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A prospective observational cohort study nested within the Hepatitis C Therapeutic Registry and Research Network (HCV- TARGET) to evaluate real world use of eltrombopag in adult patients with chronic hepatitis C virus infection who are unable to initiate or maintain optimal interferon-based therapy due to thrombocytopenia

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Joint PASS	No

Research question and objectives	The primary objective of this study was to report the incidence of hepatic decompensation in a real-world setting in patients with chronic hepatitis C virus infection who received eltrombopag therapy with interferon-based therapy that also included direct-acting anti-viral agents. Secondary objectives were reporting the real-world incidences of thromboembolic events and mortality, and identifying risk factors for hepatic decompensation, thromboembolic events and mortality. The study also reported the 3-year incidence of hepatic decompensation and mortality, comparing patients who achieved sustained virologic response to patients who did not achieve sustained virological response among eltrombopag patients treated with interferon-based therapy and direct acting agents. The study also examined the effectiveness of eltrombopag to initiate and maintain Hepatitis C virus therapy and achieve early virologic response and sustained virological response among patients specifically using direct-acting anti-virals with interferon-based therapy.
Country(-ies) of study	United States of America

Marketing authorization holder

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

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1 Abstract

Title

A prospective observational cohort study nested within the Hepatitis C Therapeutic Registry and Research Network (HCV-TARGET) to evaluate real world use of eltrombopag in adult patients with chronic hepatitis C virus infection who are unable to initiate or maintain optimal interferon- based therapy due to thrombocytopenia

Keywords

Hepatitis C virus, thrombocytopenia

Rationale and background

Hepatitis C Virus (HCV) is a leading cause of chronic liver disease worldwide. Treatment consists of combination therapy with peginterferon and ribavirin (double therapy) or where appropriate, interferon, ribavirin and a direct-acting antiviral (DAA) agent (triple therapy). Thrombocytopenia as an interferon-related adverse event, or a complication of chronic liver disease, often necessitates dose reduction and discontinuation of interferon-based therapy.

Eltrombopag (Revolade®/Promacta®) is an oral second generation thrombopoietin receptor agonist which promotes megakaryocyte differentiation and proliferation. It was approved for chronic HCV-associated thrombocytopenia to allow for the initiation and maintenance of interferon-based therapy.

The incidence of hepatic decompensation, thromboembolic events and death events has been adequately assessed in previous randomized clinical studies, and the current label for eltrombopag contains a warning for hepatotoxicity, hepatic decompensation, and thromboembolic events. However, the occurrence of hepatic decompensation and other adverse events have not been characterized in thrombocytopenic HCV patients who have received direct-acting agents in combination with interferon-based therapy. This study took a proactive pharmacovigilance approach in generating the incidence of hepatic decompensation and other events through long-term follow-up of eltrombopag users in eltrombopag HCV patients undergoing interferon-based anti-HCV treatment with DAAs.

Research question and objectives

The primary objective of this study was to report the incidence of hepatic decompensation in patients with chronic HCV infection who received eltrombopag therapy with interferon-based therapy that also included DAAs.

Secondary objectives were reporting of real-world incidences of thromboembolic events and mortality, and identifying risk factors for hepatic decompensation, thromboembolic events and mortality. The study also examined the effectiveness of eltrombopag to maintain HCV therapy and achieve early virologic response and sustained virological response among patients specifically using DAAs with interferon-based therapy.

Study design

This study was nested within the on-going Hepatitis C Therapeutic Registry and Research Network. The HCV-TARGET study, which is a longitudinal observational research registry that follows HCV patients treated with anti-HCV regimens in a real-world setting. The goals were to rapidly inform strategies for better management of populations underrepresented in clinical studies, identify and remediate gaps in treatment guidelines, and manage adverse events to optimize rates of sustained virological response. The planned enrolment was 5000 patients. It was comprised of 105 patients who received HCV therapy with DAAs (Sofosbuvir/Peg-Interferon/Ribavirin group, Boceprevir/Peg-Interferon/Ribavirin group, and Telaprevir/Peg-Interferon/Ribavirin group), including all patients treated with eltrombopag. Patients were followed for up to three years after eltrombopag initiation.

Setting

Patients were all enrolled from the [redacted]

HCV-TARGET utilizes a novel, standardized, centralized source data abstraction core to abstract data from de-identified clinical source records provided from participating sites.

Subjects and study size, including dropouts

All patients treated with eltrombopag who were participants of the HCV-TARGET were included in this study. It was estimated that between 1%-3% of the 5000 HCV-TARGET patients would receive eltrombopag and be eligible for the nested eltrombopag cohort study, for a sample size between 50 and 150 patients.

Variables and data sources

The endpoints of this study were: hepatic decompensation, thromboembolic events, mortality, and the treatment effectiveness among eltrombopag users assessed as percentage of reaching early virologic response, percentage of achieved sustained virological response, change in platelet counts before and during antiviral therapy among those able to initiate antiviral therapy.

Within HCV-TARGET, patients were enrolled prospectively at participating sites and treated per local standard of care. The source data was the original medical record.

This is the final report of this study, which is based on a pre-specified interim analysis (cut-off date: 10-May-2016). Since no patients are currently enrolled, there will be no further reports for this study.

Results

A total of 61 patients received eltrombopag with antiviral therapy. At baseline, 63.9% of patients had prior exposure to HCV treatment, 82.0% had cirrhosis, and 19.7% had prior hepatic decompensation. After enrollment on the study, 4 of 61 patients developed hepatic decompensation. One of these 4 patients had a history of prior decompensation. Treatment outcome (virologic response) was available in 48 of 61 patients enrolled in the study (34 with prior treatment and 14 treatment naive). 13 patients who were previously treated and 7 treatment naive patients achieved a sustained virologic response. Baseline platelet count ranged from 28,000 to 260,000/µL and on treatment, the platelet count ranged from 25,000 to 85,000/µL at week 4 (n=15) and 27,000 to 117,000/µL at week 16 (n=7). Seven patients (11.5%) had at least one serious adverse event on treatment. The most common serious adverse events were thrombocytopenia (5 patients, 8.2%) and anemia (4 patients, 6.6%). All patients had at least one adverse event, and 5 patients discontinued treatment early because of thrombocytopenia. There were no thromboembolic events. One death occurred as a result of fungal sepsis.

Discussion

Hepatic decompensation occurred in 4 of the 61 enrolled patients and one of these patients had evidence of prior decompensation. Eltrombopag should only be administered to chronic HCV patients with cirrhosis after careful consideration of the expected benefits in comparison with the risks. Patients with these characteristics should be closely monitored for signs and symptoms of hepatic decompensation. No patient experienced a thromboembolic event during the period covered by this report. One death occurred as a result of fungal sepsis.

As would be expected with interferon based antiviral treatment, several patients developed thrombocytopenia on treatment. Of note is that several patients had subsequent improvement in platelet counts allowing patients to remain on therapy.

This observational study provides important safety and efficacy data in HCV patients treated with eltrombopag in combination with interferon, ribavirin and a DAA (triple therapy) with respect to initiating, maintaining and completing HCV therapy. No new trends in safety were observed with the combination of eltrombopag in combination with interferon containing antiviral regimens. Of these 48 patients 20 (13 previously treated and 7 treatment naive) achieved a sustained virologic response.

Marketing Authorization Holder(s)

Novartis Europharm Limited

Name(s) and Affiliation(s) of Principal Investigator(s)

[redacted]

2 List of abbreviations

AE	Adverse Event
CCC	Clinical Coordinating Center
DAA	Direct-acting antiviral
DCC	Data Coordinating Center
HCV	Hepatitis C Virus
HCV-TARGET	Hepatitis C Therapeutic Registry and Research Network
RNA	Ribonucleic acid
SAE	Serious Adverse Event
SVR	Sustained virological response

3 Investigators

[redacted]

4 Other responsible parties

Not applicable

5 Milestones

Table 5-1 Study milestones

Milestone	Planned date	Actual date	Comments
Start of data collection	After protocol approval	12-Aug-2014	
End of data collection	2018		
Data collection for interim analysis	Mar-2016	10-May-2016	
Final report of study results	Jul-2018		

6 Rationale and background

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

Eltrombopag (Revolade®/Promacta®) is an oral second generation thrombopoietin receptor agonist, which promotes megakaryocyte differentiation and proliferation. Eltrombopag (Promacta) was approved in the U.S. in November 2012 for chronic HCV-associated thrombocytopenia to allow for the initiation and maintenance of interferon-based therapy. Eltrombopag (Revolade) was approved in the European Union in September 2013 for the treatment of thrombocytopenia in adult patients with HCV, where the degree of thrombocytopenia is the main factor preventing the initiation or limiting the ability to maintain optimal interferon-based therapy. Eltrombopag allows patients who would otherwise have been poor candidates due to low platelet counts to undergo interferon-based therapy for HCV.

In randomized clinical studies, there was an increased incidence of hepatic decompensation events that occurred in the eltrombopag arm vs. the placebo arm (10% vs 5%, respectively), an increased incidence of thromboembolic events (3% vs 1%), and a higher death event (3% vs 2%) (Afdhal et al 2014). The incidence of hepatic decompensation and thromboembolic events has been adequately assessed in previous randomized double-blinded placebo controlled clinical studies that included more than 1,500 patients and the current label for eltrombopag contains a warning for hepatotoxicity and hepatic decompensation. However, the occurrence of hepatic decompensation and other adverse events have not been characterized in thrombocytopenic HCV patients who have received direct acting agents in combination with interferon-based therapy.

