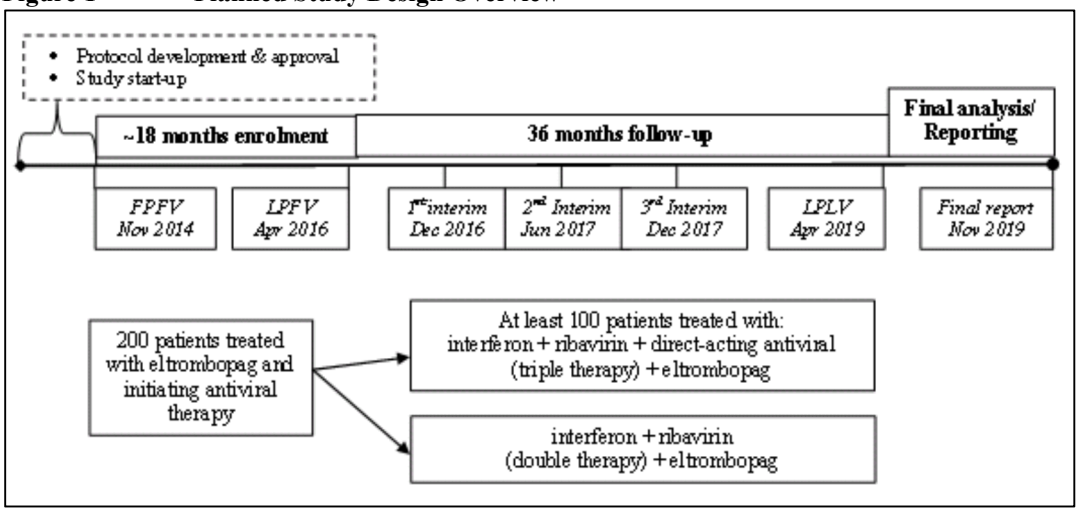
9. Research methods

9.1 Study design

This study was planned as a global, multi-center, prospective, observational study and conducted to evaluate clinical outcomes and treatment patterns in HCV patients newly initiating eltrombopag.

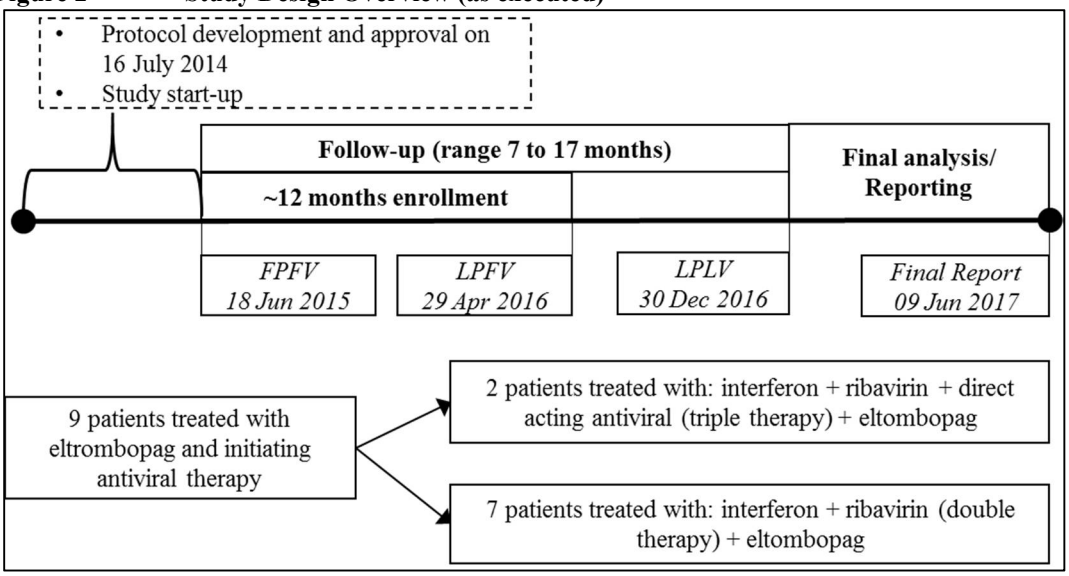
The study was designed to enroll approximately 200 patients, with a minimum of 100 patients who were treated with boceprevir, telaprevir, or newer DAAs that consisted of a backbone of interferon-based therapy, in at least 40 sites over the course of an enrollment period of at least 18 months (Figure 1). Patients were to be followed for a period of 36 months after initiating eltrombopag, though due to early study termination, follow-up duration for patients ranged from seven to 17 months (Figure 2).

Figure 1 Planned Study Design Overview



FPFV = first patient first visit; LPFV = last patient first visit; LPLV = last patient last visit
Source: Section 14, Appendix 1 (protocol version 2.0)

Figure 2 Study Design Overview (as executed)



FPFV = first patient first visit; LPFV = last patient first visit; LPLV = last patient last visit
Source: Annex 2, Listing 1 and 11

There were no protocol–mandated visits or procedures associated with the study. Assessments were conducted at the enrollment visit and every clinic visit thereafter. Due to the severity of their disease, it was expected patients were assessed regularly during interferon-based therapy and then approximately every six months thereafter, per usual care. Data were to be captured from all clinic visits regularly during antiviral therapy and every six months after completing or after discontinuing antiviral treatment.

All patients who discontinued eltrombopag were followed for clinical outcomes and survival for the remainder of the study period. Additional exposure to eltrombopag was to be captured if the

patient went on to receive additional antiviral therapy and eltrombopag during follow-up on study.

First-time new users of eltrombopag were enrolled in this study. A first-time new user was defined as any patient who met inclusion and exclusion criteria who was treated with eltrombopag for ≤3 months at the time of study enrollment. Patients with prior exposure to eltrombopag for any duration more than three months prior to study enrollment were excluded. Patients currently on, or newly initiating eltrombopag, were followed for the events of hepatic decompensation and TEEs, and for treatment effectiveness (i.e., the ability to initiate and maintain antiviral therapy and to achieve SVR).

Due to early study termination, analyses on mortality and clinical outcomes other than SVR status and AEs were not included for this CSR.

9.2 Setting

The study was designed to enroll patients in at least 40 sites over the course of an enrollment period of at least 18 months. Country selection depended on the regulatory approval and reimbursement status of eltrombopag for the HCV-associated TCP indication, but was expected to include several countries in [redacted]. Eligible patients were to be enrolled by gastroenterologists, hepatologists, and other physicians and health care providers experienced in the management of patients with HCV, consistent with local treatment practices.

Site selection criteria included projected availability of eligible patients for at least a 12-month period and the availability of physician (and other site staff) time to complete the limited, but necessary case report forms (CRFs). Selection criteria and basic site information (e.g., site size, site type) were collected via a site qualification survey. Sites were required to maintain a patient enrollment log of eligible patients at their treatment center. This log was intended to document how patients came to be included or excluded from the study, in order to assess the representativeness of the study population. Due to the reasons for and execution of the early study termination, nine patients from two sites, one in [redacted] and the others in [redacted], were enrolled. Enrollment started on 18 June 2015 and ended on 29 April 2016. Site investigators from the [redacted] site specialized in infectious disease and investigators in [redacted] site specialized in internal medicine.

9.3 Subjects

Inclusion Criteria

The following criteria must have been met in order to be enrolled in the study:

- Age ≥ 18 years at enrolment
- Diagnosis of HCV verified by the presence of detectable HCV RNA
- Initiation of first-time treatment with eltrombopag no more than three months prior to study enrolment
- Patient was unable to initiate, maintain, or restart optimal interferon-based therapy due to TCP prior to initiating eltrombopag
- Patient currently undergoing interferon-based antiviral therapy or initiation or restart of interferon-based antiviral therapy planned
- Patient (or appropriate representative) willing and able to provide written informed consent

Exclusion Criteria

Patients meeting ANY of the following criteria are not eligible for participation:

- Current participation in any interventional clinical trials in which treatment regimen and/or monitoring is dictated by a protocol

Eligible patients were enrolled in the study at the time of presentation for a routine clinic visit. No clinic visits were required as part of participation in this study. All follow-up assessments were intended to be performed at the time of a routine clinical encounter or by referencing the medical record. All patients presenting during the enrollment period were assessed for eligibility according to the defined selection criteria and all eligible patients were consecutively enrolled in the study.

Patients may have withdrawn consent and discontinued participation in the study at any time. If a patient was withdrawn prior to completing the study follow-up period, any known reason for withdrawal was to be documented in the database. All information already collected as part of the study was retained for analysis; however, no further efforts were made to obtain or record additional information regarding the patient.

9.4 Variables

9.4.1 Exposure definition and measures

This was an observational registry of real-world treatment practices in this patient population. Although initiating eltrombopag was an inclusion criterion for study participation, the protocol did not recommend the use of any specific treatments. No study medication was provided as part of participation in the study.

First-time new exposure to eltrombopag was defined as patients newly treated with eltrombopag within the past three months prior to study enrollment. This allowed for data capture of all relevant baseline variables and ensured an accurate account of the outcomes associated with use for both safety and effectiveness. If, during the study, an enrolled patient discontinued eltrombopag due to ineffectiveness of antiviral therapy and subsequently received different antiviral therapy and concomitant eltrombopag, treatment safety and effectiveness measures on the subsequent use of eltrombopag were also to be captured. Additionally, if, during the study, an enrolled patient discontinued eltrombopag due to an AE, and then subsequently received eltrombopag at a later time during the study period, this subsequent use of eltrombopag was also to be captured.

Treatment with eltrombopag was characterized as either in combination with an interferon and ribavirin (double therapy) or in combination with an interferon, ribavirin, and commercially-available DAAs (triple therapy). Where applicable, exposure was classified as current (i.e., ongoing or within 30 days of eltrombopag discontinuation at the time of the event of interest) or past (i.e., greater than 30 days since eltrombopag discontinuation).

For both eltrombopag and antiviral treatment, information on dose, duration and discontinuation was collected.

For the purposes of this study, exposure to eltrombopag was defined as time on drug plus 30 days post-discontinuation. TEEs, hepatic decompensation, and other AEs recorded during the exposure window were assessed for attribution to the drug. Explicit attribution of these events to eltrombopag triggered additional AE reporting to the Central Safety Department at GSK/Novartis.

As a long-term, observational study to evaluate treatment patterns and outcomes in patients treated in the post-marketing setting, no restrictions on concomitant treatments were associated with the study. All concomitant treatments were recorded in order to evaluate their potential influence on eltrombopag.

9.4.2 Outcome definition and measures

The planned main safety outcome of this study was the following:

- Hepatic decompensation defined by the presence of any of the following, as reported by the investigator:
    - Ascites
    - Hepatic encephalopathy
    - Variceal hemorrhage
    - Spontaneous bacterial peritonitis

The main safety outcome listed above was collected through the electronic case report form (eCRF), but due to early study termination, the analysis corresponding to this outcome was not conducted.

Other planned study outcomes included the following:

- TEEs, as reported by the investigator, included the following:
    - Acute myocardial infarction
    - Acute coronary syndrome
    - Ischemic stroke
    - Portal vein thrombosis
    - Deep vein thrombosis
    - Pulmonary embolism
    - Other arterial TEEs
    - Other venous TEEs
- Non-serious and serious adverse drug reactions (ADRs/SADRs)

These study outcomes were collected through the eCRF. However, due to early study termination, only analyses corresponding to the requirements for the short, closeout CSR were conducted.

Analyses to determine the following outcomes were planned to be conducted:

- All-cause and cause-specific mortality risk and survival rates among eltrombopag users at 6 months, 12 months, 18 months, 24 months and 36 months after starting eltrombopag
- Treatment effectiveness based on the following:
    - Ability to initiate (or re-start) interferon-based antiviral therapy, defined as the proportion of enrolled patients who received at least one dose of interferon therapy

- Ability to maintain planned interferon-based antiviral therapy, defined as the proportion of patients with no interferon dose reductions or early discontinuations related to TCP
- Achievement of SVR defined by HCV RNA negative 24 weeks after cessation of antiviral treatment
- Achievement of EVR defined as clinically significant reduction in HCV RNA ($\geq$2 $\log_{10}$ drop or undetectable) after 12 weeks of antiviral treatment

Analyses corresponding to all-cause and cause-specific mortality risk, survival rates, and most of the treatment effectiveness components were not conducted due to early study termination. Data collected through the eCRF regarding interferon-based antiviral therapy, including type of therapy, dose, and duration of therapy, as well as achievement of SVR defined by HCV RNA negative 24 weeks after cessation of antiviral treatment and incidence of AEs are included in the study analyses.

9.4.3 Other study variables

Additional variables collected at enrollment included patient demographics, HCV genotype, HCV treatment history, other relevant medical history, Child Pugh score, Model for End-Stage Liver Disease (MELD) score, liver status, TCP history, eltrombopag exposure, concomitant medications, and recent laboratory values, including platelet count.

Additional variables collected during follow-up included updated eltrombopag exposure, antiviral treatment, concomitant medications, and laboratory values (if performed as part of routine care).

9.5 Data sources and measurement

The schedule of data collection to be performed for the study is presented in Table 2 provided below. All data elements were collected from information routinely recorded in the medical records, or were prospectively recorded by the investigator for the purposes of the study. No visits or examinations, laboratory tests, or procedures were mandated as part of this study.

In addition, where allowed by local regulation and by approved informed consent, patients were asked to allow direct-to-patient contact and provide secondary contacts in order to collect limited information regarding the patient's status and minimize the potential for loss to follow-up.

Table 2 Schedule of Data Collection

	Enrollment	Follow-up every 3-6 months	End of follow-up 36 months (or early discontinuation[1])
		±4 weeks	±4 weeks
Informed consent	X		
Demography	X		
Medical history, including HCV history and previous antiviral exposure	X		
Laboratory test results (if performed)	X	X	X
Eltrombopag exposure	X	X	X
Antiviral exposure		X	X
Antiviral response		X	X
Concomitant medications	X	X	X
Outcome assessment/Specific endpoints		X	X
ADR/SADR reporting[2]	First exposure to eltrombopag ----------> X		
Reason for discontinuation (if applicable)			X

ADR: adverse drug reaction; HCV: Hepatitis C virus; SADR: serious adverse drug reaction

[1] Due to early study termination, the longest follow-up for a patient was 16.6 months.

[2] Note: At enrollment, medical records were used to assess the occurrence of ADRs/SADRs after starting eltrombopag but prior to informed consent and study enrollment.

Enrollment

The following data were collected at enrollment for all enrolled patients:

- Demographics: age, sex, race/ethnicity (where allowed by local regulations)
- Patient weight
- Relevant medical history (e.g., spleen status, cardiovascular disease, history of TEEs, diabetes mellitus, malignancies)
- HCV risk/clinical factors: probable infection route, estimated year of infection (if available), date of first positive HCV test, HCV RNA status, and HCV genotype
- IL28B polymorphism, alcohol use, smoking history, injection drug use
- Previous and current antiviral treatment (if applicable)
- Liver status
    - Clinical/histological diagnosis of cirrhosis/fibrosis
    - Child Pugh score
    - MELD score
    - Presence of steatosis, non-alcoholic steatohepatitis, or non-alcoholic fatty liver disease
- TCP history

- Eltrombopag exposure, including any dose changes
- Concomitant therapies, including:
    - Treatment with an erythropoiesis-stimulating agent (e.g., erythropoietin, darbepoetin)
    - Treatment with a granulocyte colony stimulating factor
    - Other relevant concomitant medications
- Laboratory values (if assessed as part of routine clinical practice)

Follow-up

The following data were collected for all enrolled patients at each follow-up time point:

- Patient vital status
- Updated eltrombopag exposure, including any changes
- Antiviral treatments
    - Prescribed doses and regimens
    - Planned duration of antiviral treatment
    - Antiviral exposure/duration of treatment, including any dose changes or discontinuations
    - Antiviral response (EVR, End of Treatment response, SVR)
- Reason for early discontinuation of the antiviral therapy (if applicable)
- Updated concomitant therapies
- Laboratory results, if performed as part of routine clinical practice
- Occurrence of protocol-defined hepatic decompensation and TEEs
- ADRs and SADRs related to eltrombopag use

Discontinuation

The following data were collected for all enrolled patients at the time of discontinuation:

- Date of discontinuation
- Reason for discontinuation

If discontinuation was due to patient death, date and cause(s) of death were collected.

9.6 Bias

There are some limitations associated with observational study designs and this study in particular.

Enrollment bias. There were several steps taken to mitigate enrollment bias, such as instructing sites to maintain a screening log of eligible patients, so they could be compared with the enrolled

population. However, with the small number of patients enrolled, nearly all from one site in one country ([redacted]), study patients may not reflect the clinical characteristics of the overall global HCV population who are treated with interferon therapy and eltrombopag. Therefore, there are vast limitations in generalizing the study results to the overall HCV population.

Information bias can result from differences in collected data (e.g., accuracy or completeness) that misclassify patients in terms of exposure or outcomes. In order to ensure proper data collection, systematic site training and standardized CRFs and other guidance documentation were utilized to ensure consistent data collection. Definitions of the main outcomes of interest were provided for further consistency across sites. Along with manual data review, programmable data edit checks for missing, illogical, or out-of-range values were built into the EDC system to ensure data quality for all sites.

Nevertheless, the occurrence of information bias in this study cannot be ruled out. Due to the observational nature of the study, there were no protocol-mandated procedures or patient monitoring. As a result, asymptomatic events, e.g., of portal vein thrombosis and deep vein thrombosis and those that may have occurred outside of the study site may have been missed. For patients receiving eltrombopag before baseline, detection of AEs prior to prospective data collection was dependent on sufficient detail captured in the EDC. In addition, follow-up duration was shorter than planned and also varied among the patients, resulting in uneven distribution of follow-up data collection.

9.7 Study size

In this study, the primary objective was to examine the incidence of hepatic decompensation and mortality over a three year period in patients who achieved SVR during the study compared to those who did not achieve SVR. In order to address this question, the following assumptions were used to determine the study sample size:

- Enrolling 143 patients would have provided 80% power to detect a difference in hepatic decompensation over three years of follow-up, assuming that 30% of patients achieved SVR, and that 11% of patients who reached SVR and 32% of patients who did not reach SVR experienced hepatic decompensation; and
- Enrolling 159 patients would have provided 80% power to detect a difference in mortality at three years, assuming that 30% of patients achieved SVR, and that 5% of patients who reached SVR and 22% of patients who did not reach SVR would have died during the study.

The targeted sample size for this study was 200 patients to account for the potential variance in the percentage of patients achieving SVR or experiencing hepatic decompensation, and to

account for the potential of patients being lost to follow-up. Only nine patients from two sites in two countries were enrolled due to difficulties in site and patient recruitment, which led to the decision to terminate the study.

9.8 Data transformation

Study variables that were derived or calculated are listed below and are also presented in the final version of the SAP (dated 31 March 2017) in Appendix 9:

- Follow-up time (years) was calculated using the latest date (date of last visit prior to study close-out or early discontinuation date) – date of first dose eltrombopag plus 1 day, then divided by 365.25.
- Study duration (in months) for the patients who discontinued the study, was calculated as the date of study discontinuation (as collected in the CRF) minus the enrolment date (date of informed consent) plus 1 day divided by 30.44. If a patient died before completing 36 months of follow-up, the patient's date of death was used in the calculation instead of the study discontinuation date.
- Patient age (years) and age group (<65 years of age versus ≥65 years of age) was calculated as the date of first dose of eltrombopag minus the date of birth plus 1 day, divided by 365.25.
- Body mass index (BMI) was defined as weight (kg) divided by [height (m)]^2,
- Eltrombopag exposure: current exposure (i.e., ongoing or within 30 days [inclusive] of eltrombopag discontinuation at the time of the event of interest) or past exposure (i.e., greater than 30 days since eltrombopag discontinuation).

Baseline was defined as the date of the first dose of eltrombopag administered for patients enrolled into the study.

9.9 Statistical methods

The SAP was finalized on 31 March 2017 and describes the analyses included in this report.

9.9.1 Main summary measures

QuintilesIMS performed all computations and generated the tables and listings using [redacted] version 9.4 ([redacted] Institute, [redacted]) per the final version of the SAP (31 March 2017).

The analysis population included all enrolled patients who fulfilled the study inclusion and exclusion criteria. For discontinued patients the analyses included all data that had been collected up to the point of discontinuation.

Descriptive analyses were performed to gain an understanding of the qualitative and quantitative nature of the data collected and the characteristics of the sample studied. Continuous variables were reported as n, mean, standard deviation (SD), median, 25th and 75th quartiles (Q1 and Q3), and range (min, max). Categorical variables were summarized as number and proportion (%) of subjects with observed (non-missing) data. Listings were produced to provide data as recorded in the eCRFs.

All information already collected as part of the study was retained for analysis.

9.9.2 Main statistical measures

9.9.2.1 Patient disposition and baseline characteristics

Per the final version of the SAP (31 March 2017), patient enrollment and disposition were summarized as follows:

- Total number of patients enrolled in the study
- The number and percentage of patients who discontinued the study and reasons for study discontinuation (loss to follow-up, death, withdrawal of informed consent or investigator choice)
- Total number of deaths recorded in the CRF at each follow-up time
- Patient follow-up duration.

Demographics and baseline characteristics were summarized using descriptive statistics. Listings were provided for baseline clinical characteristics, concomitant medications, previous and current antiviral treatments, pregnancy and protocol deviations.

9.9.2.2 Study treatment

Per the final version of the SAP (31 March 2017), the following study treatment and compliance were measured.

Exposure to eltrombopag and concomitant antiviral treatments was summarized at each available follow-up time, and included the number and percentage of patients treated with eltrombopag and the number and percentage of patients treated with concomitant antiviral medications.

Dose of eltrombopag at initiation and at various time points during treatment was presented categorically. Duration of eltrombopag (in days) was reported as a mean, SD, median, Q1 and Q3, and range. For eltrombopag treatment, descriptive statistics of the following variables were summarized:

- Daily dose (12.5 mg, 25 mg, 50 mg, 75 mg, 100 mg or other)

- Duration of eltrombopag treatment (days)
- Treatment change (none, permanently discontinued, temporarily discontinued or dose change)
- Primary reason for treatment change (platelets too high as assessed by the investigator, platelets too low as assessed by the investigator, treatment completed, AE, or other).

9.9.2.3 Analysis of the primary objective

The primary objective was to assess and compare the incidence of hepatic decompensation and mortality (as separate events) at three years in patients using eltrombopag who achieved SVR to patients using eltrombopag who did not achieve SVR.

Due to early study termination, the analysis corresponding to the primary objective was not performed because of lack of data.

9.9.2.4 Analysis of the secondary objectives

Due to early study termination and lack of data, the analysis included only this following secondary objective:

- Assess the incidence of AEs (including TEEs) among new users of eltrombopag.

Due to early study termination and lack of data, the percentage of patients who achieved EVR and SVR, the probability of attaining SVR by these time points presented as Kaplan-Meier estimates, along with median time to attaining SVR, and rates of early discontinuation of interferon therapy were not calculated. Data listings of interferon-based antiviral therapy, including type of therapy, dose, and duration of therapy, as well as achievement of SVR defined by HCV RNA negative 24 weeks after cessation of antiviral treatment are included in the study analyses.

Adverse events

Analyses of AEs and serious AEs (SAEs) were presented. All AE summaries (events of interest and any other events recorded in the eCRF) were planned to be summarized by system organ class (SOC) and preferred term (PT) as follows:

- Number of patients and proportion of patients with at least one AE or SAE
- Number of AEs/SAEs

AEs/SAEs tables were stratified by SOC, PT and maximum intensity (mild, moderate and severe).

Non-serious and serious adverse drug reactions

Analyses of non-serious ADRs and SADRs were provided. The analyses of ADRs and SADRs included all AEs/SAEs occurring between first eltrombopag intake until 30 days (inclusive) after the last eltrombopag administration and were planned to be summarized by SOC and PT as follows:

- Number of patients and proportion of patients with at least one ADR/SADR
- Number of ADRs/SADRs

The same analyses were performed for ADRs/SADRs leading to discontinuation of eltrombopag. Separate ADR/SADR tables were provided and stratified by SOC, PT and maximum intensity (mild, moderate, and severe).

9.9.3 Missing values

In general, missing data was not imputed, and the data were analyzed as they were recorded in the study CRFs. One exception was that for all date fields, month and day were imputed to the first of January if those data were missing (i.e., UNK/UNK /YYYY = 01/JAN/YYYY).

9.9.4 Sensitivity analyses

Not applicable.

9.9.5 Amendments to the statistical analysis plan

Due to early study termination, a significant portion of the analyses as included in the protocol were revised to account for the lower-than-expected number of patients and lack of follow-up data. This included the sample size and analyses regarding the primary and secondary objectives. Per the final version of the SAP dated 31 March 2017, only analyses involving demographics and baseline clinical characteristics, previous and current antiviral treatments, protocol deviations, exposure to eltrombopag, antiviral status, and (S)AEs and (S)ADRs were conducted.

9.10 Quality control

To ensure the quality and integrity of research, this study was conducted under the Guideline on Good Pharmacovigilance Practices (GVP) (Module VIII – Post-Authorisation Safety Studies) issued by the EMA (European Medicines Agency 2012), Guidelines for Good Pharmacoepidemiology Practice (GPP) issued by the International Society for Pharmacoepidemiology (ISPE) (International Society of Pharmacoepidemiology Public Policy

Committee 2016), the principles outlined in the Declaration of Helsinki (World Medical Association 2013), and any applicable national guidelines.

All data were collected and entered directly into the EDC system. The two sites were fully trained on using the on-line data capture system, including eCRF completion guidelines and help files. All eCRFs were completed by designated, trained personnel or the study coordinator, as appropriate. In most cases, the eCRFs were reviewed, electronically signed, and dated by the Principal Investigator. One exception involved the End of Study visit CRF page, in which the "primary reason for early discontinuation" field was left blank for all the patients, as there was no appropriate option available due to the early study termination. As such, the End of Study visit CRF page could not be signed and closed by the Principal Investigator.

A data management plan was created before data collection began, which described all functions, processes, and specifications for data collection, cleaning, and validation. The eCRFs included programmed edit checks that fired when missing or erroneous data was entered, thus helping to ensure that quality data were obtained during initial data entry. Concurrent manual data review was performed based on parameters dictated by the plan. Ad hoc queries were generated within the EDC system and followed up for resolution.

To enable evaluations and/or audits from regulatory authorities or the Sponsor, the investigator agreed to keep records, including the identity of all participating patients, all original signed informed consent forms (ICFs), copies of all CRFs, source documents and adequate documentation of relevant correspondence (e.g., letters, meeting minutes, telephone calls, or reports). The records were to be retained by the investigator according to local regulations, or as specified in the study contract, whichever was longer. In most cases, source documents were contained in the patient's medical record and data collected on the CRFs matched the data in the medical records. In some cases, the CRF, or part of the CRF, may also have served as source documents.

Each site received a study site file at study initiation that contained all documents necessary for the conduct of the registry and was updated throughout the study. This file was available for review in the event the site was selected for monitoring, audits, or inspections and was safely archived after patients completed participation in the study. Archived documents included the patient enrollment log and the signed ICFs. In the event that archiving of the file was no longer possible at the site, the site was instructed to notify the Sponsor.

During the remote site initiation visit, the monitor provided training on the conduct of the study to the investigator, co-investigator(s), and all site staff involved in the study. Site monitoring was performed by QuintilesIMS to examine compliance with the protocol and adherence to the data collection procedures, to assess the accuracy and completeness of submitted clinical data, and to

verify that records and documents were being properly maintained for the duration of the study. The monitor performed source data verification by review of original patient records.

The monitor closed out each site remotely after early study termination, all data had been entered, and all outstanding monitoring issues had been resolved or addressed. All monitoring procedures and frequency of monitoring visits were described in the Study Monitoring Plan.

10. Results

10.1 Participants

Nine patients were screened and enrolled from two sites in two countries ([redacted]). One site in [redacted] enrolled one patient, and one site in [redacted] enrolled eight patients (Annex 2, Listing 1). Follow-up ranged from 6.9 to 16.6 months, and one patient (with 8.2 months of follow-up) was lost to follow-up.

No protocol deviations were reported (Annex 2, Listing 3).

10.2 Descriptive data

10.2.1 Baseline demographics

Table 3 below summarizes the patients' demographics and baseline characteristics.

All nine patients were younger than 65 years of age, with a mean (SD) age of 46.0 (11.1) years and range of 29.0 to 62.0 years. The majority of patients were male (n=8/9, 88.9%) and of [redacted] Five out of nine patients had a normal BMI (BMI = 18.5 - <25 kg/m^2) (55.6%), and four were overweight (BMI = 25 - <30 kg/m^2) (44.4%). For more information, see Annex 1, Table 1.2 and Annex 2, Listing 4.

Table 3 Patient Demographics and Baseline Characteristics

	Measure	Total (N=9)
Age (years)[a]	Mean (SD) Min; Max	46.0 (11.1) 29.0; 62.0
Age group (years) <65 ≥65	n (%)	 9 (100.0) 0 (0.0)
Sex Male Female	n (%)	 8 (88.9) 1 (11.1)
Geographic ancestry [redacted]	n (%)	[redacted]
BMI (kg/m^2)[b]	Mean (SD) Min; Max	24.5 (3.1) 20.3; 29.8
BMI categories (kg/m^2)[b] <18.5 18.5 - <25 25 - <30 30 - <35 ≥35	n (%)	 0 (0.0) 5 (55.6) 4 (44.4) 0 (0.0) 0 (0.0)

BMI = body mass index; SD = standard deviation
[a] Age (years) = (date of first dose of eltrombopag - date of birth + 1 day)/ 365.25.
[b] Body mass index calculated as weight (kg)/[height (m)]^2
Source: Annex 1, Table 1.2

10.2.2 Medical history

In accordance with protocol inclusion criteria, all patients had a history of TCP at study enrollment (Annex 2, Listing 5). In addition to TCP, five patients reported other conditions experienced prior to the study. See Table 4 for details on relevant medical history reported for these patients.

Table 4 Other Medical History Reported in Addition to TCP

[redacted]

None of the nine patients reported having had a TEE occurrence in the last six months prior to enrollment. Also, no patient had a dependency to drug or alcohol prior to enrollment.

10.2.3 HCV risk and clinical factors

All patients were first reported to be HCV positive within four years prior to enrollment, with the exception of [redacted] (Annex 2, Listing 6). Table 5 below provides information related to each patient's HCV status.

Table 5 HCV-Related Factors Reported at Enrollment

[redacted]

No patients reported the use of alcohol in the 30 days prior to enrollment. Four patients reported using nicotine products, and another patient reported having used drug injections in the 30 days prior to enrollment (Annex 2, Listing 6).

10.2.4 Baseline liver status

Liver status was assessed at study enrollment for all patients (Annex 2, Listing 7). In regards to cirrhosis staging, three patients reported having cirrhosis (F4, Ishak 5 or 6); two patients reported bridging fibrosis (F3, Ishak 4); three patients had no evidence of fibrosis (F0, Ishak 0); and one patient reported “other stage of fibrosis (F1 or F2, Ishak 1, 2 or 3)”.

[redacted]

10.2.5 Laboratory measures

Other laboratory measures including platelet counts, hemoglobin (Hgb), hematocrit, neutrophils, alanine transaminase, aspartate aminotransferase, serum albumin, and bilirubin collected at study enrollment and follow-up are listed in Annex 2, Listing 8.

10.2.6 Previous antiviral treatments

Two patients were previously treated with antiviral agents for HCV (Annex 2, Listing 10). Seven years before baseline, one patient was treated with interferon and ribavirin for one year. The patient was reported to have relapsed during treatment, but was reported to have completed the treatment thereafter. Four years before baseline, another patient was treated with interferon and ribavirin for one year. The patient was reported to have discontinued antiviral treatment early due to the patient's choice.

10.2.7 Eltrombopag treatment exposure

Eltrombopag treatment exposure is presented in Annex 1, Table 1.3 and Annex 2, Listing 12. Eight patients (88.9%) were currently being treated with eltrombopag at enrollment with a daily dose of 12.5 mg. Seven of the eight patients reported one course of eltrombopag use during the study, [redacted] All nine patients permanently discontinued eltrombopag during the study, and seven patients did so within 40 days of eltrombopag initiation. Reasons for discontinuation were due to the patient having achieved an increased platelet count (n=7) or the completion of antiviral treatment (n=2).

10.3 Outcome data

Not applicable.

10.4 Main results

10.4.1 Antiviral treatment and response

Current antiviral treatments including interferon, ribavirin, and DAAs and patient antiviral response are presented in Annex 2, Listing 9 and 11.

Seven patients were treated with double therapy (interferon and ribavirin), and two patients were treated with triple therapy (interferon, ribavirin, and DAA) (Annex 2, Listing 11). The most commonly reported interferons used were peginterferon alfa-2b ([redacted]) (n=4) and peginterferon alfa-2a ([redacted]) (n=3), and the only reported DAA was sofosbuvir (Sovaldi) (n=2).

Two patients had dose changes in their antiviral treatments during the study (Annex 2, Listing 11). [redacted]

[redacted]

Three of nine patients achieved SVR during the study (Annex 2, Listing 11). Two of them were treated with triple therapy (sofosbuvir, peginterferon alfa-2a, and ribavirin) and achieved SVR at 267 and 280 days after eltrombopag initiation (Annex 2, Listing 9 and 11). The third patient was treated with double therapy (peginterferon alfa-2b and ribavirin) and achieved SVR at 204 days after eltrombopag initiation. In four patients, SVR was not achievable as the study ended less than 24 weeks after cessation of treatment, and two other patients were reported to not have achieved or not known to have achieved SVR by the study end (Annex 2, Listing 9).

10.5 Other analyses

Not applicable.

10.6 Adverse events/adverse reactions

All AE verbatim terms were recorded and coded using Medical Dictionary for Regulatory Activities (MedDRA), version 19.1, and are presented by SOC and PT.

10.6.1 Overall summary of adverse events

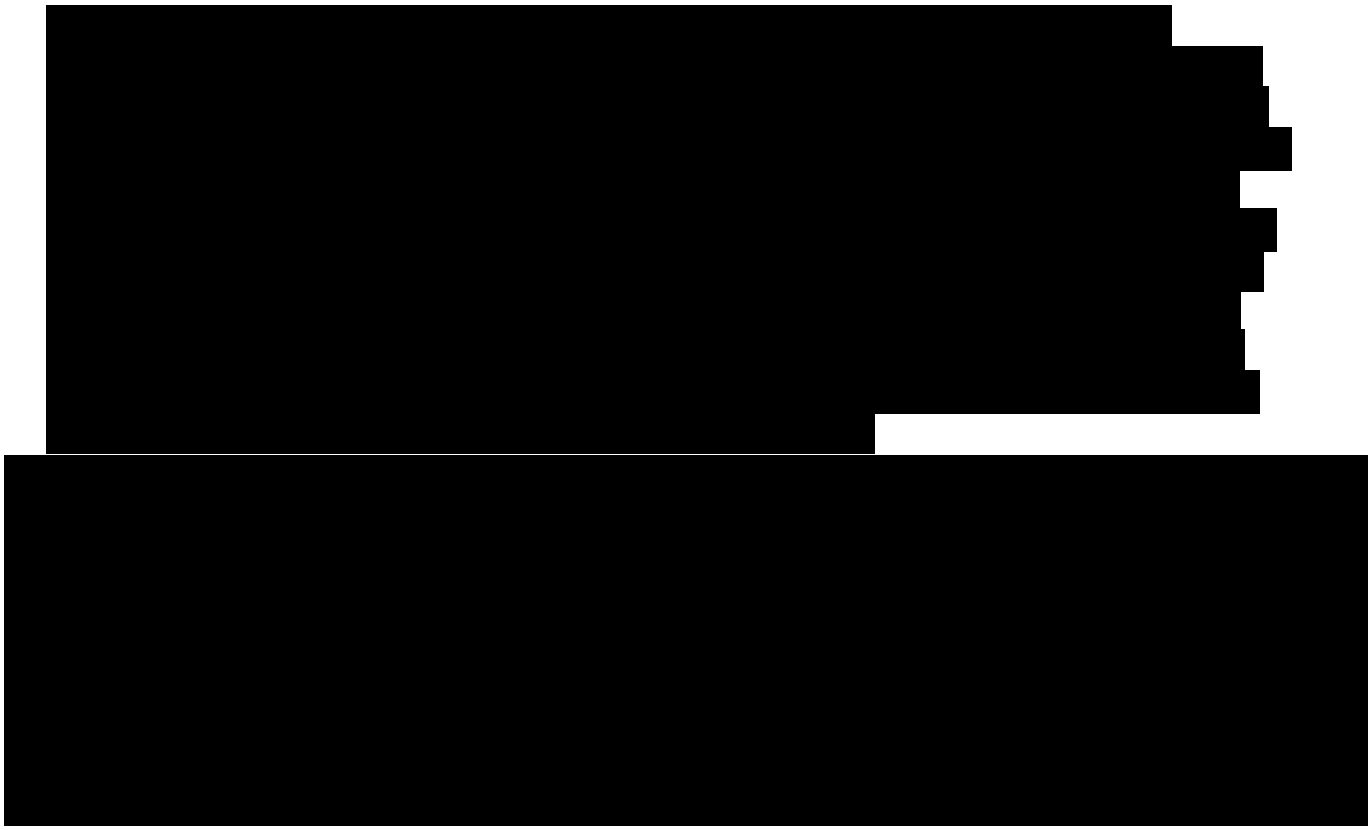
AEs are presented in Table 6 below, and Annex 1, Table 2.1, and by severity in Annex 1, Table 2.6. SAEs are presented in Annex 1, Table 2.2 and by severity in Annex 2, Table 2.7. For more details, see Annex 2, Listing 14 and 15.

Three patients (n=3/9, 33.3%) reported having four AEs (anemia, neutropenia, and TCP [n=2]) which were all under the SOC blood and lymphatic system disorders (Annex 1, Table 2.1). The AEs varied in severity (mild [n=1/9, 11.1%], moderate [n=1/9, 11.1%], and severe [n=2/9, 22.2%]) (Annex 1, Table 2.6). No patients were withdrawn from the study due to an AE (Annex 2, Listing 14). No AEs were serious or caused by the study treatment (Annex 2, Listing 14).

Table 6 Summary of Adverse Events

	N=9	
	Patients n (%)	**Events n**
Any AE	3 (33.3)	4
Primary SOC/PT		
Blood and lymphatic system disorders	3 (33.3)	4
Anemia	1 (11.1)	1
Neutropenia	1 (11.1)	1
Thrombocytopenia	2 (22.2)	2

AE: adverse event; PT: preferred term; SOC: system organ class
Source: Annex 1, Table 2.1



10.6.2 Adverse drug reactions and serious adverse drug reactions

No patients reported an ADR or SADR (Annex 1, Table 2.3, 2.4, 2.8, and 2.9).

10.6.3 Adverse drug reactions and serious adverse drug reactions leading to discontinuation

No patients reported an ADR or SADR that led to discontinuation of eltrombopag (Annex 1, Table 2.5).

10.6.4 Pregnancy

Pregnancies occurring to patients or experienced by patients' partner since the start of eltrombopag initiation are presented in Annex 2, Listing 16. [redacted]

11. Discussion

11.1 Key results

This study was conducted in patients with HCV initiating eltrombopag to assess both short and long-term effectiveness and safety of the treatment in the post-approval setting. Although the study planned to enroll 200 patients from 40 sites to be followed up for 36 months, the decision was made to end the study early due to changes in treatment paradigm for HCV resulting in unanticipated difficulties in patient enrollment. As such, only nine patients were enrolled from two sites, one site in [redacted] and the other in [redacted]. [redacted] site enrolled one patient; the [redacted] site enrolled eight patients. Follow-up ranged from 7 to 17 months.

Eight of the nine patients were male. [redacted]. The mean age was 46.0 years (range: 29; 62 years). All patients had a history of TCP at study enrollment, and no patient reported a TEE occurrence in the last six months prior to enrollment. All but one patient were treated with a 12.5 mg daily dose of eltrombopag, [redacted]
All nine patients permanently discontinued eltrombopag during the study and seven patients did so within 40 days of eltrombopag initiation. Reasons for stopping eltrombopag were due to an achieved increased platelet count (n=7) or due to the completion of antiviral treatment (n=2).

Antiviral treatment administered to the patients included the following: double therapy [interferon and ribavirin], n=7, and triple therapy [interferon, ribavirin, and DAA], n=2. Two patients had dose changes in their antiviral treatments during the study. [redacted] Eight patients completed their antiviral treatments during the study while one patient reported ongoing antiviral treatment. Three patients achieved SVR between 204 to 280 days relative to baseline, and one patient did not achieve SVR. In four patients, SVR was not achievable due to the study ending less than 24 weeks after cessation of treatment, and SVR status was unknown for one patient.

Three of nine patients (33.3%) reported AEs during the study. [redacted]

[redacted] No patients were withdrawn from the study due to an AE, and there were no SAEs. No patients reported an ADR or SADR related to eltrombopag. [redacted]

11.2 Limitations

Novartis decided to terminate the study based on consultation with the EMA due to change in treatment paradigm for HCV resulting in unanticipated difficulties in patient enrollment. The study was designed to enroll around 200 patients and collect follow-up data for 36 months. However, only nine patients from two sites in two countries were enrolled. As a result, the main planned outcomes for the study including incidence of hepatic decompensation, mortality, and TEEs were not collected and/or analyzed due to the low patient numbers and shortened duration of follow-up. Also, due to the small sample size, with the majority of patients recruited from one site, the population is not reflective of the overall global population of HCV patients. For these reasons, the results of this study are limited in providing a comprehensive picture of safety data for HCV patients treated with antivirals and eltrombopag, along with short and long-term effectiveness in the post-approval setting.

There were no protocol-mandated procedures or patient monitoring, and as such, certain events which were asymptomatic or occurred outside of the study site may not have been collected. For patients receiving eltrombopag before baseline, detection of AEs prior to prospective data collection was dependent on sufficient detail captured in the EDC.

11.3 Interpretation

Due to early study termination and the small sample size, the main objectives of the study, i.e., to assess the incidence of hepatic decompensation, TEEs, and mortality at three years and associated risk factors, were not assessed. Therefore, few conclusions can be made regarding the occurrence of these events and mortality. It is worth noting that in the shorter-than-planned follow-up period, there were no deaths, hepatic decompensation, or TEEs observed in this study. Data collected for this study do not contribute to an assessment of the long-term effects of antiviral and eltrombopag treatment.

Although few conclusions can be made regarding eltrombopag treatment effectiveness, there is some data to show that patients in this study were generally successful in completing their antiviral treatment in the short-term with little negative impact. Eight of nine patients in the study completed their antiviral treatment as planned. Similar to the ENABLE trials, the majority of patients (7 of 9) in this study achieved platelet count increases with eltrombopag use during the study. Three of nine patients achieved SVR, although four patients did not contribute sufficient follow-up time in order to assess SVR status and it is possible some may have achieved SVR after the study end. Four AEs (all non-serious) reported for this study were hematological events,

and three of them were reported to be related to the antiviral therapies. Despite these AEs, two of the three patients (two patients with one AE; one patient with two AEs) achieved SVR by the study end, while the remaining patient had not contributed enough follow-up time to assess SVR status. Results should be viewed with caution, however, due to the limitations stated above.

11.4 Generalizability

Although the study planned to enroll 200 patients from 40 sites over 36 months, only nine patients from two sites in two countries (eight patients from one site in [redacted]) were enrolled. As such, the results cannot be generalized to all HCV patients using eltrombopag along with interferon-based therapy due to TCP. Site provider characteristics may have an impact on the type of treatment and care management received as well as on patient outcomes. Patients from a certain region may also share characteristics which are not reflective of patients from other areas that may impact treatment utilization and clinical outcomes.

11.5 Other information

Not applicable.

12. Conclusion

The study was planned as a global, multi-center, prospective, observational study and conducted to evaluate the safety and effectiveness of eltrombopag in routine clinical practice in patients with HCV, who were being treated with interferon-based antiviral therapy. Due to challenges in site recruitment and enrollment resulting from the low uptake of interferon-based therapy for HCV, the study was terminated earlier than planned. Analyses addressing the main objectives of the study, including incidence of hepatic decompensation, TEEs, and mortality at three years were not conducted. Nine patients, eight from a [redacted] site and one from [redacted] site, were enrolled, with follow-up ranging from seven to 17 months. Eight of nine patients completed their antiviral therapy by study end, and all nine patients had finished at least one course of eltrombopag treatment. Three patients reported hematological AEs, and no SAEs, AEs related to eltrombopag, and deaths were reported.

13. References

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14. Appendices

The following Appendices and Annexes are provided as separate files.

List of Appendices:

- Appendix 1: Protocol and Amendments
- Appendix 2: Sample Case Report Form
- Appendix 3: List of Independent Ethics Committees and Representative Sample Consent Forms
- Appendix 4: List and Description of Investigators
- Appendix 5: Signature Page
- Appendix 6: List of Patients Receiving Test Drugs
- Appendix 7: Randomization
- Appendix 8: Audit Certificates
- Appendix 9: Statistical Analysis Plan
- Appendix 10: Laboratory Standardization
- Appendix 11: Publications Based on the Study
- Appendix 12: Important Publications

List of Annexes:

- Annex 1: Tables
- Annex 2: Listings

Appendices

Appendix 1 – Protocol and Protocol Amendments

Document	Version	Effective date
Final Protocol	Version 2.0	16 Jul 2014

No Protocol Amendments have been issued.

TITLE PAGE

Division: Worldwide Development
Information Type: Worldwide Epidemiology Study Protocol

Title:	A global, prospective cohort study to evaluate the 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:	16-JUL-2014
Subject:	Hepatitis C Virus, Thrombocytopenia, Cohort study
Authors:	[redacted]

PASS information

Title	A global, prospective cohort study to evaluate the 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	2.0
Date of last version of protocol	Not applicable
EU PAS register number	To be registered after PRAC protocol approval
Active substance	Eltrombopag
Medicinal product	Eltrombopag
Product reference	SB-497115-GR
Procedure number	Not applicable
Marketing authorisation holder	GlaxoSmithKline Trading Services Limited [redacted]
Joint PASS	No
Research question and objectives	The aim of this study is to assess the safety and effectiveness of eltrombopag in routine clinical practice in patients with HCV who are unable to initiate or maintain optimal interferon-based therapy due to thrombocytopenia. The specific objectives of the study are to: • Assess and compare the incidence of hepatic decompensation and mortality at 3 years in patients who achieve SVR with patients who do not achieve SVR • Assess the incidence of thromboembolic events among new users of eltrombopag • Assess treatment effectiveness among eltrombopag users with respect to initiating, maintaining and completing antiviral therapy and achieving sustained viral response (SVR) • Evaluate all-cause and cause-specific mortality risk and survival rates among eltrombopag users at 6 months, 12 months, 18 months, 24 months and 36 months after starting eltrombopag • Explore the factors independently related to the risk of hepatic decompensation and the risk of thromboembolic events

Countries of study	[redacted]
Author(s)	[redacted]

MARKETING AUTHORISATION HOLDER

Marketing authorisation holder	GlaxoSmithKline Trading Services Limited [redacted]
MAH contact person	[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

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1. LIST OF ABBREVIATIONS

ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse event of special interest
CI	Confidence interval
CRF	Case report form
CRO	Contract research organization
DAA	Direct-acting antiviral agents
DMP	Data management plan
eCRF	Electronic case report form
EDC	Electronic data capture
EMA	European Medicines Agency
ENABLE	Eltrombopag to INitiate and Maintain Interferon Antiviral Treatment to Benefit Subjects with Hepatitis C related Liver DiseasE
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EVR	Early viral response
FDA	U.S. Food and Drug Administration
GSK	GlaxoSmithKline
GVP	Good Pharmacovigilance Practice
GPP	Good Pharmacoepidemiology Practice
HAI	Modified Hepatic Activity Index
HCV	Hepatitis C virus
ICF	Informed consent form
ICH	International Conference on Harmonisation
IEC	Independent ethics committee
INR	International normalized ratio
IRB	Institutional review board
ISPE	International Society for Pharmacoepidemiology
MELD	Model for End Stage Liver Disease
MedDRA	Medical Dictionary for Regulatory Activities
PASS	Post-authorisation safety study
RNA	Ribonucleic acid
SAE	Serious adverse event
SAP	Statistical analysis plan
SBP	Spontaneous bacterial peritonitis
SVR	Sustained viral response
TCP	Thrombocytopenia

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
[redacted]

Trademarks not owned by the GlaxoSmithKline group of companies
[redacted]

2. RESPONSIBLE PARTIES

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: WEUSKOP7136

Sponsor Legal Registered Address:

GlaxoSmithKline Research & Development Limited
[redacted]

Sponsor Contact Address:

GlaxoSmithKline Trading Services Limited [redacted]

In some countries, the study sponsor may be the local GlaxoSmithKline affiliatecompany (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]

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

Regulatory Agency Identifying Number(s): Not applicable

[redacted]

[redacted]

SPONSOR SIGNATORY:

[redacted]

Primary Author/ Project officer

[redacted]

Date

[redacted]

Therapy Area Leader

[redacted]

Date

[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.

Investigator Name: _____

_____ _____
Investigator Signature Date

3. ABSTRACT

Title. A global, prospective cohort study to evaluate the real-world use of eltrombopag in adult patients with chronic Hepatitis C Virus infection who are unable to initiate or maintain optimal interferon-based

Rationale and background. 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 non-adherence 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 [Borroni, 2008;McHutchison, 2002; Russo 2003]. [redacted]/[redacted] (eltrombopag) is an second generation oral thrombopoeitin receptor agonist developed by GlaxoSmithKline (GSK) and approved for the treatment of chronic immune (idiopathic) thrombocytopenia (ITP) and hepatitis C associated thrombocytopenia. 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.

Research Question and Objective(s). The aim of this study is to assess the safety and effectiveness of eltrombopag in routine clinical practice in patients with HCV who are unable to initiate or maintain optimal interferon-based therapy due to thrombocytopenia.

The primary objective of this study is to:

- Assess and compare the incidence of hepatic decompensation and mortality at 3 years in patients using eltrombopag who achieve SVR to patients using eltrombopag who do not achieve SVR.

Secondary objectives of the study include:

- Assess the incidence of thromboembolic events among new users of eltrombopag;
- Assess treatment effectiveness among eltrombopag users with respect to initiating, maintaining and completing antiviral therapy and achieving sustained viral response (SVR);

- Evaluate all-cause and cause-specific mortality risk and survival rates among eltrombopag users at 6 months, 12 months, 18 months, 24 months and 36 months after staring eltrombopag; and
- Explore the factors independently related to the risk of hepatic decompensation and the risk of thromboembolic events among eltrombopag users.