The landscape of antiviral care in patients with chronic HCV has drastically changed since approval of the HCV-TARGET study. With the evolution of the 2nd generation DAA, nearly all steps of the HCV life-cycle have become sensitive to pharmacological intervention, including entry, translation, ribonucleic acid (RNA) replication, assembly and export of progeny viruses (Schmidt et al 2014). Currently, all-oral regimens offer sustained virological response (SVR) rates above 90% as well as 12-week treatment regimens for most treatment-experienced patients. There are multiple DAA combinations that can be selected to optimize SVR outcomes in patients previously treated, and these therapies can be selected to meet the needs of the patient with respect to HCV genotype and subtype, previous therapy, and presence of cirrhosis (Peter and Nelson 2015). Thus, the new 2nd generation of DAAs have afforded shortened treatment times, fewer adverse reactions, and improved achievement of SVR, and benefits could be achieved in some patients with favorable HCV genotypes without the burden of interferon.

This study took a proactive pharmacovigilance approach in generating the incidence of hepatic decompensation and other events through long-term follow-up of eltrombopag users in HCV patients undergoing interferon-based anti-HCV treatment with DAAs.

This is the final report of this study, which is based on a pre-specified interim analysis (cut-off date: 10-May-2016). Since no patients are currently enrolled, there will be no further reports for this study.

7 Research question and objectives

The primary objective of this study was to report the incidence of hepatic decompensation in patients with chronic hepatitis C virus infection who received eltrombopag therapy with interferon-based therapy that also included direct-acting antiviral agents.

Secondary objectives were reporting the real-world incidences of thromboembolic events and mortality, and identifying risk factors for hepatic decompensation, thromboembolic events and mortality. The study also examined the effectiveness of eltrombopag to maintain HCV therapy and achieve early virologic response and SVR among patients specifically using DAAs with interferon-based therapy.

The study population was limited to all eligible subjects with completed datasets identified as patients who had recorded date of the end of treatment.

8 Amendments and updates to the protocol

There were no amendments or updates to the protocol.

9 Research methods

9.1 Study design

The study was nested within the on-going Hepatitis C Therapeutic Registry and Research Network. The HCV-TARGET study was a longitudinal observational research registry that follows HCV patients treated with anti-HCV regimens in a real-world setting. The goals were to inform strategies for better management of populations under-represented in clinical studies, identify and remediate gaps in treatment guidelines, and manage adverse events to optimize rates of SVR. It was comprised of patients who received HCV therapy with DAAs. The planned enrolment was 5000 patients. This study nested with the HCV-TARGET study was planned to comprise 105 patients who received HCV therapy with DAAs (Sofosbuvir/Peg-Interferon/Ribavirin group, Boceprevir/Peg-Interferon/Ribavirin group, and Telaprevir/Peg-Interferon/Ribavirin group), including all patients treated with eltrombopag. Patients were planned to be followed for up to three years after eltrombopag initiation. An interim analysis was planned to be conducted in 2016 and the final analysis was planned for 2018.

9.2 Setting

This is an investigator conducted study. The Hepatitis C Therapeutic Registry and Research Network is a consortium of more than 103 academic and community investigators enrolling patients treated with i-HCV regimens with direct-acting agents. The first patient was enrolled on November 11, 2011. As of January 2014, 2845 patients have been enrolled in 103 [redacted]. sites.

HCV-TARGET utilizes a novel, standardized, centralized source data abstraction core to abstract data from de-identified clinical source records provided from participating sites. Demographic, clinical, adverse event, virological, and long-term post treatment follow-up, including co-morbid conditions, complications related to liver disease, mortality, and adverse events associated with HCV-treatment were obtained and subsequently verified by a separate monitoring team housed at the Data Coordinating Centre (DCC). Members of the data abstraction team are highly trained and quality control practices, including the development of standardized chart data abstraction conventions pertinent to clinically-based, real-world records have been implemented to ensure data quality, consistency, and error reductions.

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

9.3 Subjects

All patients treated with eltrombopag who were participants of the HCV-TARGET were included in this study. Most patients received DAAs as part of their HCV therapy.

9.4 Variables

9.4.1 Outcomes

The main outcomes of study:

- Hepatic decompensation, defined as new onset or worsening of baseline of any of the following: ascites, hepatic encephalopathy, variceal bleeding, hepatopulmonary syndrome, hepatorenal syndrome, hepatic hydrothorax, spontaneous bacterial peritonitis.
- Thromboembolic events: myocardial infarction, ischemic stroke, portal vein thrombosis, deep vein thrombosis, pulmonary embolism.
- Mortality (all cause and cause-specific).
- Treatment effectiveness among eltrombopag users assessed as:
  a. Percentage of eltrombopag users reaching early virologic response, defined as clinically significant reduction in HCV RNA ($\geq$ 2 log10 drop or undetectable) after 12 weeks of antiviral treatment
  b. Percentage of eltrombopag users achieving SVR, defined by HCV RNA negative 12 weeks after cessation of treatment or later
  c. Change in platelet counts before and during antiviral therapy among those able to initiate antiviral therapy

9.4.2 Exposure

The main exposure variable was treatment with eltrombopag, in combination with peginterferon, ribavirin, and DAAs (triple therapy). Dose, duration of treatment, and drug discontinuation were available only for the HCV treatment regimen and not for Eltrombopag.

9.4.3 Other Planned Covariates

Demographics: age (< 65 years and ≥ 65 years), gender (Male, Female), race (White, Black or African American, or Other), ethnicity (Hispanic or Latino, Not Hispanic or Latino).

Virology data: HCV RNA value (log10 IU/mL), HCV Genotype (1, 2, 3, 4, 5, 6, Mixed, Unknown), HCV Genotype 1 subtype (1a, 1b, Others/Unknown), Previous HCV Treatment (Naive, Experienced), Previous protease inhibitor-failure patients with protease inhibitor-containing regimens as prior HCV therapy who had virological failure: (Yes, No).

Disease History was summarized for treated patients.

Duration of treatment in categories (< 6, 6-10, 10-14, 14-20, 20-28, > 28 Weeks).

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

Concomitant Medications were medications other than DAA, PEG-Interferon, ribavirin, and eltrombopag which were taken prior to the program therapy (before first dose day) and continued to be taken on and after the program therapy or medications which were started on or after the program therapy first dose day. Concomitant medications were summarized by frequencies and percentages. Concomitant medications were reported alphabetically by anatomic class, therapeutic class and generic name assigned by the World Health Organization dictionary. For each specific concomitant medication, the number and percentage of patients who took at least 1 dose of the medication was reported.

9.5 Data sources and measurement

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

These data included:

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

9.6 Bias

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

9.7 Study size

It was estimated that between 1%-3% of the 5000 HCV-TARGET patients received eltrombopag and were eligible for the nested eltrombopag cohort study, for a sample size between 50 and 150 patients.

9.8 Data transformation

Data was transmitted to the DCC at the [redacted] via a distributed web-based data entry system that was 21 Code of Federal Regulations, Part 11 validated and compliant. The DCC in conjunction with the Clinical Coordinating Center (CCC) at the [redacted] had established standardized systems and operational protocols to ensure data quality control.

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

DCC personnel in conjunction with the CCC closely monitored clinical center adherence to study protocol and data collection practices for complete and accurate research data. Monitoring was performed following an established Data Management and Clinical Monitoring Plan to facilitate the smooth conduct of the study. At the time of the on-site visit, DCC personnel had access to all study and patient documents and to clinical center personnel. All patient and study documents were kept confidential.

Identifiers such as patient name and address can be viewed by the DCC or CCC to facilitate remote monitoring, but these identifiers were not included on any datasets used for data analyses. For the purposes of Centralized Abstraction, sites redacted all protected health information identifiers from records before transmitting to the CCC. In instances where a protected health information identifier was presented on a record received at the CCC, delegated CCC personnel redacted that information.

The DCC resides in the [redacted]. The database was housed within a secure server environment of the data center on the [redacted], and governed by the standard [redacted] security guidelines.

The REDCap based data management system implemented for the HCV-TARGET registry was adapted to the specified Food and Drug Administration recommendations, and annual internal audits were performed to ensure compliance was achieved.

9.9 Statistical methods

9.9.1 Analysis sets

The study population consisted of all eligible subjects with recorded end of treatment dates. The efficacy population included a subset of safety population with available treatment outcomes.

9.9.2 Main summary measures

Descriptive statistics used for summaries of continuous variables (collected from case report form and derived) were number of observations, mean, standard deviation, median, 25th and 75th quartiles, and range. Descriptive statistics used for summaries of categorical variables were frequencies and percentages.

9.9.3 Main statistical methods

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

9.9.4 Missing values

SVR12 was calculated as HCV-RNA being below lower limit of quantification at 64 days or later port treatment cessation. This cutoff was used to the variability in follow up performed at the participating sites. In coding HCV-RNA levels we had arbitrarily assigned a value of 0 IU/mL if the lab result stated "undetected", 1 IU/mL if the report stated not quantified, but did not specifically state detected or not and 2 IU/mL if it stated that HCV RNA was detected, but could not be quantified. However a multitude of different assays were used by sites and data was not uniform when it came to lower limit of quantification and lower limit of detection.

9.9.5 Sensitivity analyses

Not applicable

9.9.6 Amendments to the statistical analysis plan

Not applicable

9.10 Quality control

The HCV-TARGET registry team commissioned qualified resources to conduct monitoring of the data. Clinical site visits and data monitoring were performed in accordance with the Clinical Monitoring Plan. Monitors inspected the operations. All monitoring activities were completed with a formal, written report which summarized the findings and highlights all recommendations and action items.