Study Design. This study is a global, multi-center, prospective, observational study conducted to evaluate clinical outcomes and treatment patterns in HCV patients treated with eltrombopag. Country selection will depend on the regulatory approval and reimbursement status of eltrombopag for the HCV associated thrombocytopenia indication, but is expected to include several countries in [redacted] and [redacted] The study is designed to enrol approximately 200 patients, with a minimum of 100 patients who are treated with boceprevir, telaprevir or newer direct acting agents (DAAs) that consist of a backbone of interferon-based therapy in at least 40 sites over the course of an enrolment period of at least18 months.

Patients will be followed for a period of 3 years after initiating eltrombopag; based on routine care, patients will be assessed regularly during interferon-based therapy and then approximately every 6 months thereafter according to local standard practice. Patients who permanently discontinue eltrombopag will be followed for clinical outcomes and survival, according to the protocol schedule, for up to 36 months post-enrollment.

Population.
Inclusion criteria:

- Age ≥ 18 years at enrollment
- Diagnosis of HCV verified by the presence of HCV RNA
- Initiation of first-time treatment with eltrombopag no more than 3 months prior to study enrolment
- Patient was unable to initiate, maintain, or restart optimal interferon-based therapy due to thrombocytopenia
- Patient currently undergoing interferon-based antiviral therapy or initiation or re-start of interferon-based antiviral therapy planned
- Patient (or appropriate representative) willing and able to provide written informed consent

Exclusion criteria:

- Current participation in any interventional clinical trials in which treatment regimen and/or monitoring is dictated by a protocol

Variables. The main safety outcomes of this study are:

- Hepatic decompensation defined by the presence of one or more of the following events:
  - Ascites
  - Hepatic encephalopathy
  - Variceal hemorrhage
  - Spontaneous bacterial peritonitis

- Thromboembolic events, which include:
  - Acute myocardial infarction
  - Ischemic stroke
  - Portal vein thrombosis
  - Deep vein thrombosis
  - Pulmonary embolism
  - Acute coronary syndrome
  - Other arterial thromboembolic events
  - Other venous thromboembolic events
- All-cause mortality and cause-specific mortality
- Non-serious and serious adverse drug reactions (ADRs/SADRs)

Treatment effectiveness will be assessed based upon:

- Ability to initiate (or re-start) interferon-based antiviral therapy
- Ability to maintain planned interferon-based antiviral therapy
- Achievement of early viral response (EVR) and SVR

Additional variables collected at baseline include patient demographics, HCV genotype, HCV treatment history, other relevant medical history, Child Pugh score, Model for End-stage Liver Disease (MELD) score, liver status, TCP history, eltrombopag exposure, select concomitant medications and recent select laboratory values, including platelet count. Additional variables collected during follow-up include updated eltrombopag exposure, antiviral treatment, select concomitant medications and select laboratory values (if performed as part of routine care).

Data sources. All data will be provided by the investigator via an electronic case report form (eCRF). Any assessments are intended to be performed at the time of a routine clinical encounter or by referencing the medical record. No clinic visits are required as part of participation in this study.

Study size. The sample size assumptions were based on a study conducted by Iacobellis et al [Iacobellis, 2011] that reported data on SVR and long-term outcomes in an advanced HCV population treated with dual therapy. DiMarco et al [Di Marco, 2007] observed similar improvements in long-term outcomes in those achieving SVR.

The following assumptions were used to determine the study sample size:

- Enrolling 143 patients provides 80% power to detect a difference in hepatic decompensation over 3 years of follow up, assuming that 30% of patients achieve SVR, and that 11% of patients who reach SVR and 32% of patients who do not reach SVR experience hepatic decompensation; and
- Enrolling 159 patients provides 80% power to detect a difference in mortality at three years, assuming that 30% of patients achieve SVR, and that 5% of patients who reach SVR and 22% of patients who do not reach SVR die during the study.

The targeted sample size for this study is 200 patients to account for potential variance in the percentage of patients achieving SVR or experiencing hepatic decompensation and the potential for patients lost to follow-up.

Data analysis. The analysis plan, including complete analytical specifications, tables and listings, will be fully described in a written and approved statistical analysis plan. Descriptive analyses will include tables and figures showing patient demographics and characteristics of study patients including medical/disease history, virology, and laboratory information, at baseline and at 6 months, 12 months, 18 months, 24 months and 36 months of follow-up. Information will be presented for all patients and stratified by subgroups of interest, to the extent allowed by the data. Kaplan-Meier survival estimates will be calculated for 6 month, 12 month, 18 month, 24 month and 36 month observation periods for the outcomes of hepatic decompensation, thromboembolic events and all-cause mortality. Cumulative incidence rates will be calculated for the occurrence of hepatic decompensation and thromboembolic events, as separate events, over the same observation periods. For hepatic decompensation or mortality at 3 years (as separate events), incidence rate ratios comparing patients who did and did not attain SVR will be calculated, along with 95% confidence intervals (CIs).

Exposure to eltrombopag and antiviral therapies will be summarized.

Evaluation of treatment effectiveness will be based on the ability to initiate (or re-start) interferon-based antiviral therapy, the ability to maintain planned interferon-based antiviral therapy, the achievement of EVR and SVR.

Milestones, based on expected June 2014 protocol approval. Note: An earlier protocol approval will enable an earlier study start.

Milestone	**Planned date**
Start of data collection	November 2014
End of data collection	April 2019
Study progress reports	Annually following first patient enrolled
Interim report 1	December 2016
Interim report 2	June 2017
Interim report 3	December 2017
Final report of study results	November 2019

4. AMENDMENTS AND UPDATES

None.

5. MILESTONES

Milestones are based on expected June 2014 protocol approval. Note: An earlier protocol approval will enable an earlier study start.

Milestone	Planned date
Start of data collection	November 2014
End of data collection	April 2019
Study progress reports	Annually following first patient enrolled
Interim report 1	December 2016
Interim report 2	June 2017
Interim report 3	December 2017
Final report of study results	November 2019

6. RATIONALE AND BACKGROUND

6.1. Background

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. Data regarding the prevalence of TCP in HCV patients in the current literature is very limited and variable. A recent review of the literature revealed a prevalence of TCP ranging broadly from 0.2% to 45% in HCV patients, with more than half of the studies reviewed reporting a TCP prevalence of at least 24% [Louie, 2011]. In a cohort study by Roomer et al, of the 321 evaluated patients treated with peginterferon alfa and ribavirin, 42% experienced a drop in platelet count during treatment; 30 patients (9.3%) had platelet counts below 50 x 10^9/L and 2 patients (0.6%) had a platelet count below 20 x 10^9/L [Roomer 2010].

Many of the treatment-related adverse events associated with peginterferons and ribavirin combination therapy have been well-established in clinical trials and in the post-marketing setting. Interferon therapy, and in particular the peginterferons, are known to cause a substantial drop in platelet count associated with their bone marrow suppressing effects. Patients with advanced liver fibrosis and portal hypertension frequently develop TCP, which may preclude antiviral therapy. Recommended platelet counts for initiation of peginterferon alpha 2a or 2b are $\geq$ 90 x 10^9/L and $\geq$ 100 x 10^9/L, respectively; however, in routine clinical practice thresholds used vary and may be influenced by individual patient characteristics. In addition, discontinuation and non-adherence due to treatment-related adverse events associated with antiviral therapy are of concern as, not unexpectedly, patients who discontinue therapy or have less-than-optimal treatment doses experience unfavorable sustained virologic response (SVR) rates [Borroni, 2008; McHutchison, 2002; Russo, 2003]. Achievement of SVR is associated with a 99 percent chance of being HCV RNA negative during long-term follow-up [Swain, 2010], and has

been associated with decreases in all-cause mortality, liver-related death, the need for liver transplantation, hepatocellular carcinoma rates and liver-related complications [Backus, 2011; Veldt, 2007].

HCV itself, unrelated to antiviral treatment, can also be complicated by the development of extrahepatic manifestations such as TCP, particularly in patients with evidence of cirrhosis. The mechanism (or mechanisms) behind this effect is not completely understood but may be related to virus-induced bone marrow suppression, decreased thrombopoeitin production in the liver, or splenic sequestration. In addition to decreasing the peginterferon dose (while maintaining a minimum effective dose), other treatment strategies for HCV-related TCP have included intravenous immunoglobulins, corticosteroids (which are widely thought to result in more harm than benefit) and in severe cases splenectomy.

6.2. Rationale

[redacted] / [redacted] (eltrombopag) is an second generation oral thrombopoeitin receptor agonist developed by GlaxoSmithKline (GSK) and approved for the treatment of chronic immune (idiopathic) thrombocytopenia (ITP) and hepatitis C associated thrombocytopenia. Eltrombopag was approved in [redacted] in [redacted] for HCV-associated TCP to allow for the initiation and maintenance of interferon-based therapy. In [redacted], [redacted] approved eltrombopag for this indication. Use of the product in this population is intended to raise platelet counts to a level sufficient to reduce the risk of bleeding (i.e., $\geq 50 \times 10^9$/L) but not completely normalize the platelet count.

The efficacy and safety of eltrombopag for the treatment of thrombocytopenia in adult patients with HCV were evaluated in two randomized, double-blind, placebo-controlled trials. The ENABLE 1 (Eltrombopag to INitiate and Maintain Interferon Antiviral Treatment to Benefit Subjects with Hepatitis C related Liver DiseasE) trial utilized peginterferon alfa-2a ([redacted]) plus ribavirin for antiviral treatment and ENABLE 2 utilized peginterferon alfa-2b ([redacted]) plus ribavirin. These global, randomized, double-blinded Phase 3 trials evaluated the efficacy of eltrombopag in 1521 HCV patients with platelet counts of less than 75×10^9/L using a primary endpoint of achieving SVR. The vast majority of enrolled patients (95% in ENABLE 1 and 97% in ENABLE 2) achieved platelet count increases to $\geq 90 \times 10^9$/L, the threshold for initiating peginterferon plus ribavirin therapy, and most did so within 4 weeks of initiating eltrombopag treatment. In ENABLE 1, 66% of patients treated with eltrombopag plus [redacted] and ribavirin had an early virologic response (EVR), compared with 50% of patients who received [redacted] ribavirin and a placebo ($p<0.0001$). Additionally, 23% of the eltrombopag group achieved SVR versus 14% of the placebo group ($p=0.0064$) [Afdhal 2014]. Similarly, in ENABLE 2, compared with placebo eltrombopag was associated with improved SVR (19% vs. 13%, $p = 0.0202$), fewer antiviral dose reductions (54% vs. 73%, $p = 0.0001$), improved EVR (62% vs. 41%, $p < 0.0001$), and improved end-of-treatment response (38% vs. 23%, $p < 0.0001$) [Afdhal 2014].

Recent studies have demonstrated that patients with HCV patients with cirrhosis and/or thrombocytopenia are at increased risk for hepatic decompensation [Fried, 2013; Hézode 2013]. In the ENABLE studies, the hepatic decompensation events of ascites and hepatic

encephalopathy were reported more frequently for eltrombopag than placebo [Afdhal, 2012].

Several recent studies have demonstrated that patients with advanced chronic liver disease or cirrhosis are extremely susceptible to hypercoagulability and thrombotic complications despite prolonged clotting times [Lippi, 2011; Roberts, 2010]. In both of the ENABLE studies, there was an increased incidence of thromboembolic events (e.g., portal vein thrombosis, deep vein thrombosis) observed in the eltrombopag arm versus the placebo arm.

The safety and efficacy of eltrombopag use in thrombocytopenic HCV patients has not been evaluated in combination with commercially-available protease inhibitors (boceprevir or telaprevir containing regimens), which are commonly used to treat HCV. Similarly, it has not been determined in a real world setting whether the ability to achieve SVR confers long-term benefit in advanced HCV patients with significant TCP who have been treated with eltrombopag in combination with interferon-based therapy

This study represents a proactive pharmacovigilance approach in generating safety data, along with short and long-term effectiveness 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.

7. RESEARCH QUESTION AND OBJECTIVE(S)

The aim of this study is to assess the safety and effectiveness of eltrombopag in routine clinical practice in patients with HCV who are unable to initiate, maintain or re-start optimal interferon-based therapy due to TCP.

The primary objective of this study is to:

- Assess and compare the incidence of hepatic decompensation and mortality at 3 years in patients using eltrombopag who achieve SVR to patients using eltrombopag who do not achieve SVR.

Secondary objectives of the study include:

- Assess the incidence of thromboembolic events among new users of eltrombopag;
- Assess treatment effectiveness among eltrombopag users with respect to initiating, maintaining and completing antiviral therapy and achieving sustained viral response (SVR);
- Evaluate all-cause and cause-specific mortality risk and survival rates among eltrombopag users at 6 months, 12 months, 18 months, 24 months, and 36 months after starting eltrombopag; and

- Explore the factors independently related to the risk of hepatic decompensation and the risk of thromboembolic events among eltrombopag users.

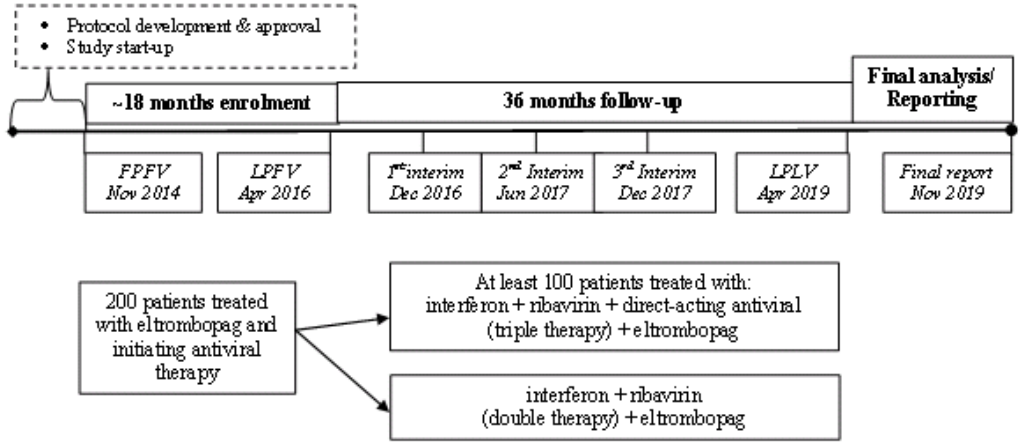
8. RESEARCH METHODS

8.1. Study Design

This study is a global, multi-centre, prospective, observational study conducted to evaluate clinical outcomes and treatment patterns in HCV patients newly initiating eltrombopag. Country selection will depend on the regulatory approval and reimbursement status of eltrombopag for the HCV associated thrombocytopenia indication, but is expected to include several countries in [redacted].

The study is designed to enrol approximately 200 patients, with a minimum of 100 patients who are treated with boceprevir, telaprevir or newer direct acting agents (DAAs) that consist of a backbone of interferon-based therapy , in at least 40 sites over the course of an enrolment period of at least 18 months (Figure 1). All milestone dates are based on protocol approval in June 2014. Eligible patients will be enrolled by gastroenterologists, hepatologists and other physicians and health care providers experienced in the management of patients with HCV, consistent with local treatment practices. Eligible patients will be enrolled in the study at the time of presentation for a routine clinic visit. No clinic visits are required as part of participation in this study. All follow-up assessments are intended to be performed at the time of a routine clinical encounter or by referencing the medical record.

Figure 1 Study Design Overview



Patients will be followed for a period of three years after initiating eltrombopag. The frequency of assessments is at baseline and every clinic visit thereafter up to 36 months post-enrolment. Due to the severity of their disease, it is expected patients will be

assessed at regularly during interferon-based therapy and then approximately every 6 months thereafter, per usual care setting. Data will be captured from all clinic visits regularly during antiviral therapy and every 6 months after completing or discontinuing antiviral treatment. All patients who discontinue eltrombopag should be followed for clinical outcomes and survival, according to the protocol schedule, for up to 36 months post-enrolment. Additional exposure to eltrombopag will be captured should the patient go on to receive additional antiviral therapy and eltrombopag during follow-up on study.

First-time new users of eltrombopag will be enrolled in this study. A first-time new user is defined as any patient meeting inclusion and exclusion criteria who has been treated with eltrombopag for ≤ 3 months at time of study enrollment. Patients with prior exposure to eltrombopag for any duration more than 3 months prior to study enrollment will be excluded. Patients currently on, or newly initiating eltrombopag, will be followed for the events of hepatic decompensation and thromboembolic events, and for treatment effectiveness (i.e., the ability to initiate and maintain antiviral therapy and to achieve SVR). Outcomes will be stratified by modality of antiviral therapy for HCV infection [i.e., interferon and ribavirin (double therapy) or interferon, ribavirin, and DAAs (triple therapy)], by age group, by race/ethnicity, and by HCV genotype, to the extent allowed by the data. The study will assess the 3-year incidence of hepatic decompensation and mortality comparing eltrombopag-treated patients who achieve sustained virologic response to eltrombopag-treated patients who do not achieve SVR.

The study will also examine effectiveness and safety data in populations not previously well studied, most notably, patients using eltrombopag in the context of currently available DAAs for treatment of HCV.

8.2. Setting

There are no protocol–mandated visits or procedures associated with the study. Each patient is expected to participate for a maximum of 36 months or until premature discontinuation (i.e., due to death, withdrawal of consent, lost to follow-up or study termination). Follow-up information will be collected approximately every 3 months while being actively treated with antiviral therapy, and approximately every 6 months thereafter. It is anticipated that the frequency of patient assessments will differ according to local standard practice.

Site selection criteria will include projected availability of eligible patients in at least an 18 month period and the availability of physician (and other site staff) time to complete the limited, but necessary case report forms. Selection criteria and basic site information (e.g., site size, site type) will be collected via a site qualification survey.

Sites will be required to maintain a patient enrolment log of eligible patients at their treatment center. This log will document how patients came to be included or excluded from the study, in order to assess the representativeness of the study population. The overall number of patients and sites may be adjusted during the study to meet enrolment goals, if needed. To the extent possible, consecutive patients meeting inclusion/exclusion criteria will be enrolled.

8.2.1. Inclusion criteria

The following criteria must be met in order to be enrolled in the study:

- Age ≥ 18 years at enrollment
- Diagnosis of HCV verified by the presence of detectable HCV RNA
- Initiation of first-time treatment with eltrombopag no more than 3 months prior to study enrolment
- Patient was unable to initiate, maintain, or restart optimal interferon-based therapy due to thrombocytopenia prior to initiating eltrombopag
- Patient currently undergoing interferon-based antiviral therapy or initiation or re-start of interferon-based antiviral therapy planned
- Patient (or appropriate representative) willing and able to provide written informed consent

8.2.2. Exclusion criteria

Patients meeting ANY of the following criteria are not eligible for participation:

- Current participation in any interventional clinical trials in which treatment regimen and/or monitoring is dictated by a protocol

8.2.3. Patient withdrawal

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

8.3. Variables

Variables included in this study are summarized below.

8.3.1. Outcome definitions

The main safety outcomes of this study are:

- Hepatic decompensation defined by the presence of any of the following, as reported by the investigator:
    - Ascites
    - Hepatic encephalopathy
    - Variceal hemorrhage
    - Spontaneous bacterial peritonitis

Sites will receive guidance on the definitions of these conditions in the Study End Points Manual and will receive training at study start up.

- Thromboembolic events , as reported by the investigator, which include:

- Acute myocardial infarction
- Acute coronary syndrome
- Ischemic stroke
- Portal vein thrombosis
- Deep vein thrombosis
- Pulmonary embolism
- Other arterial thromboembolic events
- Other venous thromboembolic events

- All-cause mortality and cause-specific mortality. Liver disease-related mortality will be captured when liver disease is noted as a primary or secondary cause of death in the medical record or death certificate.
- Non-serious and serious adverse drug reactions (ADRs/SADRs)

Treatment effectiveness will be assessed based upon:

- Ability to initiate (or re-start) interferon-based antiviral therapy, defined as the proportion of enrolled patients who receive at least one dose of interferon therapy
- Ability to maintain planned interferon-based antiviral therapy, defined as the proportion of patients with no interferon dose reductions or early discontinuations related to TCP
- Achievement of SVR defined by HCV RNA negative 24 weeks after cessation of antiviral treatment
- Achievement of EVR defined as clinically significant reduction in HCV RNA ($\geq$2 $\log_{10}$ drop or undetectable) after 12 weeks of antiviral treatment

8.3.2. Exposure definitions

First time new exposure to eltrombopag will be defined as patients newly treated with eltrombopag within the past 3 months prior to study enrolment. This is to allow for data capture of all relevant baseline variables and ensures an accurate account of the outcomes associated with use for both safety and effectiveness. If, while under study, an enrolled patient discontinues eltrombopag due to ineffectiveness of antiviral therapy and subsequently receives different antiviral therapy and concomitant eltrombopag, treatment safety and effectiveness measures on the subsequent use of eltrombopag will also be captured. Additionally, if, while under study, an enrolled patient discontinues eltrombopag due to an adverse event, and then subsequently receives eltrombopag at a later time during the study period, this subsequent use of eltrombopag will also be captured.

Treatment with eltrombopag will be characterized as either in combination with a interferon and ribavirin (double therapy) or in combination with an interferon, ribavirin, and commercially-available DAAs. Where applicable, exposure will be classified as current (i.e., ongoing or within 30 days of eltrombopag discontinuation at the time of the event of interest) or past (i.e., greater than 30 days since eltrombopag discontinuation).

For both eltrombopag and antiviral treatment, information on dose, duration and discontinuation will be collected.

For the purposes of this study, exposure to eltrombopag will be defined as time on drug plus 30 days post-discontinuation. Thromboembolic events, hepatic decompensation, and other adverse events recorded during the exposure window may be assessed to be attributable to drug. Explicit attribution of these events to eltrombopag will trigger additional adverse event reporting to the Central Safety Department at GSK (refer to Section 10)

8.3.3. Other variables

The following variables will be collected at baseline:

- Demographics: Age, sex, race/ethnicity (where allowed by local regulations)
- Patient weight
- Relevant medical history (e.g., spleen status, cardiovascular disease, history of thromboembolic events, diabetes mellitus, malignancies)
- HCV risk/clinical factors: probable infection route, estimated year of infection (if available), date of first positive HCV test, HCV RNA Status, HCV genotype, IL28B polymorphism, alcohol use, smoking history, injected drug use
- Previous and current (if applicable) antiviral treatment
- Liver status
    - Clinical/histological diagnosis of cirrhosis/fibrosis
        - ▪
    - Child Pugh score
    - MELD score
    - Presence of steatosis, non-alcoholic steatohepatitis or non-alcoholic fatty liver disease
- TCP history
- Eltrombopag exposure, including any dose changes
- Concomitant therapies, including:
    - Treatment with an erythropoiesis-stimulating agent (e.g., erythropoietin, darbepoietin)
    - Treatment with a granulocyte colony stimulating factor
    - Other relevant concomitant medications
- Select recent laboratory values (if assessed as part of routine clinical practice)

During follow-up, the data collection will include:

- Patient vital status
- Updated eltrombopag exposure, including any changes
- Antiviral treatments
    - Prescribed doses and regimens
    - Planned duration of antiviral treatment
    - Antiviral exposure/duration of treatment, including any dose changes or discontinuations
    - Antiviral response (EVR, End of Treatment response, SVR)
- Reason for early discontinuation antiviral therapy (if applicable)
- Updated concomitant therapies
- Select laboratory results, if performed as part of routine clinical practice

- Occurrence of protocol-defined hepatic decompensation and thromboembolic events
- Non-serious and serious adverse drug reactions related to eltrombopag use (ADRs and SADRs)

In the event that the patient does not complete the expected 36 months of follow-up, the date and reason for early discontinuation will be collected, where available. If discontinuation was due to patient death, date and cause(s) of death will be collected.

8.4. Data sources

The anticipated data collection schedule for the study is presented in Table 1. All data elements will be collected from information routinely recorded in the medical record. No visits or examinations, laboratory tests or procedures are mandated as part of this study.

In order to characterize the investigators and sites participating in the study, the following information will also be collected:

- Investigator medical specialty (e.g., hepatology, gastroenterology, internal medicine, infectious disease, other)
- Practice type (community/office-based, academic/hospital-based)
- Practice size

In addition, where allowed by local regulation and by approved informed consent, patients will be asked to allow direct-to-patient contact and provide secondary contacts in order to collect limited information regarding the patient's status and minimize the potential for loss to follow-up.

Table 1 Data Collection Schedule

	Baseline	Follow-up every 3-6 months	End of follow-up 36 months (or early discontinuation)
		+/- 4 weeks	+/- 4 weeks
Informed consent	X		
Demography	X		
Medical history, including HCV history and previous antiviral exposure	X		
Laboratory test results (if performed)	X	X	X
Eltrombopag exposure	X	X	X
Antiviral exposure		X	X
Antiviral response		X	X
Concomitant medications	X	X	X
Outcome Assessment/Specific Endpoints (Section 8.3.1)	X	X	X
ADR/SADR reporting*	First exposure to eltrombopag ----------> X		
Reason for discontinuation (if applicable)			X

*Note: At baseline, medical records will be used to assess the occurrence of ADRs/SADRs after starting eltrombopag but prior to informed consent and study enrolment.