Designated CCC and Abstraction Core staff received detailed protocol, REDCap database and disease specific training as well as familiarity with the Study Reference Manual prior to being authorized for access to the HCV-TARGET data management system. The HCV-TARGET training session(s) was to be completed successfully before a cancer data access system was considered certified and authorized to abstract data from submitted records. Further to this specific analysis, the abstraction staff received specialized training for eltrombopag specific data forms and related data abstraction from the medical records.

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

To help minimize the frequency of errors, the Data Manager conducted regular conference calls with the Clinical Monitoring and Abstraction Core staff to discuss any consistently observed deficiencies in the use of the data management system. The clinical research associate maintained regular contact with the cancer data access system staff and addressed identified deficiencies. Also, provision of timely data quality reports was an important aspect of the Data Management function. In addition to documenting exemplary performance, these reports were provided a basis for setting goals for high-quality data collection, and for tracking progress towards achieving those goals. Data queries were generated by the Data Manager or clinical research associate in order to identify problems on an on-going basis.

10 Results

10.1 Participants

A total of 61 patients who received eltrombopag were enrolled in the nested eltrombopag HCV-TARGET cohort study. All of these patients took DAAs:

- 3 patients in Sofosbuvir/Peg-Interferon/Ribavirin group (SOF PEG RBV).
- 18 patients in Boceprevir/Peg-Interferon/Ribavirin group (BOC PEG RBV).
- 40 patients in Telaprevir/Peg-Interferon/Ribavirin group (TEL PEG RBV).

10.2 Disposition

All but 1 patient enrolled received treatment with an antiviral agent. At the cut-off date (10-May-2016) 26 patients (42.6%) completed treatment with an antiviral agent. Details of patient disposition are provided in the table below Table 10-1.

Table 10-1 Disposition of patients

	Treatment Group			
Variable	SOF PEG RBV (N=3)	BOC PEG RBV (N=18)	TEL PEG RBV (N=40)	Total (N=61)
All	3 (100.0%)	18 (100.0%)	40 (100.0%)	61 (100.0%)
Started treatment	3 (100.0%)	17 (94.4%)	40 (100.0%)	60 (98.4%)
Discontinued Prematurely	1 (33.3%)	9 (50.0%)	24 (60.0%)	34 (55.7%)
AE	1 (33.3%)	4 (22.2%)	16 (40.0%)	21 (34.4%)
Lack of efficacy	0	4 (22.2%)	7 (17.5%)	11 (18.0%)
Lost to follow-up	0	0	1 (2.5%)	1 (1.6%)
Other	0	1 (5.6%)	0	1 (1.6%)
Completed treatment	2 (66.7%)	8 (44.4%)	16 (40.0%)	26 (42.6%)
Lost to post Tx follow-up	1	0	0	1
Results not provided by site	0	4	8	12
Died	0	0	1 (2.5%)	1 (1.6%)

Source: Table 1

10.3 Demographics and baseline data

The majority of patients were male (72.1%) and aged 40-64 years. 63.9% of patients had prior exposure to HCV treatment, 82.0% had cirrhosis and 19.7% had prior hepatic decompensation. See (Table 10-2).

Additional demographic information is provided in Table 2.

Table 10-2 Demographics

	Treatment Group			
Variable	**SOF PEG RBV (N=3)**	**BOC PEG RBV (N=18)**	**TEL PEG RBV (N=40)**	**Total (N=61)**
SEX				
Female	2 (66.7%)	3 (16.7%)	12 (30.0%)	17 (27.9%)
Male	1 (33.3%)	15 (83.3%)	28 (70.0%)	44 (72.1%)
AGE				
40-64	3 (100.0%)	18 (100.0%)	33 (82.5%)	54 (88.5%)
65+	0	0	7 (17.5%)	7 (11.5%)
RACE				
White	3 (100.0%)	18 (100.0%)	32 (80.0%)	53 (86.9%)
Black or African American	0	0	6 (15.0%)	6 (9.8%)
Other or Pending	0	0	2 (5.0%)	2 (3.3%)
PRIOR HCV TREATMENT EXPERIENCE				
Naive	2 (66.7%)	9 (50.0%)	11 (27.5%)	22 (36.1%)
Experienced	1 (33.3%)	9 (50.0%)	29 (72.5%)	39 (63.9%)
CIRRHOSIS				
Not Cirrhotic	0	4 (22.2%)	6 (15.0%)	10 (16.4%)
Cirrhotic	3 (100.0%)	14 (77.8%)	33 (82.5%)	50 (82.0%)
Not reported	0	0	1 (2.5%)	1 (1.6%)
EVIDENCE OF PRIOR DECOMPENSATION				
Yes	1 (33.3%)	4 (22.2%)	7 (17.5%)	12 (19.7%)
No	2 (66.7%)	14 (77.8%)	33 (82.5%)	49 (80.3%)
HIV				
Yes	0	0	1 (2.5%)	1 (1.6%)
No	3 (100.0%)	18 (100.0%)	39 (97.5%)	60 (98.4%)
LIVER TRANSPLANT				
No	3 (100.0%)	18 (100.0%)	40 (100.0%)	61 (100.0%)

Source: Table 2

The baseline laboratory values are shown in Table 10-3.

Table 10-3 Baseline laboratory values

	Treatment Group			
Variable	SOF PEG RBV (N=3)	BOC PEG RBV (N=18)	TEL PEG RBV (N=40)	Total (N=61)
ALT (IU/L)	3	17	39	59
Mean	93.0	92.0	117.7	109.1
Median	62.0	79.0	88.0	85.0
Std	71.71	55.85	78.88	72.55
Min Max	42.0-175.0	32.0-205.0	24.0-392.0	24.0-392.0
Q1 Q3	42.0-175.0	48.5-135.0	63.0-158.0	53.0-146.0
AST (IU/L)	3	17	39	59
Mean	138.0	110.1	112.6	113.2
Median	161.0	86.0	108.0	96.0
Std	73.26	89.19	63.77	71.26
Min Max	56.0-197.0	30.0-354.0	21.0-328.0	21.0-354.0
Q1 Q3	56.0-197.0	53.5-110.5	64.0-142.0	60.0-142.0
TOTAL BILIRUBIN				
≤ 3	2 (66.7%)	16 (88.9%)	36 (90.0%)	54 (88.5%)
>3	1 (33.3%)	0	1 (2.5%)	2 (3.3%)
Not reported	0	2 (11.1%)	3 (7.5%)	5 (8.2%)
Baseline PLT				
100,000+	0	7 (38.9%)	6 (15.0%)	13 (21.3%)
<100,000	3 (100.0%)	9 (50.0%)	33 (82.5%)	45 (73.8%)
Not reported	0	2 (11.1%)	1 (2.5%)	3 (4.9%)
Baseline ALB (cat)				
3.2+	1 (33.3%)	15 (83.3%)	33 (82.5%)	49 (80.3%)
<3.2	2 (66.7%)	1 (5.6%)	5 (12.5%)	8 (13.1%)
Not reported	0	2 (11.1%)	2 (5.0%)	4 (6.6%)
CREATININE (mg/dL)				
≤ 1.5	3 (100.0%)	17 (94.4%)	37 (92.5%)	57 (93.4%)
>2.0	0	0	1 (2.5%)	1 (1.6%)
Not reported	0	1 (5.6%)	2 (5.0%)	3 (4.9%)
CREATININE CLEARANCE				
>30	3 (100.0%)	17 (94.4%)	36 (90.0%)	56 (91.8%)
Not reported	0	1 (5.6%)	4 (10.0%)	5 (8.2%)

	Treatment Group			
Variable	SOF PEG RBV (N=3)	BOC PEG RBV (N=18)	TEL PEG RBV (N=40)	Total (N=61)
MELD CIRRHOTIC				
0-9	1 (33.3%)	6 (33.3%)	12 (30.0%)	19 (31.1%)
10-15	1 (33.3%)	2 (11.1%)	3 (7.5%)	6 (9.8%)
16-21	0	0	1 (2.5%)	1 (1.6%)
Not reported	1 (33.3%)	6 (33.3%)	17 (42.5%)	24 (39.3%)
Not cirrh	0	4 (22.2%)	6 (15.0%)	10 (16.4%)
Unknown c	0	0	1 (2.5%)	1 (1.6%)
BASELINE_MELD_CIRR_				
10+	1 (33.3%)	2 (11.1%)	4 (10.0%)	7 (11.5%)
<10	1 (33.3%)	6 (33.3%)	12 (30.0%)	19 (31.1%)
Not reported	1 (33.3%)	6 (33.3%)	17 (42.5%)	24 (39.3%)
Not cirrhotic	0	4 (22.2%)	6 (15.0%)	10 (16.4%)
Unknown	0	0	1 (2.5%)	1 (1.6%)
[1]MELD_ AMONG CIRRHOTICS	2	8	16	26
Mean	11.5	8.5	9.0	9.0
Median	11.5	8.5	8.0	8.0
Std	4.95	1.20	3.46	3.03
Min Max	8.0–15.0	7.0–10.0	6.0–20.0	6.0–20.0
Q1 Q3	8.0–15.0	7.3–9.8	7.0–9.8	7.0–10.0
HEMOGLOBIN (g/dL)	3	17	39	59
Mean	12.7	14.4	14.1	14.1
Median	12.6	14.4	13.9	14.0
Std	0.60	0.89	1.72	1.52
Min Max	12.1–13.3	12.7–16.1	10.6–17.9	10.6–17.9
Q1 Q3	12.1–13.3	13.9–15.0	13.2–15.3	13.3–15.2
HCV RNA (IU/mL)	3	17	39	59
Mean	1660333.3	3799076.5	2395970.3	2762849.9
Median	1880000.0	1964703.0	1389139.0	1682740.0
Std	1234248.89	4477937.90	2595342.05	3235013.37
Min Max	331000-2770000	59419-17600000	3147-12200000	3147-17600000
Q1 Q3	331000-2770000	308008-6130000	540863-2960000	535000-4143279
HCV RNA (IU/mL, log10)	3	17	39	59
Mean	6.1	6.1	6.1	6.1
Median	6.3	6.3	6.1	6.2
Std	0.49	0.79	0.69	0.71
Min Max	5.5-6.4	4.8-7.2	3.5-7.1	3.5-7.2
Q1 Q3	5.5-6.4	5.4-6.8	5.7-6.5	5.7-6.6