8.5. Study size

In this study, the primary objective is to examine the incidence of hepatic decompensation and mortality over a three year period in patients who achieved SVR during the study compared to those who did not achieve SVR. In order to address this question, the following assumptions were used to determine the study sample size:

- Enrolling 143 patients provides 80% power to detect a difference in hepatic decompensation over 3 years of follow up, assuming that 30% of patients achieve SVR, and that 11% of patients who reach SVR and 32% of patients who do not reach SVR experience hepatic decompensation; and
- Enrolling 159 patients provides 80% power to detect a difference in mortality at three years, assuming that 30% of patients achieve SVR, and that 5% of patients who reach SVR and 22% of patients who do not reach SVR die during the study.

The targeted sample size for this study is 200 patients to account for potential variance in the percentage of patients achieving SVR or experiencing hepatic decompensation, and potential for patients lost to follow-up.

The sample size assumptions were based on a study conducted by Iacobellis et al [Iacobellis, 2011] that reported data on SVR and long-term outcomes in an advanced HCV population treated with dual therapy. DiMarco et al [Di Marco, 2007] observed similar improvements in long-term outcomes in those achieving SVR.

In the Iacobellis et al (Iacobellis, 2011) study:

- 24 of 75 patients (32%) achieved SVR
- At 5 years of follow-up, 8 of 24 patients (33%) who achieved SVR experienced hepatic decompensation compared to 49 of 51 patients (96%) who did not achieve SVR
- The percentage who died at approximately 3 years of follow-up was 5% in patients who achieved SVR and 22% in those who did not achieve SVR

In order to obtain 3 year hepatic decompensation event rates, the 5 year percentage from Iacobellis et al (Iacobellis, 2011) was used and it was assumed that only a third of the events would occur in the first 3 years. Since the distribution of the event rate was unknown, it could not be assumed that events would occur linearly throughout the 5 year period, i.e., that 60% would occur in the first 3 years and 40% in the remaining 2 years. The estimate of 33% therefore is reasonable and may be an underestimate. This results in 11% of patients experiencing hepatic decompensation in patients who achieved SVR and 32% in those who did not. The survival rate at 3 years of follow-up was taken directly from the study.

The expected similarities in patient characteristics as compared to the ENABLE clinical trial populations allow reasonable estimates of the relevant clinical events. In the ENABLE clinical trials, an SVR rate of 21% was observed. Given that at least 100 patients in this study would be on triple therapy with possibly higher rates of SVR, an estimate of 30% SVR was used in the sample size and power calculation [Fontaine, 2013].

8.6. Data management

A data management plan will be created before data collection begins and will describe all functions, processes, and specifications for data collection, cleaning and validation. The electronic case report forms (eCRFs) will include programmable edits to obtain immediate feedback if data are missing, out of range, illogical or potentially erroneous. Concurrent manual data review will be performed based on parameters dictated by the plan. Ad hoc queries will be generated within the electronic data capture (EDC) system and followed up for resolution.

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

8.6.1. Timings of Assessment during Follow Up

Three interim analyses are planned in this study. These interim reports will include data lock points at 6 months, 12 months and 18 months after full enrolment in the study is complete.

8.6.2. Data handling conventions

Full details on handling of all missing data, which are common in observational studies, will be described separately in the statistical analysis plan (SAP). The proportion of missing data will be reported for each measured variable in the study. In general, missing data will not be imputed and the data will be analysed as they are recorded in the study eCRFs, unless otherwise specified in the SAP.

8.6.3. Data entry/Electronic data capture

All data will be collected and entered directly into an EDC system. All sites will be fully trained on using the on-line data capture system, including eCRF completion guidelines and help files. Sites will be responsible for entering extracted patient data into a secure internet-based EDC database via the eCRF. Investigators and site personnel will be able to access their account with a username and password. All eCRFs should be completed by designated, trained personnel or the study coordinator, as appropriate. The eCRF should be reviewed, electronically signed, and dated by the investigator. All changes or corrections to eCRFs are documented in an audit trail and an adequate explanation is required. All participating sites will have access to the data entered by the individual site on their own enrolled patients through the EDC system.

8.7. Data analysis

All AE verbatim terms will be recorded and coded using the most recent version of the Medical Dictionary for Regulatory Activities (MedDRA).

All computations and generation of tables, listings and data for figures will be performed using [redacted] version 9.2 or higher ([redacted] Institute, [redacted]

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.

This is a descriptive study conducted to inform the safety and effectiveness of eltrombopag in a real-world setting of HCV patients who are unable to initiate or maintain anti-viral treatment due to thrombocytopenia. There is no comparison of eltrombopag users to a non-user group. The primary objective includes hypothesis testing to examine the incidence of hepatic decompensation and of mortality at three years in eltrombopag users who achieve SVR during the study compared to eltrombopag users who do not achieve SVR. This addresses a question from the CHMP as to whether SVR confers long term benefit in advanced HCV patients with significant TCP who have been treated with eltrombopag in combination with interferon-based therapy.

Descriptive analyses will be performed to gain an understanding of the qualitative and quantitative nature of the data collected and the characteristics of the sample studied. Continuous variables will be reported as mean (and standard deviation) or median and range/quartiles where appropriate. Categorical variables will be summarized as number and proportion of the total study population, and by subgroups where appropriate.

Descriptive analyses will include tables and figures showing patient demographics and characteristics of study patients including medical/disease history, virology, and laboratory information, at baseline and at 6 months, 12 months, 18 months, 24 months and 36 months of follow-up. For AEs, events will be summarized by frequency and proportion of total patients, by MedDRA system organ class and preferred term. Separate summaries will be given for all ADRs, SADRs, and ADRs leading to discontinuation of eltrombopag.

Information will be presented for all patients and stratified by subgroups of interest, specifically, by modality of antiviral therapy for HCV infection [i.e., interferon and ribavirin (double therapy) or interferon, ribavirin, and DAAs (triple therapy)], by age group, by race/ethnicity and by HCV genotype, to the extent allowed by the data.

8.7.1. Essential analysis

Incidence of hepatic decompensation and mortality at 3 years, by SVR status

For the long term outcomes of hepatic decompensation or mortality at 3 years (as separate events), incidence rate ratios comparing patients who did and did not attain SVR will be calculated, along with 95% confidence intervals using the method outlined by Dobson et al [Dobson, 1991]. As a conservative approach, patients lost to follow-up prior to SVR determination will be presumed to not achieve SVR in the primary analysis. As a sensitivity analysis, rate of hepatic decompensation and mortality at 3 years will be repeated limited to those cases for which SVR status is known. 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 to determine independence of SVR as a predictor variable.

Incidence of hepatic decompensation and thromboembolic events

In addition to being summarized by frequency and proportion of total patients, Kaplan-Meier survival estimates will be calculated for 6 month, 12 month, 18 month, 24 month and 36 month observation periods for the outcomes of hepatic decompensation and thromboembolic events. Thromboembolic events will be presented as a single category as well as grouped by venous or arterial origin, and by individual events. These events will be presented overall and stratified by timing in relation to eltrombopag exposure (i.e., current exposure or past exposure). Confidence intervals (CI) for survival rates will be calculated using the method outlined by Simon et al [Simon, 1986].

Cumulative incidence rates will be calculated for the occurrence of hepatic decompensation and thromboembolic events, as separate events, over the same observation periods. The 95% CIs for cumulative incidence will be calculated using the method outlined by Newcombe et al [Newcombe 1998].

All-cause and cause-specific mortality risk and survival rates

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. CIs for survival rates will be calculated. Cumulative incidence rates will be calculated for all-cause mortality and liver-related mortality over the same observation periods and presented with 95% CIs.

Factors independently related to the risk of hepatic decompensation and the risk of thromboembolic events

Baseline factors potentially related to each event will be identified during exploratory analyses by comparing Kaplan-Meier survival estimates for patients with versus 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 these identified factors simultaneously and independent factors will be retained in a final model.

Eltrombopag utilization

Dose of eltrombopag at initiation and at various time points during treatment will be presented categorically. Duration of eltrombopag (in days) and cumulative exposure will be reported as mean, standard deviation, median, 25th and 75th quartiles, and range. The proportion of patients requiring dose changes or discontinuations will be summarized.

Antiviral exposure

The number and percentage of patients who undergo antiviral therapy will be summarized by type of antiviral therapy initiated. Within type of antiviral therapy, dose at initiation, duration of antiviral therapy and proportion of patients with dose changes and discontinuations will be presented.

Treatment effectiveness

Evaluation of treatment effectiveness will be based on the proportion of patients able to initiate interferon-based antiviral therapy, able to maintain planned interferon-based antiviral therapy and achieve SVR (and EVR). The number and percentage of patients who achieve EVR and SVR will be reported among patients at 6 (EVR only), 12 and 18 months of follow-up. The probability of attaining SVR by these time points will be presented as Kaplan-Meier estimates, along with median time to attaining SVR.Rates of early discontinuation of interferon therapy will be presented with a summary of the primary reasons for discontinuation, overall and by antiviral modality.

8.7.2. Exploratory analysis

Additional exploratory analyses may be performed and will be outlined in the SAP prior to analysis.

8.7.3. General considerations for data analyses

No comparison of eltrombopag users to a non-user group is planned. The one planned hypothesis test will examine the incidence of long term outcomes of interest (i.e., hepatic decompensation and of mortality at 3 years) in eltrombopag users who achieve SVR during the study compared to eltrombopag users who do not achieve SVR.

For those patients who are lost to follow-up, or who discontinue early, the analyses will include all data up to the point of the last data collected.

8.8. Quality control

A study monitoring plan, including for-cause monitoring, that is appropriate for the study design will be developed and implemented.

During the remote site initiation visit, the monitor will provide training on the conduct of the study to the investigator, any co-investigator(s), and all other site staff involved in the study. In order to ensure the integrity of the data, sites will be monitored remotely using a quality risk-based approach. Site monitoring will be performed by Quintiles Outcome to examine compliance with the protocol and adherence to the data collection procedures, to assess the accuracy and completeness of submitted clinical data, and to verify that records and documents are being properly maintained for the duration of the study. Triggers for additional risk-based, on-site monitoring visits will be detailed in the study monitoring plan. The monitor will close out each site remotely after the last patient's final follow-up assessment is completed, all data have been entered and all outstanding monitoring issues have been resolved or addressed.

Representatives of the study sponsor's quality assurance/monitoring team and competent regulatory authorities must be permitted to inspect all study-related documents and other materials at the site, including the Investigator Site File, the completed eCRFs and the patients' original medical records. Audits may be conducted at any time during or after the study to ensure the validity and integrity of the study data.

8.9. Strengths and limitations of the research methods

While clinical trials provide crucial information regarding the efficacy and safety of the drug, observational data can extend and augment what is known, including identifying optimal regimens and optimal therapies for special populations of patients (e.g., elderly patients, poor risk patients) who are unlikely to be adequately represented in clinical trials. This study is designed to gather important safety and effectiveness data in HCV patients, some of which have not been studied as part of clinical development.

A key challenge in the treatment of HCV patients, and particularly advanced HCV patients, is determining which patients are likely to benefit from (and tolerate) the available antiviral therapy regimens. Since the safety and efficacy of eltrombopag use in thrombocytopenic HCV patients has not been evaluated in combination with commercially-available DAAs (e.g., boceprevir or telaprevir containing regimens), which are commonly used to treat HCV, this study will provide important data to inform routine clinical practice decisions. In addition, by following patients long-term, the study is

designed to explore whether achievement of SVR subsequently confers long-term benefit in advanced HCV patients with significant TCP who have been treated with eltrombopag in combination with interferon-based therapy. These data should meaningfully contribute to better understanding whether the objective endpoint of SVR is associated with prevention (or delay) of progression to decompensated liver disease and, ultimately, liver disease-related mortality.

Due to the observational nature of the study, there are no protocol-mandated procedures or patient monitoring. As a result, asymptomatic events of portal vein thrombosis and deep vein thrombosis may be missed unless the treating physician routinely performs diagnostic Doppler imaging; therefore, the rates of reported embolic events may be lower than what was observed in the clinical trial but representative of rates seen in a routine care setting.

The study design is predicated on the current treatment practices for HCV, which include either interferon-based double or triple antiviral therapy. Interferon-free antiviral regimens, including novel protease inhibitors and nucleoside polymerase inhibitors, were recently approved in [redacted] and are expected to be commercially available in in the regions in which this study is conducted during study enrollment. Depending on the availability and uptake of these agents, availability of eligible patients for this study may be affected.

The assumptions around rates of SVR in the study are partially based on results seen in controlled clinical trials. Due to the observational nature of the study and the potential differences in the patient populations, these assumptions may over-estimate the rate of SVR. In addition, a small proportion of patients enrolled in the study may not be responders to eltrombopag, and therefore discontinue eltrombopag prior to interferon-based antiviral therapy for HCV.

Cirrhotic HCV patients are a challenging population to study. Long term monitoring of patients for whom the treatments of interest (eltrombopag and antiviral therapy) may not be continued throughout follow-up may increase the risk of loss to follow-up and missing key data (e.g., SVR, occurrence of hepatic decompensation). Loss to follow-up in this study may be associated with treatment or the outcomes of interest, or both, which may introduce bias into some of the planned survival-based analyses. In order to mitigate this risk, direct to patient contact (where allowed by local regulations and specific informed consent is provided) will be utilized in the event the patient is not seen for routine care within expected timeframes to garner limited information regarding the patient's status.

8.9.1. Study closure/uninterpretability of results

The study can be terminated at any time for any reason by GSK. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. The investigator will be responsible for informing IECs of the early termination of the study.

8.10. Other aspects

None.

9. PROTECTION OF HUMAN SUBJECTS

9.1. Ethical approval and subject consent

To ensure the quality and integrity of research, this study will be conducted consistent with the Guidelines for Good Pharmacoepidemiology Practices (GPP) issued by the International Society for Pharmacoepidemiology (ISPE) [ISPE, 2008], the Good Pharmacovigilance Practices (GVP) issued by the EMA [EMA, 2012] the Declaration of Helsinki and its amendments [Declaration of Helsinki, 2008], and any applicable national guidelines.

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

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

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

9.2. Patient confidentiality

In order to maintain patient confidentiality, each patient will be assigned a unique patient identifier upon study enrolment. This patient identifier will be used in place of patient name for the purpose of data analysis and reporting. Medical record number or other local reference identifiers are not collected as part of the database. All parties will ensure protection of patient personal data and will not include patient names on any study forms, reports, publications, or in any other disclosures, except where required by law. In accordance with local regulations in each of the study countries, patients will be informed about data handling procedures and asked for their consent. Data protection and privacy regulations will be observed in capturing, forwarding, processing, and storing patient data. Every effort will be made to protect participant confidentiality according to the Directive 95/46/EC on the protection of individuals, and in compliance with Safe Harbor privacy principles [Directive 95/46EC 1995; U.S. Department of Commerce, 2000].

The database will be housed at Quintiles Outcome in a physically and logically secure computer system maintained by Quintiles Outcome in accordance with a written security policy. The system meets approved established standards for the security of health information and is validated. The system also meets the standards of the International Conference on Harmonisation (ICH) guideline E6R1 regarding electronic study data handling and is available for audit upon request. Patient confidentiality will be strictly maintained.

10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

If, during the study, an AE (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 reported by the site to GSK Global Clinical Safety and Pharmacovigilance within 24 hours of becoming aware of the information.

Region	Reportable events	Timing	Contact
[redacted]	AEs/SAEs attributable to eltrombopag (or any other GSK product)	Within 24 hours of becoming aware	[redacted]
Rest of World	AEs/SAEs attributable to eltrombopag (or any other GSK product)	Within 24 hours of becoming aware	[redacted]

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

GSK will provide information on relevant AEs to the regulatory authorities, as needed, according to EMA's Guideline on Good Pharmacovigilance Practices (GVP) Module VI and other applicable local regulations.

11. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

11.1. Target Audience

The study is being conducted as a PASS and is intended to provide GSK, regulatory authorities and other stakeholders with important additional information regarding the safety and effectiveness of eltrombopag. The study design, interim results and final results will be posted on the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) register. The results will be submitted to the regulatory authorities. The protocol and final results will be posted on the GSK's Clinical Trial registry and will contribute to the published literature.

11.2. Study reporting and publications

Interim reports will be generated using datalock points at 6 months, 12 months and 18 months after the first patient is enrolled and sent to regulatory agencies. A final study report will be generated after all data collection is complete and will be submitted to the competent authority(ies) within 12 months of the end of data collection.

Any publication of the results from this study will be consistent with GSK's publication policy and guided by the Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication of the International Committee of Medical Journal Editors [ICMJE, 2010]. The rights of the individual investigator and of GSK with regard to publication of the results of this study are described in the investigator contract.

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ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

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

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)	☒	☐	☐	2, 10, 15
1.1.2 The objectives of the study?	☒	☐	☐	2, 10, 16, 17
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)	☒	☐	☐	10, 18, 19
1.2.2 Which formal hypothesis(-es) is (are) to be tested?	☒	☐	☐	25, 26
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?	☒	☐	☐	17, 18
2.2 Is the planned study population defined in terms of:				
2.2.1 Study time period?	☒	☐	☐	18
2.2.2 Age and sex?	☒	☐	☐	19
	☒	☐	☐	17

Section 2: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
2.2.3 Country of origin?	☒	☐	☐	17
2.2.4 Disease/indication?	☒	☐	☐	17, 18
2.2.5 Co-morbidity?	☐	☐	☒	
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)	☒	☐	☐	18

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?	☒	☐	☐	11, 12, 18, 19, 20
3.2 Is the study design described? (e.g. cohort, case-control, randomised controlled trial, new or alternative design)	☒	☐	☐	11, 17, 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)	☒	☐	☐	25-27
3.4 Is sample size considered?	☒	☐	☐	22-24
3.5 Is statistical power calculated?	☒	☐	☐	23

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)	☒	☐	☐	22
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)	☒	☐	☐	22
4.1.3 Covariates?	☒	☐	☐	22
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)	☒	☐	☐	20-21
4.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	19-20
4.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☒	☐	☐	21
4.3 Is the coding system described for:				
4.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10)	☐	☐	☒	
4.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory Activities(MedDRA) for adverse events)	☒	☐	☐	24
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)	☒	☐	☐	20
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)	☒	☐	☐	20
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?	☒	☐	☐	19-20
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? 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)	☒ ☐	☐ ☐	☐ ☒	28-29
7.2 Does the protocol address known confounders? (e.g. collection of data on known confounders, methods of controlling for known confounders)	☒	☐	☐	20, 28-29
7.3 Does the protocol address known effect modifiers? (e.g. collection of data on known effect modifiers, anticipated direction of effect)	☒	☐	☐	20, 28-29
7.4 Does the protocol address other limitations?	☒	☐	☐	28-29

Comments:

Section 8: Analysis plan	**Yes**	**No**	**N/A**	**Page Number(s)**
8.1 Does the plan include measurement of absolute effects?	☒	☐	☐	26
8.2 Is the choice of statistical techniques described?	☒	☐	☐	25-27
8.3 Are descriptive analyses included?	☒	☐	☐	25-27
8.4 Are stratified analyses included?	☒	☐	☐	25-27
8.5 Does the plan describe the methods for identifying:				
8.5.1 Confounders?	☒	☐	☐	25-27
8.5.2 Effect modifiers?	☒	☐	☐	25-27
8.6 Does the plan describe how the analysis will address:				
8.6.1 Confounding?	☒	☐	☐	25
8.6.2 Effect modification?	☒	☐	☐	25

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)	☒	☐	☐	24, 31
9.2 Are methods of quality assurance described?	☒	☐	☐	24, 28
9.3 Does the protocol describe quality issues related to the data source(s)?	☒	☐	☐	24, 28

Section 9: Quality assurance, feasibility and reporting	**Yes**	**No**	**N/A**	**Page Number(s)**
9.4 Does the protocol discuss study feasibility? (e.g. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	28-29
9.5 Does the protocol specify timelines for				
9.5.1 Start of data collection?	☒	☐	☐	13, 14, 17
9.5.2 Any progress report?	☒	☐	☐	13, 14, 17
9.5.3 End of data collection?	☒	☐	☐	13, 14, 17
9.5.4 Reporting? (i.e. interim reports, final study report)	☒	☐	☐	13, 14, 17, 31
9.6 Does the protocol include a section to document future amendments and deviations?	☒	☐	☐	13
9.7 Are communication methods to disseminate results described?	☒	☐	☐	31
9.8 Is there a system in place for independent review of study results?	☒	☐	☐	31

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?	☒	☐	☐	30
10.2 Has any outcome of an ethical review procedure been addressed?	☒	☐	☐	30
10.3 Have data protection requirements been described?	☒	☐	☐	30, 31

Comments:

Name of main author of study protocol: [redacted]

Date: / /

Signature: _____

Appendix 2 – Sample case report form(s)

Document	Version	Effective date
Sample Case Report Form	Version 4.2	23 Aug 2016

GlaxoSmithKline

Worldwide Epidemiology

Study Protocol

PLATELET:HCV - A global, prospective cohort study to evaluate the 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

WEUSKOP7136

Version Final 4.2
Case Report Forms
23Aug2016

QUINTILES

GlaxoSmithKline
Worldwide Epidemiology
Study
Protocol

CRF Revision History

Document Version	Version Date	Author	Description of Changes
1.0	06Aug2014	[redacted]	Initial version
2.0	2.0 11 Nov 2014	[redacted]	Page 1: Inclusion Criterion text has changed according to the Inclusion criterion text in Protocol Final Version 1 dated 16 Jul2014. Page 3 : Date of Birth has been changed to Birth Year to collect only year of birth. Inch option added for Height. Race is multi select. Page 4 : Vascular disease changed to Vascular disease(s) in label and updated as multi select. Thromboembolic events updated as multi select. Page 5:For coagulopathies/bleeding disorders thrombocytopenia has been added.

			For Coagulopathies/bleeding disorders spelling of Vitamin K deficiency. Autoimmune disease changed to Autoimmune disease(s). Page 7 : Probable mode of transmission changed to Probable mode(s) of transmission and made as multi select. Page 8 : For all the 3 questions 'have they used alcohol/nicotine/ injected drugs' changed to ' has he/she used alcohol/nicotine/ injected drugs'. Drinks have not been changed to number of glasses. Page 10 : Date of recent MELD assessment changed to Date of most recent MELD assessment. Creatinine changed to Serum creatinine. Page 12 : Changed the Instruction as 'Most recent results prior to start of eltrombopag' . Page 13 : Changed Neutrophils to Absolute Neutrophil Count (ANC) and removed % option. Added 'Not available' option for all lab values. Page14 : Agents have been separated into 3 groups Interferon, Ribavirin and DAA.

			'Ongoing 'option added and Interferon stop date changed to Stop date. Changed reason to reason(s) and multi select . Removed Cardiovascular compromise option from list of reasons of early discontinuation of Interferon therapy. Separated Unknown from the list of reasons of early discontinuation of Interferon therapy. Page15 : 'Ongoing' options added. Options to select early discontinuation of Ribavirin added. Page16 : More reasons for Early discontinuation of DAA have been updated. 'Ongoing' options added. Separated 'Unknown' from the list of reasons of early discontinuation of DAA . Page19 : Changed question as 'Is the patient currently being treated with antiviral therapy for HCV (including those whose therapy has been temporarily interrupted)?' and instruction changed to accommodate Ribavirin also. Added question 'Has a pregnancy occurred to you or experienced by your partner since the start of eltrombopag?'

			Added reminder If yes, complete site 'Pregnancy Initial Notification Form' for yourself or for your partner (This is a separate form not included in the CRF). Pages20,27,28,29,30,32 : Readjusted the wording to address "SAE CRF" completion or "AE or SAE CRF as appropriate" . Page20 : The label changed to Outcomes of Interest Checklist. Page21 : Pregnancy : Changed question as 'Has a pregnancy occurred to you or experienced by your partner since the start of eltrombopag?' Changed reminder If yes, complete site 'Pregnancy Initial Notification Form' for yourself or for your partner (This is a separate form not included in the CRF) Added 2 more questions if pregnancy was reported and for confirmation if follow up Form was completed. Added radio button to answer as Yes or No. Page23 : Added Current Antiviral treatment Form . Page24 : Added Lab Form. Pages27-34 : Changed to one time form with repeated group. Pages27,28,29,30 : Added Note to Complete the AE Form as a

			reminder for Interferon treatment change and discontinuation. Pages27,28 : Changed primary reason to reason(s) and multi select for both treatment change and Early discontinuation. Added Unknown as separate option. Page28 : Removed Cardiovascular compromise option from list of reasons of early discontinuation of Interferon therapy. Page29 : Reasons for treatment change of Ribavirin has been made as multi select and unknown is added as separate option. Unit added after the Ribavirin dose. Page30 : Removed Thrombocytopenia and Neutropenia from list of responses. Page32 : Changed primary reason to reason(s) and multi select for both treatment change and Early discontinuation. Added Unknown as separate option . Removed Cardiovascular compromise option from list of reasons

			of early discontinuation of DAA. Patient compliance and Tolerability added in the reasons for discontinuation. Page34 : Added Current weight field and also added not applicable. From reason considered serious as `Other (specify)', `specify' has been removed as `if yes, please specify' is already present in next row. Page38 : Added Current weight field. Page42 : Changed End of study form from repeated form to one time form. Updated reminder to update SAE/AE CRF .
3.0	21 Nov2014	[redacted]	Baseline: Demographics. Add hyphen to Asian-Central, Asian-East Asian, Asian-Southeast On all forms: For all multi select “Please select all that apply” in parentheses added. Baseline forms, Previous antiviral treatments and all log forms and AE/ SAE label changed to “to select more than one, you may repeat additional entries at the bottom of this form” throughout sections with repeat forms . In the pregnancy section of the Follow Up form and eltrombopag

			exposure : “ please confirm if Pregnancy Follow Up Notification Form has been completed for yourself or your partner" changed to “complete for the patient or on behalf of the patient's partner”. Page 25:Antiviral response log form changed to repeat group. Date of visit, date when EVR, end of treatment response and SVR achieved.
4.2	23Aug2016	[redacted]	Age field added to the demography page

Baseline

Baseline **Patient ID:** **Created:** 11-Nov-2016 10:14:49 **Last Updated:** 11-Nov-2016 10:14:49
Active element groups: Element Group 5001

Legend: Clear Selection Show Warnings Show History

[+] Errors

INCLUSION/EXCLUSION CRITERIA | DEMOGRAPHICS | MEDICAL HISTORY | HCV | CURRENT LIVER STATUS | TCP | LABS | ANTIVIRAL TREATMENTS - PREVIOUS | ANTIVIRAL TREATMENTS - PLANNED | ANTIVIRAL TREATMENTS - CURRENT | TREATMENT EXPOSURE

INCLUSION/EXCLUSION CRITERIA

Date of Visit: DD MMM YYYY

Date of informed consent: DD MMM YYYY

INCLUSION CRITERIA

1. Age ≥ 18 years at enrollment: Yes No

2. Diagnosis of HCV verified by the presence of detectable HCV RNA: Yes No

3. Initiation of first-time treatment with eltrombopag no more than 3 months prior to study enrollment: Yes No

4. Patient was unable to initiate or maintain or restart optimal interferon-based therapy due to thrombocytopenia prior to initiating eltrombopag: Yes No

5. Patient currently undergoing interferon-based antiviral therapy or initiation or restart of interferon-based antiviral therapy planned: Yes No

6. Patient (or appropriate representative) willing and able to provide written informed consent: Yes No

EXCLUSION CRITERIA

1. Current participation in any interventional clinical trial in which treatment regimen and/or monitoring is dictated by a protocol:

Baseline

Yes No

DEMOGRAPHICS & CHARACTERISTICS

Birth Year:

DD MMM YYYY

Age:

Sex:

Male
Female

Race/Geographical ancestry:
(Please select all that apply)

African American/African Heritage
American Indian or Alaskan Native
Asian-Central/South Asian Heritage
Asian-East Asian Heritage
Asian-Japanese Heritage
Asian-Southeast Asian Heritage
Native Hawaiian or Other Pacific Islander
White Arabic/North African Heritage
White/Caucasian/European Heritage
Other, please specify

Not provided

Ethnicity:

Hispanic/Latino
Not Hispanic/Latino
Not provided

Weight:

Kg Pounds

Height :

cm Inch

Baseline

RELEVANT MEDICAL HISTORY

Does the patient have a history of any of the following conditions?

HIV: ○ Yes ○ No

Chronic Hepatitis B infection (current): ○ Yes ○ No

Hepatitis A: ○ Yes ○ No

Portal Hypertension: ○ Yes ○ No

Esophageal varices with bleeding: ○ Yes ○ No

Esophageal varices without bleeding: ○ Yes ○ No

Malignancy (any) or myelodysplastic syndrome: ○ Yes ○ No

Diabetes: ○ Yes ○ No

Vascular disease(s): ○ Yes ○ No

If yes, please specify:
(Please select all that apply)

- ☐ Ischemic heart disease
- ☐ Atherosclerosis
- ☐ Peripheral arterial disease
- ☐ Hypertension
- ☐ Other, please specify

☐ Unknown

Baseline

Thromboembolic events: ○ Yes ○ No

If yes, please specify:
(Please select all that apply)

- ☐ Acute myocardial infarction
- ☐ Acute coronary syndrome
- ☐ Ischemic stroke
- ☐ Portal vein thrombosis
- ☐ Deep vein thrombosis
- ☐ Pulmonary embolism
- ☐ Other, arterial thromboembolism, please specify
- ☐ Other, venous thromboembolism, please specify

Did Thromboembolic event/s occur recently (within last 6 months)? ○ Yes ○ No ○ Unknown

Chronic Obstructive Pulmonary Disease (COPD): ○ Yes ○ No

Coagulopathies/bleeding disorders: ○ Yes ○ No

If yes, please specify:
(Please select all that apply)

- ☐ Thrombocytopenia
- ☐ Vitamin K deficiency
- ☐ Platelet dysfunction
- ☐ Antiphospholipid syndrome
- ☐ Thrombotic thrombocytopenic purpura (TTP)
- ☐ Immune thrombocytopenic purpura (ITP)
- ☐ Factor V Leiden deficiency
- ☐ Protein C deficiency
- ☐ Protein S deficiency
- ☐ Protein Z deficiency
- ☐ Antithrombin deficiency
- ☐ Hyperhomocystenemia/MTHFR
- ☐ Disseminated intravascular coagulation
- ☐ Other, please

Baseline

specify

Heparin-induced thrombocytopenia: ○ Yes ○ No

Hemolytic uremic syndrome: ○ Yes ○ No

Partial or total splenectomy: ○ Yes ○ No

Autoimmune disease(s): ○ Yes ○ No

If yes, please specify:
(Please select all that apply)

- ☐ Rheumatoid arthritis
- ☐ SLE
- ☐ Psoriasis
- ☐ Thyroiditis
- ☐ Other, please specify

Chronic renal insufficiency or renal failure: ○ Yes ○ No

Thyroid disorder: ○ Yes ○ No

Drug/alcohol dependency: ○ Yes ○ No

Major depressive disorder/other major psychiatric disorder (e.g. schizophrenia, bipolar): ○ Yes ○ No

Other relevant medical history:

○ Yes

○ No

To select more than one, you may repeat additional entries at the bottom of this form.

Baseline

If yes, please specify:

Done Delete Entry

Create Next Entry

HCV RISK/CLINICAL FACTORS

Date of first positive HCV test:

DD-MMM-YYYY

DD MMM YYYY

Probable mode(s) of transmission:
(Please select all that apply)

- ☐ Blood transfusion
- ☐ Organ and/or tissue transplantation
- ☐ Sexual contact
- ☐ Tattoos/piercings
- ☐ Intranasal drug use
- ☐ Injection drug use
- ☐ Unspecified drug use
- ☐ Unsafe medical practice (e.g. hospital worker)
- ☐ Other, please specify

☐ Unknown

HCV genotype:
(Please select all that apply)

- ☐ 1
- ☐ 1a
- ☐ 1b
- ☐ 2
- ☐ 3
- ☐ 4
- ☐ 5
- ☐ 6

Baseline

☐ Unknown

IL28B polymorphism (rs 12979860):
(Please select all that apply)

☐ CC
☐ CT
☐ TT
☐ Unknown

Does the patient currently drink/use alcohol or has he/she used alcohol in the last 30 days?

◯ Yes
◯ No
◯ Unknown

If Yes, Average number of drinks consumed per day in the last 30 days:

◯ 1-2
◯ 3-4
◯ >4
◯ Unknown

Does the patient currently use nicotine products (including tobacco) or has he/she used nicotine products in the last 30 days?

◯ Yes
◯ No
◯ Unknown

Does the patient currently use injected drugs or has he/she used injected drugs in the last 30 days?

◯ Yes
◯ No
◯ Unknown

CURRENT LIVER STATUS

Liver staging (biopsy or non-invasive assessment):

◯ Cirrhosis (e.g. F4, Ishak 5 or 6)
◯ Bridging fibrosis (e.g. F3, Ishak 4)
◯ Other stage of fibrosis (e.g. F1or F2, Ishak 1,2 or 3)

Baseline

○ No evidence of fibrosis (e.g. F0, Ishak 0)

Is a recent Child-Pugh evaluation available?

○ Yes
○ No

Date of most recent Child-Pugh evaluation:

DD-MMM-YYYY
DD - MMM - YYYY

a. Encephalopathy grade:

○ None
○ 1 or 2
○ 3 or 4
○ Not reported

b. Ascites:

○ Absent
○ Slight/medication-controlled
○ Refractory
○ Not reported

c. Total serum bilirubin: ○ mg/dL ○ Umol/L
☐ Unknown

d. Serum albumin: ○ g/dL ○ g/L
☐ Unknown

e. INR:
☐ Unknown

If INR not available please provide prothrombin time (PT): ○ seconds ○ %
☐ Unknown

Baseline

NOTE: Only complete the Child Pugh category and score if any of the Child Pugh components (prior responses a-e) are missing.

Child-Pugh Category:

- ○ A
- ○ B
- ○ C
- ○ Not reported

Child-Pugh Score:

☐ Unknown

MELD assessment

Is MELD assessment available?

- ○ Yes
- ○ No

Date of most recent MELD assessment:

DD-MMM-YYYY (DD / MMM / YYYY)

Model for End Stage Liver Disease (MELD) score:

☐ Unknown

a. INR:

☐ Unknown

b. Bilirubin:

○ mg/dL ○ umol/L

☐ Unknown

c. Serum creatinine:

○ umol/L ○ mg/dL

☐ Unknown

Presence of steatosis:

- ○ Yes
- ○ No
- Unknown

Baseline

Presence of non-alcoholic fatty liver disease:

- Yes
- No
- Unknown

Presence of non-alcoholic steatohepatitis (NASH):

- Yes
- No
- Unknown

THROMBOCYTOPENIA (TCP) HISTORY

Please enter the 3 most recent platelet counts

Platelet count 1 (If available): 10^9/L /mm^3

Unknown

Test date: DD-MMM-YYYY (DD MMM YYYY)

Platelet count 2 (If available): 10^9/L /mm^3

Unknown

Test date: DD-MMM-YYYY (DD MMM YYYY)

Platelet count 3 (If available): 10^9/L /mm^3

Unknown

Test date:

Baseline

DD-MMM-YYYY
DD MMM YYYY

OTHER RELEVANT RECENT LABORATORY TESTING

Most recent results prior to start of eltrombopag

Hemoglobin: ◯ g/dL ◯ mmol/L

Test date: DD-MMM-YYYY (DD MMM YYYY)

☐ Not available

Hematocrit: %

Test date: DD-MMM-YYYY (DD MMM YYYY)

☐ Not available

Absolute Neutrophils count (ANC): ◯ cells /µL ◯ /mm^3

Test date: DD-MMM-YYYY (DD MMM YYYY)

☐ Not available

ALT: U/L

Test date: DD-MMM-YYYY (DD MMM YYYY)

Baseline

DD YYYY

☐ Not available

AST: U/L

Test date:

DD-MMM-YYYY
DD MMM YYYY

☐ Not available

Serum albumin: ○ g/dL ○ g/L

Test date:

DD-MMM-YYYY
DD MMM YYYY

☐ Not available

Bilirubin: ○ µmol/L ○ mg/dL

Test date:

DD-MMM-YYYY
DD MMM YYYY

☐ Not available

PREVIOUS ANTIVIRAL TREATMENTS

Has the patient been previously treated with antivirals for HCV?

○ Yes
○ No
○ Unknown

If yes, select all agents that apply below

To select more than one, you may repeat additional entries at the bottom of this form.

Baseline

Interferon: [redacted] <1>

Other, please specify

Start date: ☐ Ongoing

DD-MMM-YYYY
DD MMM YYYY

Stop date:

DD-MMM-YYYY
DD MMM YYYY

Treatment outcome:

- ○ Null response
- ○ Relapse
- ○ Unknown

Early discontinuation of interferon therapy: *If yes, specify reason below*

- ○ Yes
- ○ No
- ○ Unknown

If yes, specify reason(s):
(Please select all that apply)

- ☐ Thrombocytopenia
- ☐ Anemia
- ☐ Neutropenia
- ☐ Patient choice
- ☐ Availability of interferon-free regimen
- ☐ Patient lost to follow-up
- ☐ Substance abuse
- ☐ Psychiatric issues
- ☐ Non-hematological toxicity
- ☐ Other, please specify
- ☐ Unknown

Ribavirin:

- ○ Yes

Baseline

○ No

Start date: ☐ Ongoing

DD-MMM-YYYY
DD MMM YYYY

Stop date:

DD-MMM-YYYY
DD MMM YYYY

Treatment outcome:

○ Null response
○ Relapse
○ Unknown

Early discontinuation of ribavirin therapy:

○ Yes
○ No
○ Unknown

If yes, specify reason(s):
(Please select all that apply)

☐ Anemia
☐ Patient choice
☐ Patient lost to follow-up
☐ Substance abuse
☐ Psychiatric issues
☐ Non-hematological toxicity
☐ Cardiovascular compromise
☐ Other, please specify

☐ Unknown

DAA: <2>

Other, please specify

Start date: ☐ Ongoing

DD-MMM-YYYY
DD MMM YYYY

Baseline

Stop date:

DD-MMM-YYYY

DD MMM YYYY

Treatment outcome:

- Null response
- Relapse
- Unknown

Early discontinuation of direct - acting antiviral:

If yes, specify reason below

- Yes
- No
- Not applicable
- Unknown

If yes, specify reason(s):
(Please select all that apply)

- Thrombocytopenia
- Anemia
- Neutropenia
- Patient choice
- Patient lost to follow-up
- Substance abuse
- Psychiatric issues
- Non-hematological toxicity
- Patient compliance
- Tolerability
- Other, please specify
- Unknown

Done Delete Entry

Create Next Entry

PLANNED ANTIVIRAL TREATMENTS

Planned duration of interferon-based antiviral treatment for

Baseline

HCV:

- 12 weeks
- 24 weeks
- 48 weeks
- 72 weeks
- Other

CURRENT ANTIVIRAL TREATMENTS

Is the patient currently being treated with antiviral therapy for HCV (including those whose therapy has been temporarily interrupted)?

- Yes
- No

If Yes, complete the Ribavirin and/or DAA and/or Interferon logs as applicable, with a new or changed regimen.

If patient's antiviral response is available (i.e. EVR, End of treatment response or SVR), please enter in the Antiviral Response Log.

TREATMENT EXPOSURE - Eltrombopag and Concomitant Medications

Is the patient currently being treated with eltrombopag?

- Yes
- No (not yet initiated)

If yes, complete Eltrombopag Treatment log

Has a pregnancy occurred to the patient or experienced by the patient's partner since the start of eltrombopag?

- Yes
- No
- Unknown

If yes, complete site 'Pregnancy Initial Notification Form' for patient or on behalf of the patient's partner (This is a separate form not included in the CRF)

Is the patient currently being treated with any concomitant medications?

- Yes
- No

If yes, complete the Concomitant Medication log

Baseline

TCP | LABS | ANTIVIRAL TREATMENTS - PREVIOUS | ANTIVIRAL TREATMENTS - PLANNED | ANTIVIRAL TREATMENTS - CURRENT | TREATMENT EXPOSURE

Please indicate the current status of the form: ○ Complete ○ Incomplete

Selection Options for Baseline

<1> - Agent, Interferon
Peginterferon alfa-2a ([redacted])
Peginterferon alfa-2b ([redacted])
Standard interferon alfa-2a (e.g., Roferon A)
Standard interferon alfa-2b (e.g., Intron A)
Consensus interferon (Infergen)
Other, please specify
None

<2> - Agent DAA
Telaprevir (Incivek)
Boceprevir (Victrelis)
Simeprevir (Olysio)
Sofosbuvir (Sovaldi)
Other, please specify
None

Follow-up

Follow-up **Patient ID:** **Created:** 11-Nov-2016 10:14:55 **Last Updated:** 11-Nov-2016 10:14:55
Active element groups: Element Group 5002

Legend: Clear Selection Show Warnings Show History

[+] Errors

OUTCOMES OF INTEREST CHECKLIST | PREGNANCY | TREATMENT EXPOSURE | ANTIVIRAL TREATMENTS - CURRENT | LABS

OUTCOMES OF INTEREST CHECKLIST

Date of Visit: DD - MMM - YYYY

To your knowledge, has the patient experienced any of the following events since last data collection?

If yes, please complete the SAE CRF

- Yes
- No
- Unknown

Thromboembolic events including:

a) Acute myocardial infarction

b) Acute coronary syndrome

c) Ischemic stroke

d) Portal vein thrombosis

e) Deep vein thrombosis

f) Pulmonary embolism

g) Other arterial thromboembolic events

h) Other venous thromboembolism events

Events related to hepatic decompensation:

a) Ascites

b) Hepatic encephalopathy

c) Variceal hemorrhage

d) Spontaneous bacterial peritonitis

Death

Since the last data collection, has the patient experienced any non-serious or serious adverse drug reactions (i.e. an AE related to eltrombopag or any other GSK product)?

If yes, please complete the AE or SAE CRF as appropriate

- Yes
- No
- Unknown

Follow-up

PREGNANCY

Since the last data collection, has a pregnancy occurred to the patient or experienced by the patient's partner since the start of eltrombopag?

- ○ Yes
- ○ No
- ○ Unknown

If yes, complete site 'Pregnancy Initial Notification Form' for the patient or on behalf of the patient's partner (This is a separate form not included in the CRF)

Has pregnancy been reported previously?

- ○ Yes
- ○ No

Please confirm if Pregnancy Follow Up Notification Form has been completed for the patient or on behalf of the patient's partner:
(This is a separate form not included in the CRF)

- ○ Yes
- ○ No

TREATMENT EXPOSURE - Eltrombopag and Concomitant Medications

Have there been any changes to the patient's eltrombopag treatment?

- ○ Yes
- ○ No

If yes, complete Eltrombopag Treatment log

Have there been any changes to the patient's concomitant medications?

- ○ Yes
- ○ No

If yes, complete the Concomitant Medication log

CURRENT ANTIVIRAL TREATMENTS

Is the patient currently being treated with antiviral therapy for HCV (including those whose therapy has been temporarily interrupted)?

○ Yes ○ No

If Yes, complete the Ribavarin and/or DAA and/or Interferon logs as applicable, with a new or changed regimen.

Follow-up

If patient's antiviral response is available (i.e. EVR, End of treatment response or SVR), please enter in the Antiviral Response Log.

LABS

Platelet count: ◯ 10^9/L ◯ /mm^3

Test date: DD-MMM-YYYY (DD MMM YYYY)

☐ Unknown

Hemoglobin: ◯ g/dL ◯ mmol/L

Test date: DD-MMM-YYYY (DD MMM YYYY)

☐ Not available

Hematocrit: %

Test date: DD-MMM-YYYY (DD MMM YYYY)

☐ Not available

Absolute Neutrophils count : ◯ cells /µL ◯ /mm^3

Test date: DD-MMM-YYYY (DD MMM YYYY)

☐ Not available

Follow-up

ALT : (U/L)

Test date: DD-MMM-YYYY (DD MMM YYYY)

Not available

AST : (U/L)

Test date: DD-MMM-YYYY (DD MMM YYYY)

Not available

Serum albumin: g/dL g/L

Test date: DD-MMM-YYYY (DD MMM YYYY)

Not available

Bilirubin: µmol/L mg/dL

Test date: DD-MMM-YYYY (DD MMM YYYY)

Not available

OUTCOMES OF INTEREST CHECKLIST | PREGNANCY | TREATMENT EXPOSURE | ANTIVIRAL TREATMENTS - CURRENT | LABS

Follow-up

Please indicate the current status of the form: ○ Complete ○ Incomplete

Selection Options for Follow-up

Log forms

Log forms **Patient ID:** **Created:** 11-Nov-2016 10:14:57 **Last Updated:** 11-Nov-2016 10:14:57
Active element groups: Element Group 5003

Legend: Clear Selection Show Warnings Show History

[+] Errors

LOGS - ANTIVIRAL RESPONSE | LOGS - INTERFERON | LOGS - RIBAVIRIN | LOGS - DAA
LOGS - ELTROMBOPAG EXPOSURE | LOGS - CONCOMITANT MEDICATION

ANTIVIRAL RESPONSE LOG

To select more than one, you may repeat additional entries at the bottom of this form.

Date of Visit: DD MMM YYYY

Did the patient achieve early viral response (EVR), defined as a clinically significant reduction in HCV RNA (≥ 2 $\log_{10}$ drop or undetectable) after 12 weeks of antiviral?

- ○ Yes
- ○ No
- ○ Unknown
- ○ Not applicable (< =12 weeks of treatment)

If yes, please provide the date when patient achieved early viral response (EVR): DD MMM YYYY

Did the patient achieve End of Treatment response?

- ○ Yes
- ○ No
- ○ Unknown
- ○ Not applicable (treatment ongoing)

If yes, please provide the date when patient achieved End of Treatment response: DD MMM YYYY

Did the patient achieve sustained viral response (SVR), defined as HCV RVA negative 24 weeks after cessation of antiviral treatment?

- ○ Yes

Log forms

○ No
○ Unknown
○ Not applicable (< 24 weeks after cessation of treatment)

If yes, please provide the date when patient achieved sustained viral response (SVR):

DD - MMM - YYYY

Done | Delete Entry

Create Next Entry

INTERFERON LOG

To select more than one, you may repeat additional entries at the bottom of this form.

Medication name:

○ Peginterferon alfa-2a ([redacted])
○ Peginterferon alfa-2b ([redacted])
○ Standard interferon alfa-2a (e.g., Roferon A)
○ Standard interferon alfa-2b (e.g., Intron A)
○ Consensus interferon (Infergen)
○ Other, please specify

Dose:

Units:

○ mg
○ mcg
○ mcg/kg
○ million IU

Regimen:

○ Three times a week
○ Once weekly
○ Other, please specify

Log forms

Start date: ☐ Ongoing

DD-MMM-YYYY
DD MMM YYYY

Stop date:

DD-MMM-YYYY
DD MMM YYYY

Treatment change?

- ○ None
- ○ Permanently discontinued
- ○ Temporarily discontinued
- ○ Dose change

If treatment change, reason(s) for treatment change:
(Please select all that apply)

Please complete the AE or SAE CRF as appropriate

- ☐ Thrombocytopenia
- ☐ Anemia
- ☐ Neutropenia
- ☐ Other, please specify
- ☐ Unknown

If permanently discontinued, planned duration of therapy completed?

If no, please complete reason(s) below

- ○ Yes
- ○ No
- ○ Unknown

If no, reason(s) for early discontinuation:
(Please select all that apply)

Please complete the AE or SAE CRF as appropriate

- ☐ Thrombocytopenia
- ☐ Anemia
- ☐ Neutropenia
- ☐ Patient choice
- ☐ Patient lost to follow-up
- ☐ Substance abuse
- ☐ Psychiatric issues
- ☐ Non-hematological toxicity
- ☐ Other, please

Log forms

specify
☐ Unknown

Done | Delete Entry

Create Next Entry

RIBAVIRIN LOG

To select more than one, you may repeat additional entries at the bottom of this form.

Total daily dose: _____ mg

Start date: ☐ Ongoing
DD-MMM-YYYY
DD MMM YYYY

Stop date:
DD-MMM-YYYY
DD MMM YYYY

Treatment change?
- ○ None
- ○ Permanently discontinued
- ○ Temporarily discontinued
- ○ Dose change

If treatment change, reason(s) for treatment change:
(Please select all that apply)
- ☐ Anemia
- ☐ Other, please specify _____
- ☐ Unknown

Please complete the AE or SAE CRF as appropriate

If permanently discontinued, planned duration of therapy completed?
If no, please complete reason(s) below
- ○ Yes
- ○ No
- ○ Unknown

Log forms

If no, reason(s) for early discontinuation:
(Please select all that apply)

- ☐ Anemia
- ☐ Patient choice
- ☐ Patient lost to follow-up
- ☐ Substance abuse
- ☐ Psychiatric issues
- ☐ Non-hematological toxicity
- ☐ Cardiovascular compromise
- ☐ Other, please specify:
- ☐ Unknown

Please complete the AE or SAE CRF as appropriate

Done | Delete Entry

Create Next Entry

DAA LOG

To select more than one, you may repeat additional entries at the bottom of this form.

Medication name:

- ◯ Telaprevir (Incivek)
- ◯ Boceprevir (Victrelis)
- ◯ Simeprevir (Olysio)
- ◯ Sofosbuvir (Sovaldi)
- ◯ Other, please specify

Dose:

Units:

- ◯ mg
- ◯ mcg
- ◯ mcg/kg
- ◯ IU

Log forms

◯ Other, please specify

Regimen:

◯ Once daily(OD)
◯ Twice daily (BID)
◯ Three times a day (TID)
◯ Three times a week
◯ Once weekly
◯ Other, please specify

Start date:

☐ Ongoing

DD-MMM-YYYY
DD MMM YYYY

Stop date:

DD-MMM-YYYY
DD MMM YYYY

Treatment change?

◯ None
◯ Permanently discontinued
◯ Temporarily discontinued
◯ Dose change

If treatment change, reason(s) for treatment change:
(Please select all that apply)

Please complete the AE or SAE CRF as appropriate

☐ Thrombocytopenia
☐ Anemia
☐ Neutropenia
☐ Other, please specify
☐ Unknown

If permanently discontinued, planned duration of therapy completed?