	Treatment Group			
Variable	SOF PEG RBV (N=3)	BOC PEG RBV (N=18)	TEL PEG RBV (N=40)	Total (N=61)
HCV RNA (cat)				
Not reported	0	1 (5.6%)	1 (2.5%)	2 (3.3%)
Quant	3 (100.0%)	17 (94.4%)	39 (97.5%)	59 (96.7%)

[1]MELD (Model for End-Stage Liver Disease) is a scoring system for assessing the severity of chronic liver disease.
Source: Table 3

10.4 Results

10.4.1 Incidence of hepatic decompensation

After enrollment on the study, 4 of 61 patients had developed hepatic decompensation Table 2a. As shown in the Kaplan-Meier plot Appendix 1.2 no patient had a decompensation event beyond day 100.

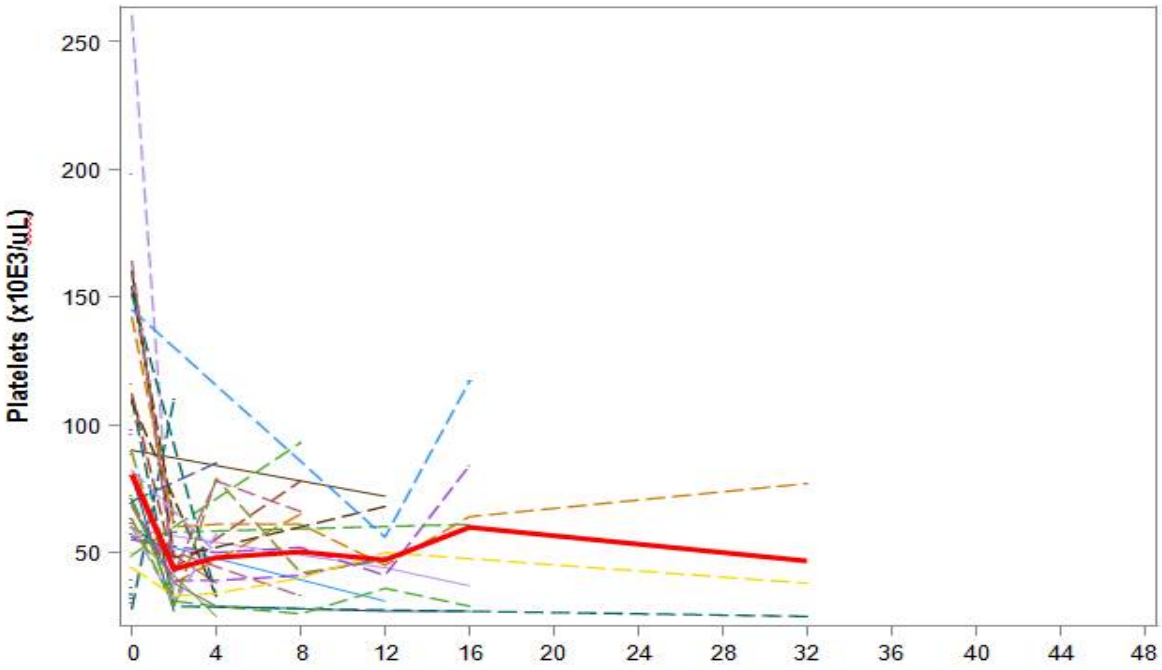
10.4.2 Response to antiviral therapies

Treatment outcome was available in 48 of 61 patients enrolled in the study (34 with prior treatment and 14 treatment naive). In total of 48 patients, 13 patients who were previously treated and 7 treatment naive patients achieved a SVR. Additional efficacy data is provided in Table 8a.

10.4.3 Platelet data

At baseline, the median platelet counts for 58 eltrombopag treated patients was 69,000/µL (range 28,000 to 260,000/µL) and 45 patients (73.8%) had a platelet count lower than 100,000/ µL. On treatment the platelet count ranged from 25,000 to 85,000/µL at week 4 (n=15) and 27,000 to 117,000/µL at week 16 (n=7). Changes in individual platelet data is presented in the graph below (Figure 10-1). As would be expected, after treatment with a combination of anti HCV therapy and interferon, several patients had a drop in platelet count. Of note is that several patients had a subsequent improvement in platelet counts.

Figure 10-1 Platelet values over the course of treatment (mean value of platelet shown in red bold line)



Source: Figure 6

10.5 Other analyses

Other analysis are provided in Figure 1 to Figure 8.

10.6 Adverse events/adverse reactions

An overall summary of AEs associated with anti-HCV therapy is provided in Table 10-4.

10.6.1 Adverse events

As shown in Table 10-4, all patients had at least one AE. The most common AEs were thrombocytopenia (47 patients, 77.0%), followed by anemia (46 patients, 75.4%), rash (32 patients, 52.5%), neutropenia (19 patients, 31.1%), and anorectal discomfort (17 patients, 27.9%).

Hepatic encephalopathy (n=5) was the most frequently reported decompensating event, followed by ascites (n=2).

Table 10-4 Adverse events associated with anti-HCV therapy by system organ class, number and percentage of patients, by treatment regimen group and overall (incidence greater than 5% in PT of overall arm)

	Treatment Group							
	SOF PEG RBV (N=3)		BOC PEG RBV (N=18)		TEL PEG RBV (N=40)		Overall (N=61)	
TXT_AEDECOD	nPt nPt/N	nAE	nPt nPt/N	nAE	nPt nPt/N	nAE	nPt nPt/N	nAE
TOTAL PATIENT WITH AE	3 (100.0)		18 (100.0)		40 (100.0)		61 (100.0)	
BLOOD AND LYMPHATIC SYSTEM DISORDERS	2 (66.7)	4	18 (100.0)	45	38 (95.0)	76	58 (95.1)	125
Thrombocytopenia	2 (66.7)	2	17 (94.4)	17	28 (70.0)	28	47 (77.0)	47
Anaemia	2 (66.7)	2	13 (72.2)	14	31 (77.5)	32	46 (75.4)	48
Neutropenia	0	0	9 (50.0)	9	10 (25.0)	12	19 (31.1)	21
Leukopenia	0	0	4 (22.2)	4	1 (2.5)	1	5 (8.2)	5
GASTROINTESTINAL DISORDERS	1 (33.3)	2	6 (33.3)	10	21 (52.5)	34	28 (45.9)	46
Anorectal Discomfort	0	0	4 (22.2)	4	13 (32.5)	13	17 (27.9)	17
Nausea	0	0	2 (11.1)	2	6 (15.0)	6	8 (13.1)	8
Diarrhoea	1 (33.3)	1	1 (5.6)	1	2 (5.0)	2	4 (6.6)	4
GENERAL DISORDERS AND ADMINISTRATION	2 (66.7)	5	7 (38.9)	8	11 (27.5)	19	20 (32.8)	32
Oedema Peripheral	1 (33.3)	1	4 (22.2)	4	3 (7.5)	3	8 (13.1)	8
Fatigue	1 (33.3)	1	2 (11.1)	2	4 (10.0)	4	7 (11.5)	7
Pyrexia	1 (33.3)	1	1 (5.6)	1	3 (7.5)	3	5 (8.2)	5
Influenza Like Illness	1 (33.3)	1	1 (5.6)	1	2 (5.0)	2	4 (6.6)	4
METABOLISM AND NUTRITION DISORDERS	0	0	3 (16.7)	3	7 (17.5)	16	10 (16.4)	19
Decreased Appetite	0	0	2 (11.1)	2	2 (5.0)	2	4 (6.6)	4
MUSCULOSKELETAL AND CONNECTIVE TISSUE	1 (33.3)	2	0	0	4 (10.0)	6	5 (8.2)	8
Arthralgia	1 (33.3)	1	0	0	3 (7.5)	3	4 (6.6)	4
NERVOUS SYSTEM DISORDERS	1 (33.3)	2	4 (22.2)	4	8 (20.0)	10	13 (21.3)	16
Hepatic Encephalopathy	0	0	2 (11.1)	2	3 (7.5)	3	5 (8.2)	5
PSYCHIATRIC DISORDERS	1 (33.3)	1	2 (11.1)	2	9 (22.5)	10	12 (19.7)	13
Depression	0	0	1 (5.6)	1	4 (10.0)	4	5 (8.2)	5
Insomnia	0	0	1 (5.6)	1	4 (10.0)	4	5 (8.2)	5
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	0	0	7 (38.9)	7	26 (65.0)	35	33 (54.1)	42
Rash	0	0	7 (38.9)	7	25 (62.5)	28	32 (52.5)	35

Source: Table 4

10.6.2 Deaths

One patient died during the study as a result of fungal sepsis Supplement 1.3 causes of death.