If no, please complete reason(s) below

◯ Yes
◯ No
◯ Unknown

Log forms

If no, reason(s) for early discontinuation:
(Please select all that apply)

- ☐ Thrombocytopenia
- ☐ Anemia
- ☐ Neutropenia
- ☐ Patient choice
- ☐ Patient lost to follow-up
- ☐ Substance abuse
- ☐ Psychiatric issues
- ☐ Non-hematological toxicity
- ☐ Patient compliance
- ☐ Tolerability
- ☐ Other, please specify
- ☐ Unknown

Please complete the AE or SAE CRF as appropriate

Done | Delete Entry | Create Next Entry

ELTROMBOPAG EXPOSURE LOG

To select more than one, you may repeat additional entries at the bottom of this form.

Daily dose:

- ◯ 12.5 mg
- ◯ 25 mg
- ◯ 50 mg
- ◯ 75 mg
- ◯ 100 mg
- ◯ Other, please specify

Start date:

☐ Ongoing

DD-MMM-YYYY

DD MMM YYYY

Log forms

Stop date:

DD-MMM-YYYY

DD MMM YYYY

Treatment change?

- None
- Permanently discontinued
- Temporarily discontinued
- Dose change

If treatment change, primary reason for treatment change:

- Platelets too high
- Platelets too low
- Treatment completed
- Adverse Event
- Other, please specify

Please complete the AE or SAE CRF as appropriate

Done Delete Entry

Create Next Entry

CONCOMITANT MEDICATIONS LOG INCLUDING ESAs AND GCSF

Please enter Concomitant Medications which have been taken from Informed Consent

To select more than one, you may repeat additional entries at the bottom of this form.

Medication name:

Note: Coded terms variables to be added in eCRF

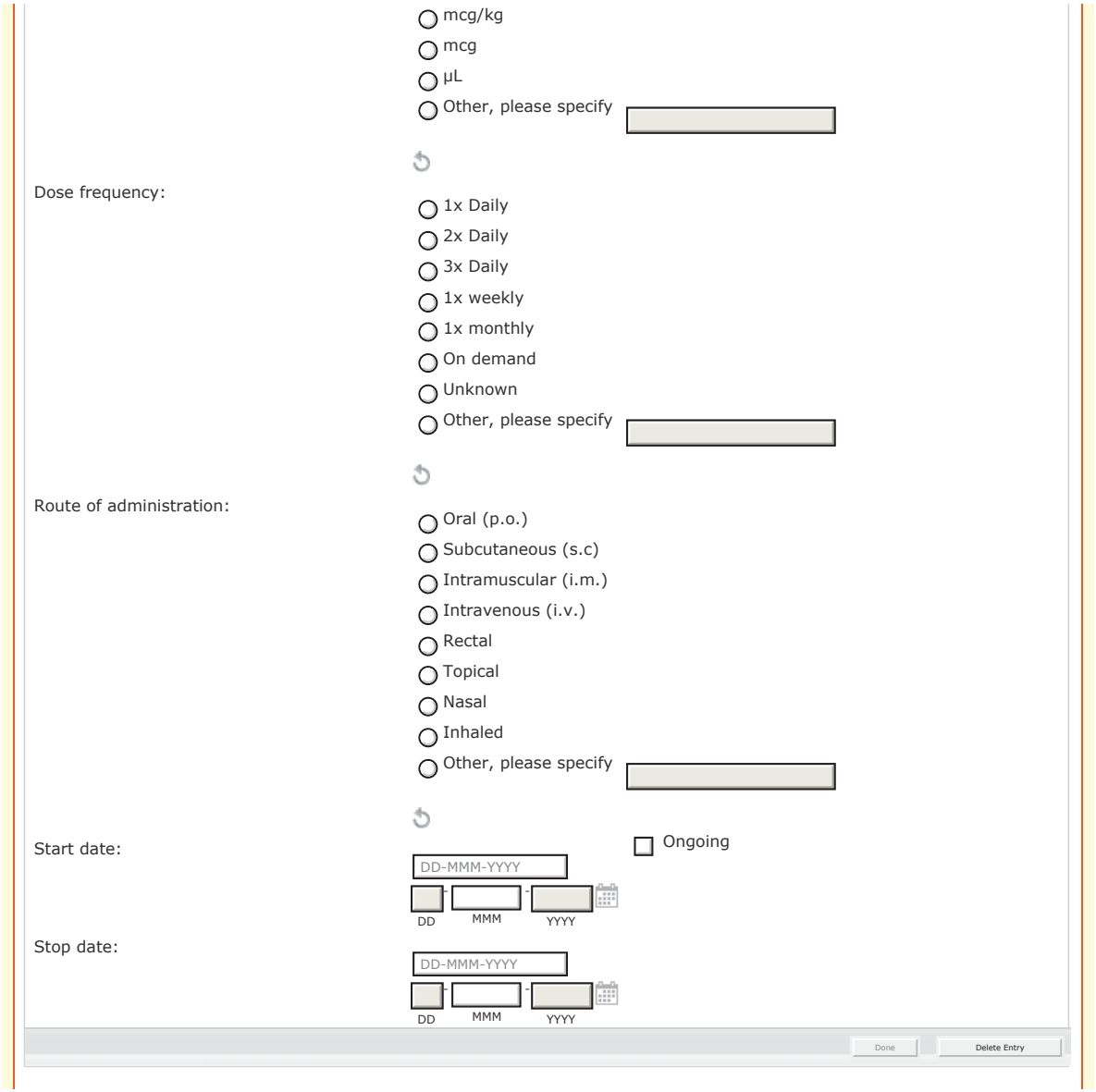
Indication:

Dose:

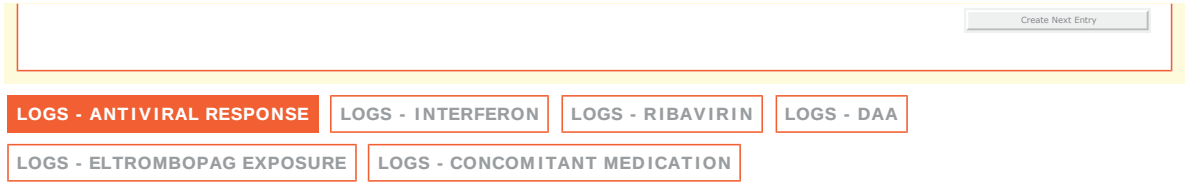
Dose unit:

- mg
- mL
- Ui
- million IU

Log forms


mcg/kg
mcg
µL
Other, please specify
Dose frequency:
1x Daily
2x Daily
3x Daily
1x weekly
1x monthly
On demand
Unknown
Other, please specify
Route of administration:
Oral (p.o.)
Subcutaneous (s.c)
Intramuscular (i.m.)
Intravenous (i.v.)
Rectal
Topical
Nasal
Inhaled
Other, please specify
Start date:
Ongoing
DD-MMM-YYYY
DD
MMM
YYYY
Stop date:
DD-MMM-YYYY
DD
MMM
YYYY
Done
Delete Entry

Log forms



Please indicate the current status of the form: ○ Complete ○ Incomplete

Selection Options for Log forms

Adverse Event

Adverse Event **Patient ID:** **Created:** 11-Nov-2016 10:15:01 **Last Updated:** 11-Nov-2016 10:15:01
Active element groups: Element Group 5004

Legend: Clear Selection Show Warnings Show History

[+] Errors

SERIOUS ADVERSE EVENTS | NON-SERIOUS ADVERSE EVENTS

SERIOUS ADVERSE EVENTS

Make a separate entry for all new or changing SERIOUS adverse events

On this form to select more than one entry where required, you may repeat additional entries at the bottom of each entry added.

Adverse Event: *Note: Coded terms variables to be added in eCRF*

Was the event a serious adverse event (SAE)? ○ Yes ○ No *Only **Serious Adverse Events** must be reported on this CRF. Report non-serious adverse events on the Non-Serious Adverse Events CRF*

Reason considered serious:
(Please select all that apply)

- ☐ Results in death
- ☐ Life threatening
- ☐ Requires hospitalization/prolonged hospitalization
- ☐ Results in disability/ incapacity
- ☐ Congenital anomaly /birth defect
- ☐ Possible drug-induced liver injury
- ☐ Other, please specify

Start date: DD - MMM - YYYY ☐ Ongoing

Start time: <1> hours : <2> minutes 24:00hr ☐ Unknown

End date: *(If fatal, record date of death)* DD - MMM - YYYY

Adverse Event

End time: <1> hours : <2> minutes 24:00hr ☐ Unknown

Outcome status: Recovered/resolved <3>

Maximum Intensity:
- ○ Mild
- ○ Moderate
- ○ Severe
- ○ Not applicable

Current Weight: ○ kg ○ Pounds

☐ Not applicable

Action taken with study treatment: Not applicable <4>

Did the subject withdraw from the study as a results of this SAE? ○ Yes ○ No

Is there a reasonable possibility that the SAE may have been caused by the study treatment? ○ Yes ○ No

If study treatment was stopped, did the reported event recur after further treatment was administered?
- ○ Yes
- ○ No
- ○ Not applicable
- ○ Not known at time

Possible causes of SAE other than study treatment *(Please select all that apply):*
- ☐ Disease under study
- ☐ Medical condition, Other please specify:
- ☐ Lack of efficacy
- ☐ Withdrawal of study treatment
- ☐ Concomitant medication, Other please specify:
- ☐ Activity related to study participation
- ☐ Other, please specify

Adverse Event

Are there any relevant medical conditions (past or current medical disorders, allergies, surgeries) that can help explain the SAE?

If yes, please specify below

○ Yes
○ No

Relevant medical condition:

Date of onset:

DD-MMM-YYYY
DD MMM YYYY

Present at the time of the SAE?

○ Yes ○ No

If no, Date of last occurrence:

DD-MMM-YYYY
DD MMM YYYY

Done | Delete Entry

Create Next Entry

Are there other risk factors relevant to the SAE?

○ Yes ○ No

Provide any family history (e.g. smoking, alcohol, diet, drug abuse, occupational hazard) relevant to the SAE

If Yes, please specify:

Done | Delete Entry

Create Next Entry

Was subject taking study treatment?

○ Yes ○ No

If Yes, please specify details of study treatment:

Done | Delete Entry

Create Next Entry

Adverse Event

Were any tests or procedures carried out to diagnose or confirm the SAE? ○ Yes ○ No

If Yes, please provide details of any tests or procedures carried out (E.g. Laboratory date with units and normal range):

Done | Delete Entry

Create Next Entry

Narrative remarks:

Done | Delete Entry

Create Next Entry

Were there any relevant concomitant medications taken that may help explain the AE, may have caused the AE or were used to treat the AE? ○ Yes ○ No

Medication name:

Reason for medication:

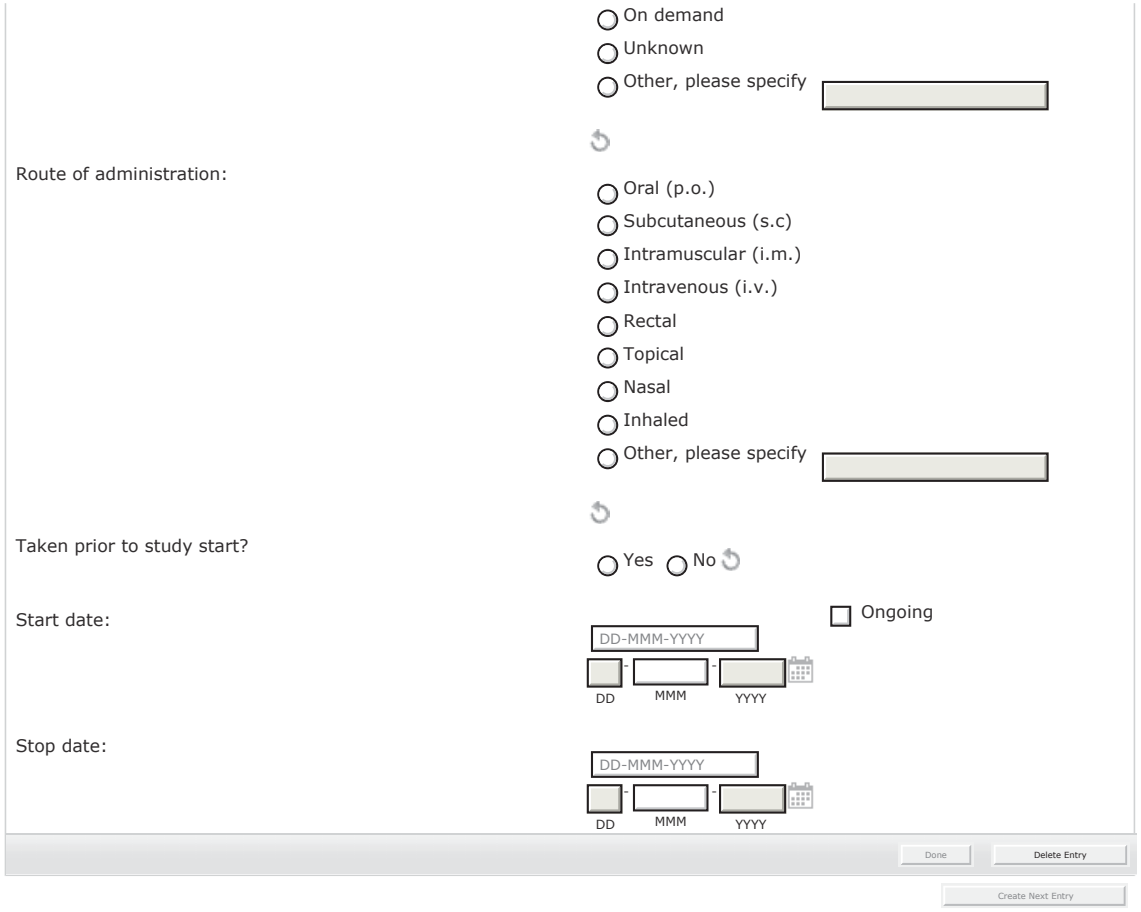
Dose:

- ○ mg
- ○ mL
- ○ Ui
- ○ million IU
- ○ mcg/kg
- ○ mcg
- ○ µL
- ○ Other, please specify

Dose frequency:

- ○ 1x Daily
- ○ 2x Daily
- ○ 3x Daily
- ○ 1x weekly
- ○ 1x monthly

Adverse Event



NON-SERIOUS ADVERSE EVENTS

Make a separate entry for all new or changing NON-SERIOUS adverse events

On this form to select more than one entry where required, you may repeat additional entries at the bottom of each entry added.

Adverse Event

Adverse Event: *Note: Coded terms variables to be added in eCRF*

Was the event a serious adverse event (SAE)? ○ Yes ○ No *Only Non-Serious Adverse Events must be reported on this CRF. Report serious adverse events on the Serious Adverse Events CRF*

Start date: ☐ Ongoing
DD MMM YYYY

Start time: <1> hours : <2> minutes 24:00hr ☐ Unknown

End date: *(If fatal, record date of death)*
DD MMM YYYY

End time: <1> hours : <2> minutes 24:00hr ☐ Unknown

Outcome status: Recovered/resolved <5>

Maximum Intensity:
○ Mild
○ Moderate
○ Severe
○ Not applicable

Current weight: ○ Kg ○ Pounds

Action taken with GSK product/s: Not applicable <6>

Did the subject withdraw from the study as a results of this AE? ○ Yes ○ No

Is there a reasonable possibility that the AE may have been caused by the GSK product/s? ○ Yes ○ No

If GSK product/s was stopped, did the reported event recur after further GSK product/s was administered?
○ Yes
○ No

Adverse Event

Not applicable
Not known at time

Possible causes of AE other than GSK product/s:
(Please select all that apply)

Disease under study
Medical condition
Lack of efficacy
Withdrawal of GSK product/s
Concomitant medication
Transmission of an infectious agent via a medicinal product
Other, please specify

Are there any relevant medical conditions (past or current medical disorders, allergies, surgeries) that can help explain the AE?

If yes, please specify below

Yes
No

Relevant medical condition:

Date of onset:

DD-MMM-YYYY
DD MMM YYYY

Present at the time of the AE?

Yes No

If no, Date of last occurrence:

DD-MMM-YYYY
DD MMM YYYY

Done Delete Entry

Create Next Entry

Are there other risk factors relevant to the AE?

Yes No

Provide any family history (e.g. smoking, alcohol, diet, drug abuse, occupational hazard) relevant to the AE

Adverse Event

If Yes, please specify:

Done Delete Entry

Create Next Entry

Any AEs which are clinically or temporarily related?

Yes No

If Yes, please specify:

Done Delete Entry

Create Next Entry

Adverse drug reaction summary/comments:

Done Delete Entry

Create Next Entry

Were there any Concomitant Medications taken that may help explain the AE, may have caused the AE or were used to treat the AE?

Yes No

Medication name:

Reason for medication:

Dose:

mg
mL
Ui
million IU
mcg/kg
mcg
µL
Other, please specify

Adverse Event

Dose frequency:

- 1x Daily
- 2x Daily
- 3x Daily
- 1x weekly
- 1x monthly
- On demand
- Unknown
- Other, please specify

Route of administration:

- Oral (p.o.)
- Subcutaneous (s.c)
- Intramuscular (i.m.)
- Intravenous (i.v.)
- Rectal
- Topical
- Nasal
- Inhaled
- Other, please specify

Start date: DD-MMM-YYYY (DD MMM YYYY) Ongoing

Stop date: DD-MMM-YYYY (DD MMM YYYY)

Done Delete Entry

Create Next Entry

Was subject taking GSK product/s? Yes No

If yes, medication name:

Adverse Event

Reason for medication:

Dose:

- mg
- mL
- Ui
- million IU
- mcg/kg
- mcg
- µL
- Other, please specify

Dose frequency:

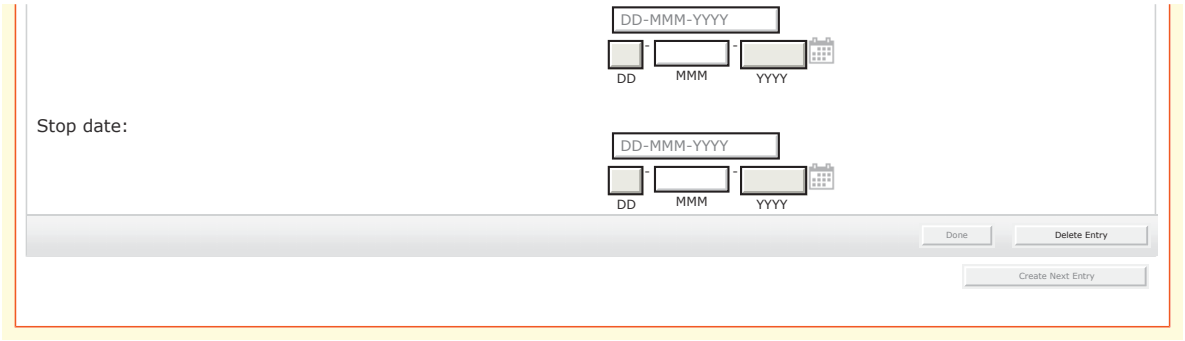
- 1x Daily
- 2x Daily
- 3x Daily
- 1x weekly
- 1x monthly
- On demand
- Unknown
- Other, please specify

Route of administration:

- Oral (p.o.)
- Subcutaneous (s.c)
- Intramuscular (i.m.)
- Intravenous (i.v.)
- Rectal
- Topical
- Nasal
- Inhaled
- Other, please specify

Start date: Ongoing

Adverse Event



SERIOUS ADVERSE EVENTS | NON-SERIOUS ADVERSE EVENTS

Please indicate the current status of the form: ○ Complete ○ Incomplete

Selection Options for Adverse Event

<1> - SAE start time, hours , SAE end time, hour , AE start time, hour , AE end time, hour
00
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Adverse Event

16
17
18
19
20
21
22
23

<2> - SAE start time, minute , SAE end time, minute , AE start time, minute , AE end time, minute
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Adverse Event

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44
45
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47
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Adverse Event

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<3> - SAE Outcome status

Recovered/resolved
Recovering/resolving
Not recovered / Not resolved
Recovered/resolved with sequelae
Fatal

<4> - SAE Action taken with study treatment

Not applicable
Study treatment(s) withdrawn
Dose reduced
Dose increased
Dose not changed
Dose interrupted/delayed

<5> - Outcome status

Recovered/resolved
Recovering/resolving
Not recovered / Not resolved
Recovered/resolved with sequelae

<6> - Action taken with GSK product/s

Not applicable
GSK product(s) withdrawn
Dose reduced

Adverse Event

Dose increased
Dose not changed
Dose interrupted/delayed

END OF STUDY - Study DiscontinuationCompletion

END OF STUDY - Study DiscontinuationCompletion **Patient ID:** **Created:** 11-Nov-2016 10:15:04 **Last Updated:** 11-Nov-2016 10:15:04
Active element groups: Element Group 5001

Legend: Clear Selection Show Warnings Show History

[+] Errors

END OF STUDY

END OF STUDY - Study Discontinuation/Completion

Did the patient complete the study (i.e. 36 months of follow-up)?
- ○ Yes
- ○ No

Discontinuation/completion date:
DD-MMM-YYYY
DD MMM YYYY

If no, please provide the primary reason for early discontinuation:
- ○ Lost to follow-up
- ○ Death
- ○ Withdrawal of Informed Consent
- ○ Investigator choice

If death, date of death:
DD MMM YYYY

Primary cause of death: Note: Coded terms variables to be added in eCRF

Secondary causes of death (if any): Note: Coded terms variables to be added in eCRF

In the opinion of the Investigator, was the patient's death liver-related?
- ○ Yes
- ○ No
- ○ Unknown

END OF STUDY - Study DiscontinuationCompletion

END OF STUDY

Please indicate the current status of the form: ○ Complete ○ Incomplete

Selection Options for END OF STUDY - Study DiscontinuationCompletion

Appendix 3 – List of Independent Ethics Committees (IECs) or Institutional Review Boards (IRBs) and representative written information for patients and sample consent form

Document	Version	Effective date
List of Independent Ethics Committees	Version 1.0	20 Apr 2017
Patient Information Sheet and Consent Form for PLATELET:HCV	Version 1.0	26 Aug 2014

[redacted]

PATIENT INFORMATION SHEET FOR PLATELET: HCV

Study Title: PLATELET:HCV: A global, prospective cohort study to evaluate the 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 (hereinafter the "Study").

Protocol Number: WEUSKOP7136

Study Sponsor: GlaxoSmithKline (GSK), with an address at [redacted], [redacted]. ("GSK" or the "Sponsor")

Introduction

You are being invited to participate in this Study because of your treatment with [redacted] / [redacted] (*choose the appropriate name*), commercialized name of eltrombopag.

Please review this information and ask your physician any questions you may have to be sure that you understand what it means for you to participate in this study.

The Study is being sponsored by GSK. GSK is the pharmaceutical company that makes [redacted] / [redacted] (*choose the appropriate name*)

The Study will be managed on behalf of GSK by Quintiles, which is located in the United States of America, together with its affiliated companies and subsidiaries (collectively "Quintiles"). Quintiles is a clinical research company.

[redacted] / [redacted] is commercialised in [*enter here the name of the country*] by GlaxoSmithKline.

What is the purpose of this Study?

The aim of this study is to assess the safety and effectiveness of [redacted] / [redacted] (*choose the appropriate name*)in routine clinical practice in patients with hepatitis C virus (HCV) infection who are unable to initiate or maintain optimal interferon-based therapy due to low platelet counts (thrombocytopenia). The Study will be performed globally at approximately 50 sites. The Study intends to enrol approximately 200 patients being treated with [redacted] / [redacted] (*choose the appropriate name*).

In [enter here the name of the country] the study aims to enrol approximately [enter here the approximate number of patients for the country].

Do I have to take part?

You do not have to take part in this Study. Your participation in this Study is entirely voluntary. If you decide not to participate in this Study or if you decide to withdraw from the Study at any time, your medical care will not be affected in any way.

GSK or a regulatory authority may terminate the Study at any time. If this happens, the Study doctor will inform you and will explain to you the reasons for the termination. In this case, the recording and collection of your information within the Study will stop but you will continue to receive your normal standard of care treatment.

What do I have to do?

Participation in the Study means that your doctor will record some of your medical information to be included in the Study, as explained below.

You will have no additional medical procedures as part of this Study. Participation in this Study does not change your normal standard of care.

For the study, medical information about you will be collected:

- At baseline (first study data collection timepoint) :

Data collection includes information on the severity of your liver disease, blood clotting events, demographics, HCV genotype, HCV treatment history, other relevant medical history, liver status, thrombocytopenia history, previous [redacted] / [redacted] (*choose the appropriate name*)use, laboratory values.

- Regularly during your interferon–based therapy
- Approximately every 6 months during 3 years after starting [redacted] / [redacted] (*choose the appropriate name*) (based on the regular visits your doctor recommends)

Data collection includes the severity of your liver disease, blood clotting events, updated information on your [redacted] / [redacted] (*choose the appropriate name*)use, laboratory values

Some of the personal data collected are regarded as sensitive data (such as information relating to your health). If you do not agree to the collection and use of this information, you may not participate in the Study.

If you decide to participate in this Study, and you permanently stop taking [redacted] / [redacted] (*choose the appropriate name*), you will be followed for clinical outcomes and survival, for up to 36 months after you started the study.

What is your responsibility in this Study?

It is important that you tell the Study doctor or Study staff about all your symptoms and any medications you are taking and any potential adverse events (if any).

What are the potential risks of taking part in this study?

There are no medical risks connected with your participation in this Study because no procedures will be performed outside of your usual medical care.

What are the potential benefits of taking part in this study?

You will not personally benefit from taking part in this Study; however, the information gained will help us learn more about the effectiveness and safety of [redacted] /[redacted] (*choose the appropriate name*) in real-life clinical practice.