10.6.3 Serious adverse events

Seven patients (11.5%) had at least one serious adverse event (SAE) on treatment. The most common SAEs were thrombocytopenia (5 patients, 8.2%) and anaemia (4 patients, 6.6%) (Table 10-5).

Table 10-5 Serious adverse events by system organ class, number and percentage of patients, by treatment regimen group and overall

	Treatment Group							
	SOF PEG RBV (N=3)		BOC PEG RBV (N=18)		TEL PEG RBV (N=40)		Overall (N=61)	
TXT_AEDECOD	nPt nPt/N	nSAE	nPt nPt/N	nSAE	nPt nPt/N	nSAE	nPt nPt/N	nSAE
TOTAL PATIENT WITH SAE	1 (33.3)		1 (5.6)		5 (12.5)		7 (11.5)	
BLOOD AND LYMPHATIC SYSTEM DISORDERS	0	0	1 (5.6)	2	5 (12.5)	14	6 (9.8)	16
Thrombocytopenia	0	0	1 (5.6)	1	4 (10.0)	4	5 (8.2)	5
Anaemia	0	0	0	0	4 (10.0)	4	4 (6.6)	4
Neutropenia	0	0	0	0	2 (5.0)	4	2 (3.3)	4
Disseminated Intravascular Coagulation	0	0	0	0	1 (2.5)	1	1 (1.6)	1
Leukocytosis	0	0	0	0	1 (2.5)	1	1 (1.6)	1
Leukopenia	0	0	1 (5.6)	1	0	0	1 (1.6)	1
CARDIAC DISORDERS	0	0	0	0	1 (2.5)	1	1 (1.6)	1
Supraventricular Tachycardia	0	0	0	0	1 (2.5)	1	1 (1.6)	1
EAR AND LABYRINTH DISORDERS	0	0	0	0	1 (2.5)	1	1 (1.6)	1
Vertigo	0	0	0	0	1 (2.5)	1	1 (1.6)	1
ENDOCRINE DISORDERS	0	0	0	0	1 (2.5)	1	1 (1.6)	1
Hypothyroidism	0	0	0	0	1 (2.5)	1	1 (1.6)	1
GASTROINTESTINAL DISORDERS	0	0	0	0	4 (10.0)	10	4 (6.6)	10
Anorectal Discomfort	0	0	0	0	3 (7.5)	3	3 (4.9)	3
Nausea	0	0	0	0	2 (5.0)	2	2 (3.3)	2
Abdominal Pain	0	0	0	0	1 (2.5)	1	1 (1.6)	1
Chelitis	0	0	0	0	1 (2.5)	1	1 (1.6)	1
Colitis	0	0	0	0	1 (2.5)	1	1 (1.6)	1
Haematemesis	0	0	0	0	1 (2.5)	1	1 (1.6)	1
Vomiting	0	0	0	0	1 (2.5)	1	1 (1.6)	1
GENERAL DISORDERS AND ADMINISTRATION	1 (33.3)	3	1 (5.6)	1	1 (2.5)	3	3 (4.9)	7
Oedema Peripheral	1 (33.3)	1	1 (5.6)	1	1 (2.5)	1	3 (4.9)	3
Fatigue	1 (33.3)	1	0	0	1 (2.5)	1	2 (3.3)	2
Pyrexia	1 (33.3)	1	0	0	1 (2.5)	1	2 (3.3)	2
HEPATOBILIARY DISORDERS	0	0	0	0	1 (2.5)	1	1 (1.6)	1
Hyperbilirubinaemia	0	0	0	0	1 (2.5)	1	1 (1.6)	1

	Treatment Group							
	SOF PEG RBV (N=3)		BOC PEG RBV (N=18)		TEL PEG RBV (N=40)		Overall (N=61)	
TXT_AEDECOD	nPt nPt/N	nSAE	nPt nPt/N	nSAE	nPt nPt/N	nSAE	nPt nPt/N	nSAE
INFECTIONS AND INFESTATIONS	0	0	0	0	2 (5.0)	6	2 (3.3)	6
Fungal Sepsis	0	0	0	0	1 (2.5)	2	1 (1.6)	2
Oral Candidiasis	0	0	0	0	1 (2.5)	1	1 (1.6)	1
Parotitis	0	0	0	0	1 (2.5)	1	1 (1.6)	1
Pneumonia	0	0	0	0	1 (2.5)	1	1 (1.6)	1
Septic Shock	0	0	0	0	1 (2.5)	1	1 (1.6)	1
INVESTIGATIONS	0	0	0	0	1 (2.5)	1	1 (1.6)	1
Troponin Increased	0	0	0	0	1 (2.5)	1	1 (1.6)	1
METABOLISM AND NUTRITION DISORDERS	0	0	0	0	2 (5.0)	9	2 (3.3)	9
Blood Albumin Decreased	0	0	0	0	1 (2.5)	1	1 (1.6)	1
Blood Creatinine Increased	0	0	0	0	1 (2.5)	1	1 (1.6)	1
Decreased Appetite	0	0	0	0	1 (2.5)	1	1 (1.6)	1
Dehydration	0	0	0	0	1 (2.5)	1	1 (1.6)	1
Hyperglycaemia	0	0	0	0	1 (2.5)	1	1 (1.6)	1
Hypocalcaemia	0	0	0	0	1 (2.5)	1	1 (1.6)	1
Hyponatraemia	0	0	0	0	1 (2.5)	1	1 (1.6)	1
Hyperglycaemia	0	0	0	0	1 (2.5)	1	1 (1.6)	1
Metabolic Acidosis	0	0	0	0	1 (2.5)	1	1 (1.6)	1
MUSCULOSKELETAL AND CONNECTIVE TISSUE	1 (33.3)	2	0	0	2 (5.0)	3	3 (4.9)	5
Arthralgia	1 (33.3)	1	0	0	1 (2.5)	1	2 (3.3)	2
Joint Effusion	1 (33.3)	1	0	0	0	0	1 (1.6)	1
Myalgia	0	0	0	0	1 (2.5)	1	1 (1.6)	1
Rhabdomyolysis	0	0	0	0	1 (2.5)	1	1 (1.6)	1
NERVOUS SYSTEM DISORDERS	1 (33.3)	2	1 (5.6)	1	1 (2.5)	1	3 (4.9)	4
Dizziness	1 (33.3)	1	0	0	0	0	1 (1.6)	1
Hepatic Encephalopathy	0	0	1 (5.6)	1	0	0	1 (1.6)	1
Syncope	1 (33.3)	1	0	0	0	0	1 (1.6)	1
Trigeminal Neuralgia	0	0	0	0	1 (2.5)	1	1 (1.6)	1
PSYCHIATRIC DISORDERS	0	0	0	0	1 (2.5)	1	1 (1.6)	1
Depression	0	0	0	0	1 (2.5)	1	1 (1.6)	1
RENAL AND URINARY DISORDERS	0	0	0	0	1 (2.5)	1	1 (1.6)	1
Renal Failure Acute	0	0	0	0	1 (2.5)	1	1 (1.6)	1
REPRODUCTIVE SYSTEM AND BREAST DISORDER	0	0	0	0	1 (2.5)	1	1 (1.6)	1
Scrotal Oedema	0	0	0	0	1 (2.5)	1	1 (1.6)	1

	Treatment Group							
	SOF PEG RBV (N=3)		BOC PEG RBV (N=18)		TEL PEG RBV (N=40)		Overall (N=61)	
TXT_AEDECOD	nPt nPt/N	nSAE	nPt nPt/N	nSAE	nPt nPt/N	nSAE	nPt nPt/N	nSAE
RESPIRATORY, THORACIC AND MEDIASTINAL	1 (33.3)	1	0	0	1 (2.5)	1	2 (3.3)	2
Dyspnoea Exertional	1 (33.3)	1	0	0	0	0	1 (1.6)	1
Respiratory Failure	0	0	0	0	1 (2.5)	1	1 (1.6)	1
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	0	0	0	0	2 (5.0)	5	2 (3.3)	5
Rash	0	0	0	0	2 (5.0)	2	2 (3.3)	2
Blisters	0	0	0	0	1 (2.5)	1	1 (1.6)	1
Lichen Planus	0	0	0	0	1 (2.5)	1	1 (1.6)	1
Pruritus	0	0	0	0	1 (2.5)	1	1 (1.6)	1

Source: Table 5

10.6.4 Thromboembolic events

As of the cut-off date (10-May-2016), there were no thromboembolic events.

10.6.5 Other significant adverse events

5 patients were discontinued from the study for thrombocytopenia (Table 10-6). Other AEs leading to discontinuation are also shown in the table below, occurring in 1 patient each. Of note, 1 patient each discontinued for anasarca, ascites, hepatic encephalopathy, cerebral hemorrhage and conjunctival hemorrhage. Further information on whether these events were in patients with decompensation or whether these events were suspected to anti-virals or eltrombopag is not available. These and other events could occur in this patient population or could be associated with therapies used.

Table 10-6 AE leading to discontinuation

	Treatment regimen			
	SOF PEG RBV (N=1)	BOC PEG RBV (N=4)	TEL PEG RBV (N=16)	Total (N=21)
Variable	**n**	**n**	**n**	**n**
AE leading to discontinuation				
AE NOS	0	1	2	3
Abdominal pain	0	0	1	1
Anasarca	0	0	1	1
Ascites	0	1	0	1
Rash	0	0	1	1
Death NOS	0	0	1	1
Hepatic Encephalopathy	0	0	1	1
Cerebral Hemorrhage	0	0	1	1
Pneumonia	0	1	0	1
Neutropenia	0	1	0	1
Conjunctival Haemorrhage	0	0	1	1
Colitis	0	0	1	1
Pyrexia	0	0	1	1
Syncope	1	0	0	1
Thrombocytopenia	0	0	5	5

Source: Supplement 1.1

11 Discussion

11.1 Key results

A total of 61 patients received eltrombopag with antiviral therapy. At baseline, 63.9% of patients had prior exposure to HCV treatment, 82.0% had cirrhosis, and 19.7% had prior hepatic decompensation. After enrollment on the study, 4 of 61 patients developed hepatic decompensation. One of the 4 patients who developed decompensation on study, had prior evidence of decompensation. No patient experienced a thromboembolic event during the period covered by this report. SVR was achieved in 20 patients (13 with prior treatment and 7 treatment naive). On treatment the platelet count ranged from 25,000 to 85,000/µL at week 4 (n=15) and 27,000 to 117,000/µL at week 16 (n=7). Seven patients (11.5%) had at least one SAE on treatment. The most common SAEs were thrombocytopenia (5 patients, 8.2%) and anaemia (4 patients, 6.6%). All patients had at least one AE, and 5 patients discontinued treatment early because of thrombocytopenia. One death occurred as a result of fungal sepsis.

11.2 Limitations

The lack of randomization limits the ability to directly compare treatment groups, which is further compounded by the small number of patients enrolled in the study.

11.3 Interpretation

Small number of patients (61 patients) were in this study. Hepatic decompensation occurred in 4 patients and one of these patients had evidence of prior decompensation. The data also show that hepatic decompensation, if it occurs, develops early by day 100.

Safety data are in keeping with this patient population and treatment regimens. As would be expected with interferon based antiviral treatment, several patients developed thrombocytopenia on treatment. Of note is that several patients had subsequent improvement in platelet counts allowing patients to remain on therapy. In this cohort of 61 patients, only 5 patients discontinued the study for thrombocytopenia. No new trends in safety were observed with the combination of eltrombopag in combination with interferon containing antiviral regimens. No thromboembolic events occurred and 1 patient died of a fungal infection. Treatment outcome was available in 48 of 61 patients (34 with prior treatment and 14 treatment naive). Of these 48 patients 20 (13 previously treated and 7 treatment naive) achieved a sustained virologic response.

11.4 Generalizability

Data from this cohort cannot be generalized to other populations.

12 Other information

None.

13 Conclusion

This observational study provides important safety and efficacy data in HCV patients treated with eltrombopag in combination with interferon, ribavirin and a DAA (triple therapy) with respect to initiating, maintaining and completing HCV therapy. The incidence of hepatic decompensation was low with no new events occurring beyond day 100. As would be expected from interferon based antiviral regimens, several patients developed thrombocytopenia. However several patients had subsequent improvements in platelet counts allowing patients to remain on therapy. Only 5 patients discontinued the study for thrombocytopenia. Adverse event data is in keeping with the patient population being studied and the treatments used. No new trends in safety were noted with the use of eltrombopag in combination with interferon based antiviral regimens. A clinically significant number of patients achieved a SVR on therapy. This implies that the use of eltrombopag allows patients to be treated with interferon containing antiviral regimens.

14 References

Afdhal NH, Dusheiko GM, Giannini EG, et al (2014) Eltrombopag increases platelet numbers in thrombocytopenic patients with HCV infections and cirrhosis, allowing for effective antiviral therapy. Gastroenterology; 146(2):442-52.

Schmidt WN, Nelson DR, Pawlotsky JM, et al (2014) Direct acting agents and the path to interferon independence. Clin Gastroenterol Hepatol; 12:728-37.

Peter J, Nelson DR (2015) Optimal interferon-therapy in treatment experienced chronic hepatitis C patients. Liver Int; 35 Suppl 1:65-70.

Appendices

Protocol

Statistical Analysis Plan

CSR Signature page

Outcomes Part 1

Outcomes Part 2

Outcomes Part 3

TITLE PAGE

Division: Worldwide Development
Information Type: Worldwide Epidemiology Study Protocol

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

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

PASS information

Title	A prospective observational cohort study nested within the Hepatitis C Therapeutic Registry and Research Network (HCV-TARGET) to evalute real world use of eltrombopag in adult patients with chronic hepatitis C virus infection who are unable to initiate or maintain optimal interferon-based therapy due to thrombocytopenia.
Protocol version identifier	02
Date of last version of protocol	20-MAR-2014
EU PAS register number	To be registered after PRAC approval
Active substance	Eltrombopag
Medicinal product	Eltrombopag
Product reference	SB-497115-GR
Procedure number	Not applicable
Marketing authorisation holder(s)	GlaxoSmithKline Trading Services Limited [redacted]
Joint PASS	No
Research question and objectives	The primary objective of this study is to report the incidence of hepatic decompensation in a real-world setting in patients with chronic hepatitis C virus infection who receive eltrombopag therapy with interferon-based therapy that also includes direct acting anti-viral agents, a group not studied in the Phase III randomized clinical trials. Secondary objectives include reporting the real-world incidence of thromboembolic events and mortality and identifying risk factors for hepatic decompensation, thromboembolic events and mortality in this group of understudied patients. The study will also report the 3-year incidence of hepatic decompensation and mortality, comparing patients who achieve sustained

	virologic response to patients who do not achieve SVR among eltrombopag patients treated with interferon-based therapy and direct acting agents, which has not yet been studied. The study will also examine effectiveness of eltrombopag to initiate and maintain HCV therapy and achieve EVR and SVR among patients specifically using direct-acting anti-virals with interferon-based therapy.
Country(-ies) of study	[redacted]
Author	[redacted]

MARKETING AUTHORISATION HOLDER(S)

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

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1. LIST OF ABBREVIATIONS

AE	Adverse Event
EMA	European Medicines Agency
ENABLE 1	Eltrombopag to INitiate and Maintain Interferon Antiviral Treatment to Benefit Subjects with Hepatitis C related Liver DiseasE
ENABLE 2	Eltrombopag to INitiate and Maintain Interferon Antiviral Treatment to Benefit Subjects with Hepatitis C related Liver DiseasE
GSK	GlaxoSmithKline
HCV	Hepatitis C Virus
HCV-TARGET	Hepatitis C Therapeutic Registry and Research Network
IFN	Interferon
DAA	Direct acting anti-virals
SAE	Serious adverse event
EVR	Early virologic response
SVR	Sustained virologic response
PI	Principal Investigator
RNA	Ribonucleic acid
TCP	Thrombocytopenia

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
PROMACTA / REVOLADE

Trademarks not owned by the GlaxoSmithKline group of companies
SAS

2. RESPONSIBLE PARTIES

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

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

WWEpi Project Identifier: WEUSKOP7135

Sponsor Legal Registered Address:

GlaxoSmithKline Research & Development Limited
[redacted]

Sponsor Contact Address:

GlaxoSmithKline Trading Services Limited
[redacted]

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

Sponsor Medical Monitor Contact Information: [redacted]

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

Regulatory Agency Identifying Number(s): Not applicable.

SPONSOR SIGNATORY:

[redacted]

[redacted]

[redacted]

[redacted]

INVESTIGATOR PROTOCOL AGREEMENT PAGE

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

Co-Investigator Name:_____

_____ _____
Co-Investigator Signature Date

Co-Investigator Name:_____

_____ _____
Co-Investigator Signature Date

3. ABSTRACT

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

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

Eltrombopag (Revolade™/Promacta™) is an oral second generation thrombopoietin receptor agonist which promotes megakaryocyte differentiation and proliferation. Eltrombopag (Promacta) was approved in the U.S. in November 2012 for chronic hepatitis C virus (HCV)-associated thrombocytopenia to allow for the initiation and maintenance of interferon-based therapy. Eltrombopag (REVOLADE) was approved by the European Commission in September 2013 for the treatment of thrombocytopenia in adult patients with HCV, where the degree of thrombocytopenia is the main factor preventing the initiation or limiting the ability to maintain optimal interferon-based therapy. Eltrombopag allows patients who would otherwise have been poor candidates due to low platelet counts to undergo interferon-based therapy for HCV.

In the randomized clinical trials program, there was an increased incidence of hepatic decompensation events that occurred in the eltrombopag arm vs. the placebo arm (10% vs 5%, respectively), an increased incidence of thromboembolic events (3% vs 1%), and a higher death event (3% vs 2%). The incidence of hepatic decompensation and thromboembolic events has been adequately assessed in previous randomized double-blinded placebo controlled clinical trials that included more than 1,500 patients and the current label for eltrombopag contains a warning for hepatotoxicity and hepatic decompensation. However, the occurrence of hepatic decompensation and other adverse events have not been characterized in thrombocytopenic HCV patients who have received direct acting agents in combination with interferon-based therapy.

GSK will take a proactive pharmacovigilance approach in generating incidence of hepatic decompensation and other events through long-term follow-up of eltrombopag users in eltrombopag HCV patients undergoing interferon-based anti-HCV treatment with direct acting agents. Results will be reported to the EMA and the FDA and other regulatory agencies. Information will be made available publically through the Clinical Trial Registry and, if approved by the HCV-

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

***Research question and Objective(s).** The primary objective of this study is to report the incidence of hepatic decompensation in patients with chronic hepatitis C virus infection who receive eltrombopag therapy with interferon-based therapy that also includes direct acting anti-viral agents, a group not studied in the Phase III randomized clinical trials. Secondary objectives include reporting the real-world incidence of thromboembolic events and mortality and identifying risk factors for hepatic decompensation, thromboembolic events and mortality in this group of understudied patients. The study will also report the 3-year incidence of hepatic decompensation and mortality, comparing patients who achieve sustained virologic response to patients who do not achieve SVR among eltrombopag patients treated with interferon-based therapy and direct acting agents, which has not yet been studied. The study will also examine effectiveness of eltrombopag to initiate and maintain HCV therapy and achieve EVR and SVR among patients specifically using direct-acting anti-virals with interferon-based therapy.