What happens to my personal and medical information?

It is very important that your personal and medical information stay confidential and secure. GSK will protect your information in accordance with current law.

When you sign this consent form you agree that GSK can use your personal and medical information as described here:

- Your personal and medical information may be checked by GSK and others (like agencies that approve and monitor studies). This is to make sure that the study is being run properly.
- Besides that, only the researchers at this study site can use information that identifies you (such as name and address) and only for the purpose of the study.
- Your study information will be labelled with a code number (for example, 1234782). It will not include your name or address. The study doctor will have the link between your name and the code number.
- The link between your name and the code number will not be shared. Only the code number and coded information will be sent to GSK.
- GSK will use your coded information for research only. This may include research looking at improving the quality and efficiency in conducting clinical research trials in general.

GSK may:

- keep your coded information electronically, and analyse it by computer to find out what the study is telling us. This may be done by GSK or a third party, in which case GSK will ensure that the third party is required to keep your data secure,
- share the information with regulatory agencies that approve new medicines,
- share the information with people who check that the study is done properly (like the ethics committee or review boards),

- combine the information with results from other studies to learn more about the medicine and other medicines, and this Hepatitis C Virus Infection and other diseases and conditions. This may help us to assess the risks and benefits of GSK (or other) medicines, or to improve disease understanding,
- publish study results for medical journals, meetings and on the internet for other researchers to use; your name will not appear in any publication,
- share coded information with other companies, organisations or universities to carry out research. This may include research looking at improving the quality and efficiency in conducting clinical research trials in general.

Personal and medical data collected during the study may be moved, stored and used in the country where you live or another country where GSK or those working with GSK work.

Use of this information may take place in countries with lower data protection rules than the country where you live. GSK will make sure that if your data are moved to another country, it will still be treated as stated in this Informed Consent Form.

A description of this clinical study will be available on the GSK Clinical Study Register: http://www.gsk-clinicalstudyregister.com/ and may also appear in clinical trial/study registries in countries in which the clinical study is conducted.

GSK will be the owner of the study results. GSK plans to use the results, and may get patents, or sell the drug in the future, or make profits other ways. You will not be paid any part of this.

If you withdraw your consent for use of your personal information, you will no longer be able to continue in the study. However all the information collected before you left the study, or at any follow up visit, will still be used as set out in this consent form.

At any time, you may ask the study doctor to see your personal information and correct it, if necessary. In some circumstances, you may not be able to access your study information while the study is ongoing. However, the study doctor will share any important medical information if it is relevant to your health during the course of the study.

<**Delete this paragraph if the study is not in** [redacted]>. You should know that once identifiable medical information about you is given to someone that is not a health care provider, it is not protected by the US federal privacy rules called the HIPAA Privacy Regulations.

<**Delete this paragraph if the study is not in** [redacted]**>.** The Genetic Information Non-discrimination Act (GINA), generally makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information.

Will I be compensated for my participation in the Study?

You will not be paid or reimbursed for your participation in this Study. There will be no extra costs to you as a result of your participation in this Study.

The Study doctor or the hospital is being compensated for the time he or she will spend completing study forms by the Sponsor for conducting this Study *[to be adapted per country]*.

Who can be contacted for further information?

This Study has been reviewed and approved by ***[independent ethics committee name]***. *[To be adapted per country]*

Please contact the Study doctor at any time if you have any questions about the Study.

Study Doctor Name: ……

Tel: ……

Address: ……

……

Thank you for taking the time to read this Patient Information Sheet. Before you sign the attached consent form, please ask any questions you have about the study.

PATIENT CONSENT FORM FOR PLATELET: HCV STUDY

Full Title: : PLATELET:HCV: A global, prospective cohort study to evaluate the 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 Number: WEUSKOP7136

Study Sponsor: GlaxoSmithKline, with an address at [redacted]

- I confirm that I have received, carefully read and understand the Patient Information Sheet/Informed Consent Form for this Study, dated *08 August 2014 version 1.0.*
- I confirm that I have had sufficient time to review the information, consider my participation, ask questions, and have had these answered satisfactorily.
- I am aware that my participation in the Study is completely voluntary and that I am free to withdraw from the Study at any time without giving any reason, without my medical care or legal rights being affected.
- I am aware that because the data is being processed for scientific and research purposes in order to ensure scientific accuracy if I withdraw from the Study for any reason any data collected before my withdrawal will not be removed from the Study and will continue to be processed in key-coded form as permitted for scientific and research purposes by country-specific data protection laws *[To be adapted per country]*, but no further data will be collected.
- I understand and agree that the relevant sections of my medical records and data collected during the study may be reviewed and studied by individuals from the Sponsor and Quintiles, from their representatives and agents, and/or from health authorities including the FDA, European Medicines Agency and ethics committees, where it is relevant.
- After careful consideration, I understand, acknowledge, consent and give my express permission to the following:

(i) the recording of my key-coded personal data, including sensitive data such as information relating to my health;

(ii) the transfer of these data for research purposes of the Study to (a) GSK and its representatives and agents (b) Quintiles and its representatives and agents, (c) the health authorities, including the FDA, European Medicines Agency, and ethics committees for review at their request; and

(iii) The transfer and/or archive of my personal data to third parties in countries, where the privacy protections may not offer the same level of privacy protection in the country where I live. I understand that GSK has also entered into agreements with third parties working for GSK that requires these other parties to secure and provide adequate protection of your

data.

By signature on this form, I voluntarily agree to take part in this Study.

_____	_____	_____
Name in block capitals of the Patient/ Patient's Legal Representative	Signature	Date (MM/DD/YYYY)
_____	_____	_____
Name in block capitals of the person conducting the review of the Consent	Signature	Date (MM/DD/YYYY)

Appendix 4 – List and description of investigators

[redacted]

[redacted]

Redacted

Appendix 5 – Clinical Study Report Signature Page

Study Title: **PLATELET:HCV** - A global, prospective cohort study to evaluate the 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

CONTRACT RESEARCH ORGANISATION SIGNATURE PAGE

1 Signatures of the report authors

I have read this report and confirm that to the best of my knowledge this report accurately describes the conduct and results of the study WEUSKOP7136

[redacted] Outcome Sciences, LLC. a Quintiles company	Signature	Date (dd/mmm/yyyy)

2 Signatures of the reviewers

[redacted] Outcome Sciences, LLC. a Quintiles company	Signature	Date (dd/mmm/yyyy)
[redacted] Outcome Sciences, LLC. a Quintiles company	Signature	Date (dd/mmm/yyyy)
[redacted] Outcome Sciences, LLC. a Quintiles company	Signature	Date (dd/mmm/yyyy)

SPONSOR SIGNATORY SIGNATURE PAGE

I have read this report and confirm that to the best of my knowledge this report accurately describes the conduct and results of the study WEUSKOP7136

3 Signature of the sponsor's responsible medical officer

[redacted]	Signature	Date (dd/mmm/yyyy)
Novartis Pharma AG		

Appendix 6 – Listing of patients receiving test drug(s) / investigational product(s) from specific batches, where more than one batch was used

** This Appendix is not applicable **

Appendix 7 – Randomization scheme and codes

** This Appendix is not applicable **

Appendix 8 – Audit certificates

** No Internal Investigator Site Audits or Health Authority Inspections have been conducted **

Appendix 9 – Statistical Analysis Plan and Shells for Tables and Listings (TLs)

Document	Effective date
Statistical Analysis Plan	31 Mar 2017
Shells for Tables and Listings (TLs)	31 Mar 2017

NOVARTIS

Clinical Development

SB-497115-GR / Eltrombopag / [redacted]

WEUSKOP7136; ETB115A2409

A global, prospective cohort study to evaluate the 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

Statistical Analysis Plan (SAP)

Authors:
[redacted]

Document type: SAP Documentation

Document status: Final Version

Release date: 31-Mar-2017

Number of pages: 13

Document History – Changes compared to previous final version of SAP

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
08-Jan-2016	Prior to DB lock	First Draft	N/A - First version	NA
05-Feb-2016	Prior to DB lock	Second Draft	Incorporate Novartis comments on first version.	Section 2.1.1.4 Time-to-event calculations: changed unit to months instead of years. Section 2.2.1: Subgroups of interest: Clarification added for SVR status. Ethnicity removed from subgroups of interest.
02DEC2016	Prior to DB lock	Second version	Update due to early study termination	The analysis plan has been updated based on available data at the time of study termination.
19DEC2016	Prior to DB lock	Final version	Incorporate Novartis comments on second version.	
27MAR2017	Post DB lock	Final version	Deleting text related to incidence rate and some minor edits	

Table of content

List of abbreviations

ADR	Adverse drug reaction
AE	Adverse event
BMI	Body Mass Index
CI	Confidence Interval
CRF	Case Report Form
DAA	Direct-acting antiviral agents
DB	Database
eCRF	Electronic Case Report Form
EMA	European Medicines Agency
ENABLE	Eltrombopag to INitiate and Maintain Interferon Antiviral Treatment to Benefit Subjects with Hepatitis C related Liver DiseasE
EVR	Early Viral Response
HCV	Hepatitis C Virus
LPLV	Last patient last visit
MedDRA	Medical Dictionary for Drug Regulatory Affairs
PASS	Post-authorization Safety Study
PT	Preferred Term
RNA	Ribonucleic Acid
SADR	Serious Adverse Drug Reaction
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SOC	System Organ Class
SVR	Sustained Virological Response
TCP	Thrombocytopenia

1 Introduction

The purpose of this Statistical Analysis Plan (SAP) is to describe how data collected in this study will be reported. This is a short version of the SAP that has been outlined in the WEUSKOP7136, version 1.0 (draft 2), dated 05-Feb-2016. The decision to produce this abbreviated version of the SAP has been taken in agreement with Novartis. The sponsor has decided to terminate the study due to insufficient recruitment (nine patients at the time of drafting this SAP) and based on consultation with the European Medicines Agency (EMA) (decision received on 13-OCT-2016). The collected data will be presented as tables and listings using available data.

The same tense is used as in previous versions of this SAP.

2 Study design

2.1 Per protocol study design

This is a global, multi-center, prospective, observational study conducted to evaluate clinical outcomes and treatment patterns in Hepatitis C Virus (HCV) patients treated with eltrombopag. It is expected to include several countries in [redacted] The study plans to enroll approximately 200 patients, with a minimum of 100 patients who are treated with boceprevir, telaprevir or newer direct acting agents (DAAs) in at least 40 sites over at least 18 months enrolment period. Eligible patients will be enrolled at the time of presentation for a routine clinic visit by gastroenterologists, hepatologists and other physicians and health care providers experienced in the management of patients with HCV, consistent with local treatment practice. There are no protocol-mandated visits or procedures associated with the study. All follow-up assessments are intended to be performed at the time of a routine clinical encounter or by referencing the medical record.

The primary analysis endpoint will be evaluated at 3 years (36 months). Each patient will be followed for a period of maximum of 36 months after initiating eltrombopag or until premature discontinuation (due to death, withdrawal of consent, loss to follow-up). Based on routine care, patients will be assessed regularly approximately every 3 months during antiviral therapy and approximately every 6 months thereafter, according to local standard practice. Patients who permanently discontinue eltrombopag will be followed for clinical outcomes and survival for up to 36 months after enrollment, according to the protocol schedule.

2.2 Current Situation and Update

As the study only managed to enroll 9 patients by Last patient last visit (LPLV) on 30-Apr-2016, the sponsor consulted with the European Medicines Agency (EMA) who agreed to terminate the study (decision received on 13-Oct-2016). Therefore the decision was taken by the sponsor to terminate the study earlier and to perform the analysis using the available data from the nine enrolled patients.

3 Study objectives

The aim of this study is to assess the safety and effectiveness of eltrombopag in routine clinical practice in patients with HCV who are unable to initiate or maintain optimal interferon-based therapy due to thrombocytopenia.

3.1 Primary objective

The primary objective is to assess and compare the incidence of hepatic decompensation and mortality (as separate events) at 3 years in patients using eltrombopag who achieved sustained viral response (SVR) to patients using eltrombopag who did not achieve SVR.

Due to early study termination, the analysis corresponding to this objective will not be performed because of lack of data.

3.2 Secondary objectives

The secondary objectives include:

- Assess the incidence of thromboembolic events among new users of eltrombopag;
- Assess treatment effectiveness among eltrombopag users with respect to initiating, maintaining and completing antiviral therapy and achieving SVR;
- Evaluate all-cause and cause-specific mortality risk and survival rates among eltrombopag users at 6 months, 12 months, 18 months, 24 months and 36 months after starting eltrombopag;
- Explore the factors independently related to the risk of hepatic decompensation and the risk of thromboembolic events among eltrombopag users.

Due to early study termination and lack of data, the analysis will include only this following secondary objective:

- Assess the prevalence of AEs (including thromboembolic events) among new users of eltrombopag.

3.3 Sample size

The targeted sample size for this study is 200 patients to account for potential variance in the percentage of patients achieving SVR or experiencing hepatic decompensation, and potential for patients lost to follow-up.

At time of the current SAP revision, 9 patients have been recruited into the study.

4 Statistical methods

4.1 Data analysis general information

The analysis will be conducted by QuintilesIMS (Clinical Research Organization) on behalf of Novartis. Analyses will be performed using [redacted] version 9.4 ([redacted] Institute, [redacted]). Continuous variables will be reported as n, mean, standard deviation (SD), median, 25th and 75th quartiles (Q1 and Q3), and range (min, max). Categorical variables will be summarized as

number and proportion (%) of subjects with observed (non-missing) data. Listings will be produced to provide data as recorded in the eCRFs.

Mean, SD and median will be reported with one decimal place . Percentages will be reported to one decimal place. Minimum and maximum will be reported to the same decimal place as the original data. The number of patients with missing and non-missing data will be presented.

As per the protocol, patients may withdraw consent and discontinue participation in the study at any time, with no impact to their medical care or access to treatment. If a patient is withdrawn prior to completing the study, any known reason for withdrawal will be documented in database. All information already collected as part of the study will be retained for analysis. No stratification (e.g., by center, country) are planned for this analysis.

4.2 General definitions

4.2.1 Study treatment and definition of exposure

For both eltrombopag and antiviral treatment, information on dose, duration and discontinuation will be collected.

First time exposure to eltrombopag is defined as patients newly treated with eltrombopag within the past 3 months prior to study enrolment. If an enrolled patient discontinues eltrombopag early (either due to ineffectiveness of antiviral therapy or due to an adverse event) and later receives different antiviral therapy and concomitant eltrombopag, treatment safety and effectiveness measures on the subsequent use of eltrombopag will also be collected.

For the purposes of this study, exposure to eltrombopag is defined as time on drug plus 30 days post-discontinuation. Adverse events recorded during the exposure window will be reported as attributable to the drug.

Where applicable, eltrombopag exposure will be classified as current (i.e., ongoing or within 30 days [inclusive] of eltrombopag discontinuation at the time of the event of interest) or past (i.e., greater than 30 days since eltrombopag discontinuation).

4.2.2 Baseline

Baseline is defined as the date of the first dose of eltrombopag administered for patients enrolled into the study. Baseline data will be collected at the time of the first routine clinic visit in which the patient was enrolled.

4.2.3 Study Period and Follow-up time

The study period begins at baseline. The original study design aimed that all enrolled patients will be followed for a period of up to 36 months from the date of first dose of eltrombopag. For patients who discontinued the study before completing 36 months of follow-up the date of early discontinuation is the latest date among: date of loss to follow-up, date of withdrawal of informed consent, date of study termination, or date of death. In all other cases and where the early discontinuation date is missing the latest date will be the last known date in the CRFs.

Follow-up time (years) will be calculated using the latest date (date of completing the study or early discontinuation date) – date of first dose eltrombopag + 1 day, then divided by 365.25.

4.2.4 Incidence

For each type of event, incidence is defined as the proportion of patients with at least one new event out of the total number of enrolled patients during a certain period.

4.2.5 Incidence rate

Due to lack of complete dates for some events, the incidence rate will not be reported, prevalence will be reported instead.

4.2.6 Antiviral response

Achievement of SVR is defined by HCV ribonucleic acid (RNA) negative 24 weeks after cessation of antiviral treatment. Achievement of early viral response (EVR) is defined as clinically significant reduction in HCV RNA (≥2 log10 drop or undetectable) after 12 weeks of antiviral treatment. The assessment of antiviral outcome response is entered directly by the investigator in the Case Report Form (CRF) (not derived programmatically).

4.3 Analysis sets

A single analysis population is defined for the study that includes all enrolled patients who provided consent to release information and who fulfilled the study inclusion and exclusion criteria. For discontinued patients the analyses will include all data that have been collected up to the point of discontinuation.

4.4 Patient disposition, demographics and other baseline characteristics

4.4.1 Patient disposition

Patient enrollment and disposition will be summarized as follows:

- Total number of patients enrolled in the study.
- The number and percentage of patients who discontinued the study and reasons for study discontinuation (loss to follow-up, death, withdrawal of informed consent or investigator choice).
- Total number of deaths recorded in the CRF at each follow-up time
- Study duration (in months) for the patients who discontinued the study, was calculated as date of study discontinuation (as collected in the CRF) minus enrolment date (date of informed consent) plus 1 day divided by 30.44. If a patient died before completing 36 months of follow-up, the patient's date of death will be used in the calculation instead of study discontinuation date.

4.4.2 Inclusion and Exclusion Criteria

The following criteria must be met in order to be enrolled in the study:

- Age ≥ 18 years at enrollment
- Diagnosis of HCV verified by the presence of detectable HCV RNA

- Initiation of first-time treatment with eltrombopag no more than 3 months prior to study enrolment
- Patient was unable to initiate, maintain, or restart optimal interferon-based therapy due to thrombocytopenia prior to initiating eltrombopag
- Patient currently undergoing interferon-based antiviral therapy or initiation or restart of interferon-based antiviral therapy planned
- Patient (or appropriate representative) willing and able to provide written informed consent

Patients meeting ANY of the following criteria are not eligible for participation:

- Current participation in any interventional clinical trials in which treatment regimen and/or monitoring is dictated by a protocol

Inclusion and exclusion criteria will be described in a listing.

4.4.3 Demographics

Demographics and baseline characteristics will be summarized using descriptive statistics.

Demographic variables will include:

- Age (years) and age group (< 65 years of age vs ≥ 65 years of age) , calculated as date of first dose of eltrombopag minus date of birth plus 1 day, divided by 365.25
- Sex (male, female)
- Ethnicity (Hispanic/Latino, not Hispanic/Latino, or not provided)
- Race/geographic ancestry
  - African American/African Heritage
  - American Indian or Alaskan Native
  - Asian Central/South Asian Heritage
  - Asian East Asian Heritage
  - Asian - Japanese Heritage
  - Asian Southeast Asian Heritage
  - Native Hawaiian or Other Pacific Islander
  - White Arabic/North African Heritage
  - White/Caucasian/European Heritage
  - Other Geographic Ancestry
- Height (cm)
- Weight (kg)
- Body mass index (BMI) defined as weight (kg) divided by [height (m)]² . BMI will be presented using these categories (Underweight <18.5 kg/m2, Normal BMI ≥18.5 to <25 kg/m2, Overweight ≥25 to <30 kg/m2, Obese ≥30 to <35 kg/m2, Extremely obese ≥ 35 kg/m2)

4.4.4 Baseline clinical characteristics

Baseline clinical characteristics include relevant medical history, HCV risk/clinical factors, current liver status, thrombocytopenia (TCP) history, relevant recent laboratory testing and previous antiviral treatment.

For each of the following baseline clinical characteristics, one listing of all collected data will be provided:

- Relevant medical history (including TCP)
- HCV risk/clinical factors
- Current liver status
- TCP history
- Relevant recent laboratory testing
- Previous antiviral treatment.

4.4.5 Concomitant medications

A listing of eltrombopag exposure log (daily dose, treatment change, reason for treatment change) will be provided.

A listing will be provided for concomitant medications log (medication name, indication, dose, dose frequency, route of administration and start/stop date).

4.4.6 Protocol deviations

Clinical sites will be monitored by QuintilesIMS to examine compliance with the protocol and adherence to the data collection procedures, to assess the accuracy and completeness of submitted clinical data, and to verify that records and documents are being properly maintained for the duration of the study.

Protocol deviations include violations of study inclusion and exclusion criteria (e.g., age < 18 years at enrollment, or diagnosis of HCV not verified by the presence of HCV RNA) and protocol violations relating to conduct of study, clinical assessment of patient.

A listing of protocol deviations will be provided at the final analysis.

4.5 Treatments (study treatment, rescue medication, concomitant therapies, compliance)

4.5.1 Study treatment / compliance

Exposure to eltrombopag and concomitant antiviral treatments will be summarized at each available follow-up time, and will include the number and percentage of patients currently being treated with eltrombopag (yes or no [not yet initiated]) and the number and percentage of patients currently being treated with concomitant antiviral medications (yes or no).

Dose of eltrombopag at initiation and at various time points during treatment will be presented categorically. Duration of eltrombopag (in days) will be reported as mean, standard deviation, median, 25th and 75th quartiles, and range. For eltrombopag treatment, descriptive statistics of the following variables will be summarized:

- Daily dose (12.5 mg, 25 mg, 50 mg, 75 mg, 100 mg or other)
- Duration of eltrombopag treatment (days)
- Treatment change (none, permanently discontinued, temporarily discontinued or dose change)
- Primary reason for treatment change (platelets too high as assessed by the investigator, platelets too low as assessed by the investigator, treatment completed, adverse event or other).

4.5.2 Current antiviral treatments

Current antiviral treatments including interferon, ribavirin, and DAAs and patient antiviral response will be presented in listings by visit.

4.5.3 Prior, concomitant and post therapies

4.5.3.1 Previous antiviral treatments

Listing will be provided for antiviral agents used previously for HCV: interferon, ribavirin or DAAs.

4.5.3.2 Concomitant medications

A listing will be provided for concomitant medications including treatment with an erythropoiesis-stimulating agent (e.g., erythropoietin, darbepoetin), treatment with a granulocyte colony stimulating factor and other relevant concomitant medications.

4.6 Adverse events (AEs)

Analyses of AEs and SAEs will be presented in separate tables. All AE summaries (events of interest and any other events recorded in the eCRF) will be summarized by System Organ Class (SOC) and preferred term (PT) as follows:

- Number of patients and proportion of patients with at least one (S)AEs
- Number of (S)AEs

Separate (S)AEs tables will be provided stratified by SOC, PT and maximum intensity (mild, moderate and severe).

4.6.1 Non-serious and serious adverse drug reactions (ADRs/SADRs)

Analyses of non-serious and serious adverse drug reactions [(S)ADRs)] will be presented in separate tables. The analyses of (S)ADRs include all (S)AEs occurring between first eltrombopag intake until 30 days (inclusive) after the last eltrombopag administration and will be summarized by System Organ Class (SOC) and preferred term (PT) as follows:

- Number of patients and proportion of patients with at least one (S)ADRs
- Number of (S)ADRs

The same analysis will be performed for (S)ADRs leading to discontinuation of eltrombopag. Separate (S)ADRs tables will be provided stratified by SOC, PT and maximum intensity (mild, moderate and severe).

4.7 Pregnancy

Pregnancies occurring to patients or experienced by patients' partner since the start of eltrombopag initiation will be reported in a listing.

4.8 Laboratory data

Hemoglobin, hematocrit, neutrophils, alanine transaminase, aspartate aminotransferase, serum albumin, and bilirubin, as measured at baseline, will be described in a listing.

4.9 Handling of Missing Data

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

4.10 Change to protocol specified analyses

Due to early study termination, a significant portion of the analyses as included in the protocol have been revised to account for the lower-than-expected number of patients and lack of follow-up data.

Clinical Development

SB-497115-GR / Eltrombopag /[redacted]; [redacted]

WEUSKOP7136; ETB115A2409

A global, prospective cohort study to evaluate the 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

Tables and Listings (TLs) Shells

Author(s):
[redacted]

Document type: RAP Document: TFL shells

Document status: Final version

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Document History - Changes compared to previous final version

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
08-Jan-2-015	Prior to DB lock	Creation of first draft	N/A - First version	NA
12-Dec-2016	Prior to DB lock	Final Draft	Update due to early study termination	All figures initially planned have been removed 44 tables among the 57 initially planned have been removed
21-Dec-2016	Prior to DB lock	Final Draft	Incorporate Novartis comments on second version.	All figures are removed. All listings are be kept. Among Demographics, Baseline and treatment tables, only the following tables are kept: • 1.1. Patients Disposition • 1.2. Demographics Characteristics • 1.19. Eltrombopag Treatment Exposure by visit Among Safety tables only tables 2.23 to 2.31 are kept.
27MAR2017	Post DB lock	Final version	Deleting text related to incidence rate Alligning the shells with the outputs	

Shells and specifications

1. Landscape orientation is used in this document for all TLF output.
2. Enter "Page x of y" as the page header, centered right to the listing/table number .
3. Enter the header (Novartis, followed by study code) on the upper left corner.
4. Enter the time the TFL was last ran (as captured via the appropriate [redacted] functions) in the last row of each output.
5. Page header applies to real TLFs. *Date* shows the production date in the format of ddMMMyyyy.
6. The % character will not appear in the percentages, unless it is explicitly included in the shell.
7. If only 1 data point is used to obtain the standard deviation the SD will be replaced with '-', for example if the mean is 5, mean (SD) would be displayed as : 5 (-)
8. Unless explicitly stated otherwise, the denominator of percentages for categorical variables is the number of subjects without missing data. Subjects with missing data are not included in the denominator, but are included as an extra category as indicated in the shells.
9. Missing + non-missing data displayed should add up to a logical overall value (e.g. header N, or the subset of subjects with Yes – as appropriate).
10. In case there is no data to be reported, the following message will be inserted in the table: "Nothing to report".

Table of contents

Listings

Redacted

Tables – Demographics, baseline and treatments

Table 1.1 Patient disposition

		All patients (N=xxx)
Number of patients enrolled		xx
Early discontinuation	n (%)	xx (xx.x)
Reason for discontinuation		
Lost to follow-up	n (%)	xx (xx.x)
Death	n (%)	xx (xx.x)
Withdrawal of informed consent	n (%)	xx (xx.x)
Investigator choice	n (%)	xx (xx.x)
Time on study (months) [if discontinued]	n	xx
	Mean (SD)	xx.x (xx.x)
	Median	xx.x
	Q1; Q3	xx.x; xx.x
	Min, Max	xx.x, xx.x

Note: Study early termination was decided by the sponsor, in agreement with EMA, due to low enrollment. Early discontinuation reasons do not include study termination.

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Table 1.2 Demographic Characteristics

Population characteristics		All patients (N=xxx)
Age (years)[1]	n	xx
	Mean (SD)	xx.x (xx.x)
	Median	xx.x
	Q1; Q3	xx.x; xx.x
	Min, Max	xx, xx
	Missing	xx
Age group (years)	n	xx
	<65	xx (xx.x)
	>=65	xx (xx.x)
	Missing	xx
Sex	n	xx
	Male	xx (xx.x)
	Female	xx (xx.x)
	Missing	xx
Ethnicity	n	xx
	Hispanic/Latino	xx (xx.x)
	Not Hispanic/Latino	xx (xx.x)
	Not provided	xx (xx.x)
Geographic Ancestry	n	xx
	African American/African Heritage	xx (xx.x)

Population characteristics		All patients (N=xxx)
	American Indian or Alaskan Native	xx (xx.x)
	Asian Central/South Asian Heritage	xx (xx.x)
	Asian East Asian Heritage	xx (xx.x)
	Asian - Japanese Heritage	xx (xx.x)
	Asian Southeast Asian Heritage	xx (xx.x)
	Native Hawaiian or Other Pacific Islander	xx (xx.x)
	White Arabic/North African Heritage	xx (xx.x)
	White/Caucasian/European Heritage	xx (xx.x)
	Other	xx (xx.x)
	Missing	xx
Height (cm)	n	xx
	Mean (SD)	xx.x (xx.x)
	Median	xx.x
	Q1; Q3	xx.x; xx.x
	Min, Max	xx, xx
	Missing	xx
Weight (kg)	n	xx
	Mean (SD)	xx.x (xx.x)
	Median	xx.x
	Q1; Q3	xx.x; xx.x
	Min, Max	xx, xx
	Missing	xx

Population characteristics		All patients (N=xxx)
BMI (kg/m^2)	n	xx
	Mean (SD)	xx.x (xx.x)
	Median	xx.x
	Q1; Q3	xx.x; xx.x
	Min, Max	xx.x, xx.x
	Missing	xx
BMI categories (kg/m^2)	<18.5	xx (xx.x)
	>=18.5 - <25	xx (xx.x)
	>=25 - <30	xx (xx.x)
	>=30 - <35	xx (xx.x)
	>=35	xx (xx.x)
	Missing	xx

[1] Age (years) = (date of first dose of eltrombopag - date of birth + 1 day)/ 365.25.
BMI: Body mass index calculated as weight (kg)/[height (m)]^2
Program Path: Y:\Novartis\.[redacted]

Table 1.3 Eltrombopag Treatment Exposure by visit

Time/Item	Category	All patients (N=xxx)
Baseline		
Currently being treated with eltrombopag	n	xx
	Yes	xx (xx.x)
	No (not yet initiated)	xx (xx.x)
If yes, daily dose [1]	n	xx
	12.5 mg	xx (xx.x)
	25 mg	xx (xx.x)
	50 mg	xx (xx.x)
	75 mg	xx (xx.x)
	100 mg	xx (xx.x)
	Other	xx (xx.x)
	Missing	xx
Duration of eltrombopag treatment (days) [2]	n	xx
	Mean (SD)	xx.x (xx.x)
	Median	xx.x
	Q1; Q3	xx.x; xx.x
	Min, Max	xx.x, xx.x
	Missing	xx
Treatment change	n	xx

Time/Item	Category	All patients (N=xxx)
	None	xx (xx.x)
	Permanently discontinued	xx (xx.x)
	Temporarily discontinued	xx (xx.x)
	Dose change	xx (xx.x)
	Missing	xx
Primary reason for treatment change [3]	n	xx
	Platelets too high	xx (xx.x)
	Platelets too low	xx (xx.x)
	Treatment completed	xx (xx.x)
	Adverse event	xx (xx.x)
	Other	xx (xx.x)
	Missing	xx
Post Baseline: Entry 1		
Any changes to eltrombopag treatment?	n	xx
	Yes	xx (xx.x)
	No	xx (xx.x)
If yes, daily dose [1]	n	xx
	12.5 mg	xx (xx.x)
	25 mg	xx (xx.x)
	50 mg	xx (xx.x)
	75 mg	xx (xx.x)

Time/Item	Category	All patients (N=xxx)
	100 mg	xx (xx.x)
	Other	xx (xx.x)
	Missing	xx
Duration of eltrombopag treatment (days) [2]	n	xx
	Mean (SD)	xx.x (xx.x)
	Median	xx.x
	Q1; Q3	xx.x; xx.x
	Min, Max	xx.x, xx.x
	Missing	xx
Treatment change	n	xx
	None	xx (xx.x)
	Permanently discontinued	xx (xx.x)
	Temporarily discontinued	xx (xx.x)
	Dose change	xx (xx.x)
	Missing	xx
Primary reason for treatment change [3]	n	xx
	Platelets too high	xx (xx.x)
	Platelets too low	xx (xx.x)
	Treatment completed	xx (xx.x)
	Adverse event	xx (xx.x)
	Other	xx (xx.x)

Time/Item	Category	All patients (N=xxx)
	Missing	xx

Repeated for **Post Baseline: Entry 2,3….**

…

[1] Percentages are calculated using number of patients who answered “Yes” in previous question.

[2] Duration of eltrombopag treatment (days) = eltrombopag treatment stop date – start date + 1 day.

[3] Percentages are based on number of patients who chose “Permanently/Temporarily discontinued” and “Dose change”.

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Part 2: Safety outcomes

Tables – Safety

Table 2.1 Prevalence of adverse events by system organ class and preferred term

System Organ Class / Preferred Term	Patients with at least one event N= xx	Total number of events
Any Adverse Event (n)	xx (xx.x)	xx
Yes	xx (xx.x)	
No	xx (xx.x)	
Missing	xx	
System Organ Class 1	xx (xx.x)	xx
Preferred Term 1	xx (xx.x)	xx
Preferred Term 2	xx (xx.x)	xx
System Organ Class 2	xx (xx.x)	xx
Preferred Term 1	xx (xx.x)	xx
Preferred Term 2	xx (xx.x)	xx
etc		

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Table 2.2 Prevalence of adverse events by system organ class and preferred term and maximum severity

System Organ Class / Preferred Term	Patients with at least one event N= xx	Total number of events
Any Adverse Event (n)	xx (xx.x)	xx
Yes	xx (xx.x)	
No	xx (xx.x)	
Missing	xx	
Severity		
Mid	xx (xx.x)	xx
Moderate	xx (xx.x)	xx
Severe	xx (xx.x)	xx
System Organ Class 1	xx (xx.x)	xx
Severity		
Mid	xx (xx.x)	xx
Moderate	xx (xx.x)	xx
Severe	xx (xx.x)	xx
Preferred Term 1	xx (xx.x)	xx
Severity		
Mid	xx (xx.x)	xx
Moderate	xx (xx.x)	xx
Severe	xx (xx.x)	xx

System Organ Class / Preferred Term	Patients with at least one event N= xx	Total number of events
Preferred Term 2	xx (xx.x)	xx
Severity		
Mid	xx (xx.x)	xx
Moderate	xx (xx.x)	xx
Severe	xx (xx.x)	xx
etc		

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The following are repeats of the above format:

Table 2.3 Prevalence of serious adverse events (SAEs) by system organ class and preferred term
Table 2.4 Prevalence of adverse drug reactions (ADRs) by system organ class and preferred term
Table 2.5 Prevalence of serious adverse drug reactions (SADRs) by system organ class and preferred term
Table 2.6 Prevalence of serious/non-serious adverse drug reactions [(S)ADRs] leading to discontinuation of eltrombopag by system organ class and preferred term

Table 2.7 Prevalence of adverse events by system organ class and preferred term and maximum severity

System Organ Class / Preferred Term	Patients with at least one event N=xxx	Total number of events
Any Adverse Event	xx (xx.x)	xx
Yes	xx (xx.x)	
No	xx (xx.x)	
Missing	xx	
Severity		
Mid	xx (xx.x)	xx
Moderate	xx (xx.x)	xx
Severe	xx (xx.x)	xx
System Organ Class 1	xx (xx.x)	xx
Severity		
Mid	xx (xx.x)	xx
Moderate	xx (xx.x)	xx
Severe	xx (xx.x)	xx
Preferred Term 1	xx (xx.x)	xx
Severity		
Mid	xx (xx.x)	xx
Moderate	xx (xx.x)	xx
Severe	xx (xx.x)	xx

System Organ Class / Preferred Term	Patients with at least one event N=xxx	Total number of events
Preferred Term 2	xx (xx.x)	xx
Severity		
Mid	xx (xx.x)	xx
Moderate	xx (xx.x)	xx
Severe	xx (xx.x)	xx
etc		

Program Path: Y:\Novartis\..[redacted]

The following are repeat tables of the above format:

Table 2.8 Prevalence of serious adverse events (SAEs) by system organ class and preferred term and maximum severity

Table 2.9 Prevalence of adverse drug reactions (ADRs) by system organ class and preferred term and maximum severity

Table 2.10 Prevalence of serious adverse drug reactions (SADRs) by system organ class and preferred term and maximum severity

Appendix 10 – Documentation of inter-laboratory standardization methods and quality assurance procedures

** This Appendix is not applicable **

Appendix 11 – Publications based on the study

** There are no publications based on the study **

Appendix 12 – Important Publications

Literature cited in the Clinical Study Report is provided upon request.

1. Afdhal NH, Dusheiko GM, Giannini EG, et al (2014). Eltrombopag increases platelet numbers in thrombocytopenic patients with HCV infection and cirrhosis, allowing for effective antiviral therapy. Gastroenterology; 146(2):442-452.

2. Backus LI, Boothroyd DB, Phillips BR, et al (2011). A sustained virologic response reduces risk of all-cause mortality in patients with hepatitis C. Clinical Gastroenterology and Hepatology; 9(6):509-516.

3. Borroni G, Andreoletti M, Casiraghi M, et al (2008). Effectiveness of pegylated interferon/ribavirin combination in 'real world' patients with chronic hepatitis C virus infection. Alimentary Pharmacology & Therapeutics; 27(9):790-797.

4. European Medicines Agency (2012). Guideline on good pharmacovigilance practices (GVP). Module VIII – Post-authorisation safety studies. Available from http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/02/WC500123204.pdf (Accessed 07 Mar 2017).

5. International Society of Pharmacoepidemiology Public Policy Committee. (2016). Guidelines for Good Pharmacoepidemiology Practice (GPP). Pharmacoepidemiology and Drug Safety; 25(1):2.

6. Louie K, Micallef J, Pimenta J, et al (2011). Prevalence of thrombocytopenia among patients with chronic hepatitis C: a systematic review. Journal of Viral Hepatitis; 18(1):1-7.

7. McHutchison JG, Manns M, Patel K, et al (2002). Adherence to combination therapy enhances sustained response in genotype-1–infected patients with chronic hepatitis C. Gastroenterology; 123(4):1061-1069.

8. Roomer R, Hansen BE, Janssen HL, et al (2010). Thrombocytopenia and the risk of bleeding during treatment with peginterferon alfa and ribavirin for chronic hepatitis C. Journal of Hepatology; 53(3):455-459.

9. Swain MG, Lai MY, Shiffman ML, et al (2010). A sustained virologic response is durable in patients with chronic hepatitis C treated with peginterferon alfa-2a and ribavirin. Gastroenterology; 139(5):1593-1601.

10. Veldt BJ, Heathcote EJ, Wedemeyer H, et al (2007). Sustained virologic response and clinical outcomes in patients with chronic hepatitis C and advanced fibrosis. Annals of Internal Medicine; 147(10):677-684.

11. World Medical Association (2013). World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. Journal of the American Medical Association; 310(20):2191.

Annexes

Annex 1 – Tables

Table 1.1 Patient disposition

	All patients (N=9)
Number of patients enrolled, n	9
Early discontinuation, n (%)	1 (11.1)
Reason for discontinuation, n (%)	
Lost to follow-up	1 (100.0)
Death	0 (0.0)
Withdrawal of informed consent	0 (0.0)
Investigator choice	0 (0.0)
Time on study (months) [if discontinued]	
n	1
Mean (SD)	8.2 (-)
Median	8.2
Q1; Q3	8.2; 8.2
Min, Max	8.2, 8.2

Note: Study early termination was decided by the sponsor, in agreement with EMA, due to low enrollment. Early discontinuation reasons do not include study termination.

Table 1.2 Demographic Characteristics

Population characteristics		All patients (N=9)
Age (years)[1]	n	9
	Mean (SD)	46.0 (11.1)
	Median	45.0
	Q1; Q3	36.0; 55.0
	Min, Max	29.0, 62.0
	Missing	0
Age group (years)	n	9
	< 65	9 (100.0)
	>= 65	0
	Missing	0
Sex	n	9
	Male	8 (88.9)
	Female	1 (11.1)
	Missing	0
Ethnicity	n	9
	Hispanic/Latino	0
	Not Hispanic/Latino	7 (77.8)
	Not provided	2 (22.2)
	Missing	0
Geographic Ancestry	n	9
	[redacted]	[redacted]
Height (cm)	n	9
	Mean (SD)	174.1 (6.7)
	Median	172.0
	Q1; Q3	169.0; 180.0
	Min, Max	165.0, 183.0
	Missing	0

[1] Age (years) = (date of first dose of eltrombopag - date of birth + 1 day)/ 365.25.
BMI: Body mass index calculated as weight (kg)/[height (m)]^2

Table 1.2 Demographic Characteristics

Population characteristics		All patients (N=9)
Weight (kg)	n	9
	Mean (SD)	74.0 (8.0)
	Median	70.2
	Q1; Q3	70.0; 76.5
	Min, Max	66.5, 90.2
	Missing	0
BMI (kg/m^2)	n	9
	Mean (SD)	24.5 (3.1)
	Median	24.6
	Q1; Q3	21.6; 26.1
	Min, Max	20.3, 29.8
	Missing	0
BMI categories (kg/m^2)	n	9
	< 18.5	0
	18.5 - < 25	5 (55.6)
	25 - < 30	4 (44.4)
	30 - < 35	0
	>= 35	0
	Missing	0

[1] Age (years) = (date of first dose of eltrombopag - date of birth + 1 day)/ 365.25.
BMI: Body mass index calculated as weight (kg)/[height (m)]^2

Table 1.3 Eltrombopag Treatment Exposure by Visit

Time/Item	Category	All patients (N=9)
Baseline		
Currently being treated with eltrombopag	n	9
	Yes	8 (88.9)
	No (not yet initiated)	1 (11.1)
If yes, daily dose [1]	n	8
	12.5 mg	8 (100.0)
	25 mg	0 (0.0)
	50 mg	0 (0.0)
	75 mg	0 (0.0)
	100 mg	0 (0.0)
	Other	0 (0.0)
	Missing	0
Duration of eltrombopag treatment (days) [2]	n	8
	Mean (SD)	13.9 (11.3)
	Median	9.0
	Q1; Q3	6.5; 17.5
	Min, Max	6.0, 39.0
	Missing	0
Treatment change [1]	n	8
	None	0 (0.0)
	Permanently discontinued	7 (87.5)
	Temporarily discontinued	1 (12.5)
	Dose change	0 (0.0)
	Missing	0
Primary reason for treatment change [3]	n	8
	Platelets too high	0 (0.0)
	Platelets too low	0 (0.0)
	Treatment completed	1 (12.5)
	Adverse event	0 (0.0)
	Other	7 (87.5)
	Missing	0

[1] Percentages are calculated using number of patients who answered “Yes” in previous question.
[2] Duration of eltrombopag treatment (days) = eltrombopag treatment stop date – start date + 1 day.
[3] Percentages are based on number of patients who chose “Permanently/Temporarily discontinued” or “Dose change”.

Table 1.3 Eltrombopag Treatment Exposure by Visit

Time/Item	Category	All patients (N=9)
Post Baseline: Entry 1		
Any changes to eltrombopag treatment?	n	9
	Yes	1 (11.1)
	No	8 (88.9)
If yes, daily dose [1]	n	1
	12.5 mg	0 (0.0)
	25 mg	1 (100.0)
	50 mg	0 (0.0)
	75 mg	0 (0.0)
	100 mg	0 (0.0)
	Other	0 (0.0)
	Missing	0
Duration of eltrombopag treatment (days) [2]	n	1
	Mean (SD)	4.0 (-)
	Median	4.0
	Q1; Q3	4.0; 4.0
	Min, Max	4.0, 4.0
	Missing	0
Treatment change [1]	n	1
	None	0 (0.0)
	Permanently discontinued	0 (0.0)
	Temporarily discontinued	0 (0.0)
	Dose change	1 (100.0)
	Missing	0
Primary reason for treatment change [3]	n	1
	Platelets too high	0 (0.0)
	Platelets too low	1 (100.0)
	Treatment completed	0 (0.0)
	Adverse event	0 (0.0)
	Other	0 (0.0)
	Missing	0

[1] Percentages are calculated using number of patients who answered “Yes” in previous question.
[2] Duration of eltrombopag treatment (days) = eltrombopag treatment stop date – start date + 1 day.
[3] Percentages are based on number of patients who chose “Permanently/Temporarily discontinued” or “Dose change”.

Table 1.3 Eltrombopag Treatment Exposure by Visit

Time/Item	Category	All patients (N=9)
Post Baseline: Entry 2		
Any changes to eltrombopag treatment?	n	8
	Yes	2 (25.0)
	No	6 (75.0)
If yes, daily dose [1]	n	2
	12.5 mg	1 (50.0)
	25 mg	0 (0.0)
	50 mg	1 (50.0)
	75 mg	0 (0.0)
	100 mg	0 (0.0)
	Other	0 (0.0)
	Missing	0
Duration of eltrombopag treatment (days) [2]	n	2
	Mean (SD)	40.0 (46.7)
	Median	40.0
	Q1; Q3	7.0; 73.0
	Min, Max	7.0, 73.0
	Missing	0
Treatment change [1]	n	2
	None	0 (0.0)
	Permanently discontinued	2 (100.0)
	Temporarily discontinued	0 (0.0)
	Dose change	0 (0.0)
	Missing	0
Primary reason for treatment change [3]	n	2
	Platelets too high	0 (0.0)
	Platelets too low	0 (0.0)
	Treatment completed	1 (50.0)
	Adverse event	0 (0.0)
	Other	1 (50.0)
	Missing	0

[1] Percentages are calculated using number of patients who answered “Yes” in previous question.
[2] Duration of eltrombopag treatment (days) = eltrombopag treatment stop date – start date + 1 day.
[3] Percentages are based on number of patients who chose “Permanently/Temporarily discontinued” or “Dose change”.

Table 1.3 Eltrombopag Treatment Exposure by Visit

Time/Item	Category	All patients (N=9)
Post Baseline: Entry 3		
Any changes to eltrombopag treatment?	n	1
	Yes	0 (0.0)
	No	1 (100.0)
If yes, daily dose [1]	n	0
	12.5 mg	0 (0.0)
	25 mg	0 (0.0)
	50 mg	0 (0.0)
	75 mg	0 (0.0)
	100 mg	0 (0.0)
	Other	0 (0.0)
	Missing	0
Duration of eltrombopag treatment (days) [2]	n	0
	Mean (SD)	
	Median	
	Q1; Q3	
	Min, Max	
	Missing	
Treatment change [1]	n	0
	None	0 (0.0)
	Permanently discontinued	0 (0.0)
	Temporarily discontinued	0 (0.0)
	Dose change	0 (0.0)
	Missing	0
Primary reason for treatment change [3]	n	0
	Platelets too high	0 (0.0)
	Platelets too low	0 (0.0)
	Treatment completed	0 (0.0)
	Adverse event	0 (0.0)
	Other	0 (0.0)
	Missing	0

[1] Percentages are calculated using number of patients who answered “Yes” in previous question.
[2] Duration of eltrombopag treatment (days) = eltrombopag treatment stop date – start date + 1 day.
[3] Percentages are based on number of patients who chose “Permanently/Temporarily discontinued” or “Dose change”.

Table 1.3 Eltrombopag Treatment Exposure by Visit

Time/Item	Category	All patients (N=9)
Post Baseline: Entry 4		
Any changes to eltrombopag treatment?	n	1
	Yes	0 (0.0)
	No	1 (100.0)
If yes, daily dose [1]	n	0
	12.5 mg	0 (0.0)
	25 mg	0 (0.0)
	50 mg	0 (0.0)
	75 mg	0 (0.0)
	100 mg	0 (0.0)
	Other	0 (0.0)
	Missing	0
Duration of eltrombopag treatment (days) [2]	n	0
	Mean (SD)	
	Median	
	Q1; Q3	
	Min, Max	
	Missing	
Treatment change [1]	n	0
	None	0 (0.0)
	Permanently discontinued	0 (0.0)
	Temporarily discontinued	0 (0.0)
	Dose change	0 (0.0)
	Missing	0
Primary reason for treatment change [3]	n	0
	Platelets too high	0 (0.0)
	Platelets too low	0 (0.0)
	Treatment completed	0 (0.0)
	Adverse event	0 (0.0)
	Other	0 (0.0)
	Missing	0

[1] Percentages are calculated using number of patients who answered “Yes” in previous question.
[2] Duration of eltrombopag treatment (days) = eltrombopag treatment stop date – start date + 1 day.
[3] Percentages are based on number of patients who chose “Permanently/Temporarily discontinued” or “Dose change”.

Table 2.1 Prevalence of adverse events by system organ class and preferred term

	Total Number of Patients N=9	
System Organ Class/ Preferred Term	Patients with Events n(%)	Total number of events
Any Adverse Event (n)	3 (33.3)	4
Blood and lymphatic system disorders	3 (33.3)	4
Anaemia	1 (11.1)	1
Neutropenia	1 (11.1)	1
Thrombocytopenia	2 (22.2)	2

Table 2.2 Prevalence of serious adverse events (SAEs) by system organ class and preferred term

System Organ Class/ Preferred Term	Patients with Events n(%)	Total number of events

Nothing to Report

Table 2.3 Prevalence of adverse drug reactions (ADRs) by system organ class and preferred term

System Organ Class/ Preferred Term	Patients with Events n(%)	Total number of events

Nothing to Report

Table 2.4 Prevalence of serious adverse drug reactions (SADRs) by system organ class and preferred term

System Organ Class/ Preferred Term	Patients with Events n(%)	Total number of events

Nothing to Report

Table 2.5 Prevalence of serious/non-serious adverse drug reactions [(S)ADRs] leading to discontinuation of eltrombopag by system organ class and preferred term

System Organ Class/ Preferred Term	Patients with Events n(%)	Total number of events

Nothing to Report

Table 2.6 Prevalence of adverse events by system organ class and preferred term and maximum intensity

	Total Number of Patients N=9	
System Organ Class/ Preferred Term	Patients with Events n(%)	Total number of events
Any Adverse Event (n)	3 (33.3)	4
Intensity		
Mild	1 (11.1)	1
Moderate	1 (11.1)	1
Severe	2 (22.2)	2
Blood and lymphatic system disorders	3 (33.3)	4
Intensity		
Mild	1 (11.1)	1
Moderate	1 (11.1)	1
Severe	2 (22.2)	2
Anaemia	1 (11.1)	1
Intensity		
Mild	1 (11.1)	1
Moderate	0 (0.0)	0
Severe	0 (0.0)	0
Neutropenia	1 (11.1)	1
Intensity		
Mild	0 (0.0)	0
Moderate	0 (0.0)	0
Severe	1 (11.1)	1
Thrombocytopenia	2 (22.2)	2
Intensity		
Mild	0 (0.0)	0
Moderate	1 (11.1)	1
Severe	1 (11.1)	1

Table 2.7 Prevalence of serious adverse events (SAEs) by system organ class and preferred term and maximum intensity

System Organ Class/ Preferred Term	Patients with Events n(%)	Total number of events

Nothing to Report

Table 2.8 Prevalence of adverse drug reactions (ADRs) by system organ class and preferred term and maximum intensity

System Organ Class/ Preferred Term	Patients with Events n(%)	Total number of events

Nothing to Report

Table 2.9 Prevalence of serious adverse drug reactions (SADRs) by system organ class and preferred term and maximum intensity

System Organ Class/ Preferred Term	Patients with Events n(%)	Total number of events

Nothing to Report

Annex 2 – Listings

Redacted