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

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

***Variables.** Outcome variables include: hepatic decompensation, thromboembolic events, overall and cause-specific mortality, ability to initiate interferon-based antiviral therapy, ability to maintain interferon-based antiviral therapy, and ability to reach early and sustained virologic response. The main exposure variables include treatment with eltrombopag, peginterferon, ribavirin, direct acting anti-viral agents, and other antiviral therapy.

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

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

***Data analysis**

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

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

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

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

4. AMENDMENTS AND UPDATES

None.

5. MILESTONES

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

6. RATIONALE AND BACKGROUND

6.1. Background

Hepatitis C Virus (HCV) is a leading cause of chronic liver disease worldwide. Treatment consists of combination therapy with peginterferon and ribavirin (double therapy) or interferon, ribavirin and a direct acting anti-viral agent (triple therapy). Thrombocytopenia as a treatment related adverse event or a complication of chronic liver disease often necessitates dose reduction and discontinuation in these patients.

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

Eltrombopag (Promacta) was approved in the U.S. in Novemer 2012 for chronic hepatitis C virus (HCV)-associated thrombocytopenia to allow for the initiation and maintenance of interferon-based therapy. Eltrombopag (Revolade) was approved by the European Commission in September 2013 with indication as follows: *Revolade is indicated in adult patients with chronic hepatitis C virus (HCV) infection for the treatment of thrombocytopenia, where the degree of thrombocytopenia is the main factor preventing the initiation or limiting the ability to maintain optimal interferon-based therapy.*

Eltrombopag allows patients who would otherwise have been poor candidates due to low platelet counts to undergo interferon-based therapy for HCV.

6.2. Rationale

In the randomized clinical trials program, there was an increased incidence of hepatic decompensation events that occurred in the eltrombopag arm vs. the placebo arm (10% vs 5%, respectively), an increased incidence of thromboembolic events (3% vs 1%), and a higher death event (3% vs 2%) (Afdhal, 2014). The incidence of hepatic decompensation and thromboembolic events have been adequately assessed in previous randomized double-blinded placebo controlled clinical trials that included more than 1,500 patients and the current label for eltrombopag contains a warning for hepatotoxicity and hepatic decompensation. However, the occurrence of hepatic decompensation and other adverse events has not been characterized in thrombocytopenic HCV patients who have received direct acting agents in combination with interferon-based therapy.

GSK will take a proactive pharmacovigilance approach in generating incidence of hepatic decompensation and other events through long-term follow-up of eltrombopag users in eltrombopag HCV patients undergoing interferon-based anti-HCV treatment with direct acting agents. Results will be reported to the EMA and the FDA and other regulatory agencies. Information will be made available publically through the Clinical Trial

Registry and, if approved by the HCV-TARGET Publication Committee, results will be published in one or more peer-reviewed journal publications.

7. RESEARCH QUESTION AND OBJECTIVE(S)

The primary objective of this study is to report the incidence of hepatic decompensation in patients with chronic hepatitis C virus infection who receive eltrombopag therapy with interferon-based therapy that also includes direct acting anti-viral agents, a group not studied in the Phase III randomized clinical trials. Secondary objectives include reporting the real-world incidence of thromboembolic events and mortality and identifying risk factors for hepatic decompensation, thromboembolic events and mortality in this group of understudied patients. The study will also report the 3-year incidence of hepatic decompensation and mortality, comparing patients who achieve sustained virologic response to patients who do not achieve SVR among eltrombopag patients treated with interferon-based therapy and direct acting agents, which has not yet been studied. The study will also examine effectiveness of eltrombopag to initiate and maintain HCV therapy and achieve EVR and SVR among patients specifically using direct-acting anti-virals with interferon-based therapy.

Specific Study Aims

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

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

8. RESEARCH METHODS

8.1. Study Design

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

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

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

8.2. Setting

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

The data in the registry is of published high quality [Fried, 2013]. The Clinical Coordinating Center (CCC) resides at the [redacted] and the Data Coordinating Center (DCC) resides at the [redacted]

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

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

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

8.3. Variables

Variables included in this study are summarized below:

8.3.1. Outcomes

The main outcomes of this study are:

- Hepatic decompensation, defined as new onset or worsening of baseline of any of the following:
  - Ascites
  - Hepatic encephalopathy
  - Variceal Bleeding
- Thromboembolic events
  - Myocardial infarction (MI)
  - Ischemic Stroke (IS)
  - Portal vein thrombosis (PVT)
  - Deep vein thrombosis (DVT)
  - Pulmonary embolism (PE)
- Mortality (all cause and cause-specific)
- Treatment effectiveness among eltrombopag users, assessed as
  - Percentage of eltrombopag users able to initiate antiviral therapy
  - Percentage of eltrombopag users requiring no, one, two, three, or four or more interferon dose reductions
  - Percentage of eltrombopag users reaching early virologic response, defined as clinically significant reduction in HCV RNA (≥2 log10 drop or undetectable) after 12 weeks of antiviral treatment
  - Percentage of eltrombopag users achieve SVR, defined by HCV RNA negative 24 weeks after cessation of treatment
  - Change in platelet counts before and during antiviral therapy among those able to initiate antiviral therapy

8.3.2. Exposure

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

8.3.3. Other Covariates

Demographics: Age, Sex, Race/ethnicity

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

Virology data

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

Concomitant Medications

8.4. Data sources

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

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

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

8.5. Study size

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

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

The event rate of hepatic decompensation in this specific population is unknown. The rate that occurred among eltrombopag users in the combined ENABLE trials, which was 10% (Afdhal, 2014), , is used as an estimate, and for sample size calculation this rate is varied from 8% to 12% .

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

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

A similar figure is presented for the event rate for thromboembolic events, using the ENABLE trials event rate of 3% (Afdhal, 2014) as the mid-point and varying the rate from 1% to 5% (Figure 2).

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

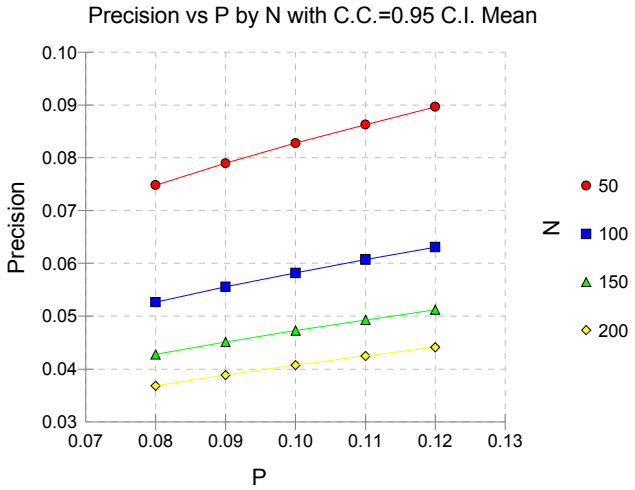
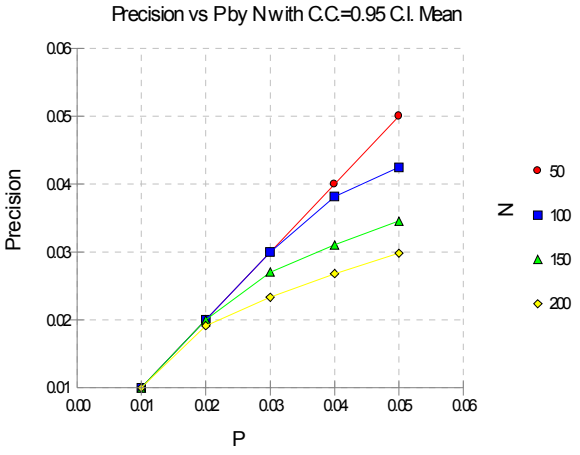


Figure 2 **Precision (y-axis) for event rates (x-axis) ranging from 1%-5% for the outcome of thromboembolic events for 4 potential sample sizes of eltrombopag users**



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

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

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

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

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

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

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

8.6. Data management

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

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

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

The DCC resides in the [redacted] The database is housed within a secure server environment of the data center on the UNC campus, and is governed by the standard [redacted] security guidelines.

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

8.6.1. Timings of Assessment during follow-up

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

8.7. Data analysis

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

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

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

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

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

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

8.8. Quality control

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

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

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

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

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

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

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

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

8.9. Strenghts and limitations of the research methods

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

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

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

9. PROTECTION OF HUMAN SUBJECTS

9.1. Ethical approval and subject consent

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

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

9.2. Subject confidentiality

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

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

10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

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

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

Cases from Rest of World should be sent to: [redacted]

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

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

11. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

11.1. Target Audience

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

11.2. Study reporting and publications

An interim analysis will be conducted in 2016 to coincide with twice-annual cleaning. The final analysis will be completed in 2018. Study reports from both the interim and final analyses will be completed and submitted to the EMA, FDA, and other regulatory agencies. Information will be made available publically through the Clinical Trial Registry, and the intent is to work with the HCV-TARGET Publications committee to submit manuscripts to peer-reviewed journals.

12. REFERENCES

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

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

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

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

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

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

ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

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

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Section 1: Research question	**Yes**	**No**	**N/A**	**Page Number(s)**
1.1 Does the formulation of the research question clearly explain:				
1.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	11, 15
1.1.2 The objectives of the study?	☒	☐	☐	12, 15
1.2 Does the formulation of the research question specify:				
1.2.1 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	12,15,26
1.2.2 Which formal hypothesis(-es) is (are) to be tested?	☒	☐	☐	23, 24
1.2.3 if applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

Section 2: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
2.1 Is the source population described?	☒	☐	☐	12, 16, 17
2.2 Is the planned study population defined in terms of:				
2.2.1 Study time period?	☒	☐	☐	12, 16
2.2.2 Age and sex?	☒	☐	☐	12, 16

Section 2: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
2.2.3 Country of origin?	☒	☐	☐	12, 17
2.2.4 Disease/indication?	☒	☐	☐	12, 15
2.2.5 Co-morbidity?	☒	☐	☐	12, 16
2.2.6 Seasonality?	☐	☐	☒	
2.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	12, 13, 16

Comments:

Section 3: Study design	**Yes**	**No**	**N/A**	**Page Number(s)**
3.1 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	☒	☐	☐	12, 15, 16
3.2 Is the study design described? (e.g. cohort, case-control, randomised controlled trial, new or alternative design)	☒	☐	☐	12, 16
3.3 Does the protocol describe the measure(s) of effect? (e.g. relative risk, odds ratio, deaths per 1000 person-years, absolute risk, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☒	☐	☐	23
3.4 Is sample size considered?	☒	☐	☐	19-21
3.5 Is statistical power calculated?	☒	☐	☐	21

Comments:

Section 4: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
4.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
4.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc)				
4.1.2 Endpoints? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics, etc)	☒	☐	☐	19
4.1.3 Covariates?	☒	☐	☐	19
	☒	☐	☐	19
4.2 Does the protocol describe the information available from the data source(s) on:				
4.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)				
4.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	18
4.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☒	☐	☐	17
	☒	☐	☐	18, 19
4.3 Is the coding system described for:				
4.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10)				
4.3.2 Endpoints? (e.g. Medical Dictionary for	☐	☐	☒	

Section 4: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
Regulatory Activities(MedDRA) for adverse events)	☐	☒	☐	
4.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System)	☐	☐	☒	
4.4 Is the linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments:

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
5.1 Does the protocol describe how exposure is defined and measured? (e.g. operational details for defining and categorising exposure)	☒	☐	☐	18
5.2 Does the protocol discuss the validity of exposure measurement? (e.g. precision, accuracy, prospective ascertainment, exposure information recorded before the outcome occurred, use of validation sub-study)	☐	☐	☒	
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☒	☐	☐	17, 18
5.4 Is exposure classified based on biological mechanism of action?	☐	☒	☐	
5.5 Does the protocol specify whether a dose-dependent or duration-dependent response is measured?	☐	☐	☒	

Comments:

Section 6: Endpoint definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
6.1 Does the protocol describe how the endpoints are defined and measured?	☒	☐	☐	17, 18
6.2 Does the protocol discuss the validity of endpoint measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☐	☐	☒	

Comments:

Section 7: Biases and Effect modifiers	**Yes**	**No**	**N/A**	**Page Number(s)**
7.1 Does the protocol address:				
7.1.1 Selection biases?	☒	☐	☐	26
7.1.2 Information biases?	☒	☐	☐	26
(e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)				
7.2 Does the protocol address known confounders? (e.g. collection of data on known confounders, methods of controlling for known confounders)	☒	☐	☐	18,19,23,24
7.3 Does the protocol address known effect modifiers? (e.g. collection of data on known effect modifiers, anticipated direction of effect)	☐	☒	☐	
7.4 Does the protocol address other limitations?	☒	☐	☐	26

Comments:

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

Comments:

Section 9: Quality assurance, feasibility and reporting	**Yes**	**No**	**N/A**	**Page Number(s)**
9.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	22
9.2 Are methods of quality assurance described?	☒	☐	☐	22, 24

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

Comments:

Section 10: Ethical issues	**Yes**	**No**	**N/A**	**Page Number(s)**
10.1 Have requirements of Ethics Committee/Institutional Review Board approval been described?	☒	☐	☐	26
10.2 Has any outcome of an ethical review	☒	☐	☐	26

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

Comments:

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

Date: / /

Signature: _____

ANNEX 3. ADDITIONAL INFORMATION

None

NOVARTIS

Clinical Development

Compound code/Generic name/Trade name®

Study number A2408/201110

Study title: "A prospective observational cohort study nested within the Hepatitis C Therapeutic Registry and Research Network (HCVTARGET) to evaluate real world use of eltrombopag in adult patients with chronic hepatitis C virus infection who are unable to initiate or maintain optimal interferon-based therapy due to thrombocytopenia"

Statistical Analysis Plan (SAP)

Author: [redacted]

Document type: SAP Documentation

Document status: Final

Release date: 01-Dec-2015

Number of pages: 25

Table of contents

List of abbreviations

AE	adverse events
SAE	serious adverse event
MedDRA	Medical Dictionary for Regulatory Affairs
HCV	Hepatitis C Virus
HCV-TARGET	Hepatitis C Therapeutic Registry and Research Network
SVR	Sustained virological response
EVR	Early virological response

1 Introduction

1.1 Study design

The HCV-TARGET study is a carefully maintained longitudinal observational research registry to prospectively enrol and follow HCV patients treated with anti-HCV regimens in a real-world setting in order to rapidly inform strategies for better management of populations underrepresented in clinical trials, identify and remediate gaps in treatment guidelines and adverse event management in order to optimize rates of SVR. It's comprised of patients that receive HCV therapy with direct acting antiviral agents. All adult patients (age 18 or older) who are prescribed HCV treatment with direct acting antiviral agents outside of a clinical trial are eligible for participation, provided they provide written informed consent and are not participating in any other registry or study where HCV treatment outcomes are reported, except where approved or conducted as an adjunct project of the HCV-TARGET registry.

This study is an eltrombopag cohort study nested within HCV-TARGET, comprising all patients treated with eltrombopag. Nesting the eltrombopag cohort study within the HCV-TARGET is an efficient way to identify and study eltrombopag users in a realworld setting. All patients treated with eltrombopag will be included in the nested cohort study. No patients who have not been exposed to eltrombopag will be included in the nested cohort study. The major safety outcome is hepatic decompensation. Incidence of thromboembolic events and mortality will also be determined. Thromboembolic events include myocardial infarction, ischemic stroke, pulmonary embolism, deep vein thrombosis, portal vein thrombosis, and other events. The major effectiveness outcomes include ability to maintain anti-viral therapy, early virologic response and sustained virologic response. The incidence of hepatic decompensation and of mortality at three years will be compared between eltrombopag users who achieve SVR and those users who do not achieve SVR. An interim analysis will be conducted in 2016 and the final analysis will be completed in 2018.

It is estimated that between 1-3% of the 5000 HCV-TARGET patients will receive eltrombopag and be eligible for the nested eltrombopag cohort study, for a sample size between 50 and 150 patients. Almost all of these patients will be taking direct acting antivirals. As of January 2014, approximately 2700 patients have been enrolled into HCV-TARGET; 2.1% of patients have used eltrombopag. The study will be observational and non-interventional. Longitudinal data are available on adverse events and virological data only for follow-up for up to 12 weeks after end of treatment for those patients that have achieved SVR. For the rest of patients (i.e., viral breakthrough, relapsers, nonresponders, lost on/for treatment follow-up, and deceased) adverse events and virological data are only registered up to the date of failure. Laboratory values are collected through the end of HCV treatment.

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

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

1.2 Study objectives and endpoints

The primary objective of this study is to determine the incidence of hepatic decompensation among patients receiving eltrombopag with interferon-based therapy and direct acting anti-viral agents.

Secondary objectives include reporting the real-world incidence of thromboembolic events and mortality and identifying risk factors for hepatic decompensation, thromboembolic events and mortality in this group of understudied patients. The study will also examine effectiveness of eltrombopag to maintain HCV therapy and achieve EVR and SVR among patients specifically using direct-acting anti- virals with interferon-based therapy.

The *study* population will be limited to all eligible subjects with complete datasets identified as patients who have recorded date of the End of Treatment (EOT).

Specific Study Aims of Secondary objectives:

- Determine the incidence of thromboembolic events and mortality among patients receiving eltrombopag with interferon-based therapy and direct acting anti-viral agents
- Explore factors associated with risk of hepatic decompensation and risk of thromboembolic events among patients receiving eltrombopag with interferon- based therapy and direct acting anti-viral agents
- Obtain information on treatment effectiveness among patients receiving eltrombopag with interferon-based therapy and direct acting anti-virals with respect to maintaining and completing HCV therapy, and achieving EVR and SVR

2 Statistical methods

This section presents the statistical approaches that are anticipated for this study. These approaches may at times require modifications due to unanticipated features of the data. Any deviations from the planned analyses will be documented in prospective amendments to the statistical analysis plan.

Data summaries covered by this analysis plan will include all subjects in the safety and efficacy populations. In general, data will be summarized by treatment regimen.

The safety population will consist all eligible subjects with complete records.

The efficacy population will include a subset of safety population with available treatment outcomes.

2.1 Data analysis general information

The eltrombopag cohort study nested within HCV-TARGET is is a descriptive studyconducted to provide primarily incidence of hepatic decompensation and secondarily other important outcomes such as thromboembolic events and mortality in HCV patients who are treated with direct acting anti-viral agents as part of their interferon-based regimen, a group of patients not previously studied in the randomized clinical trials.

Longitudinal data are available on adverse events and virological data only for follow-up for up to 12 weeks after end of treatment for those patients that have achieved SVR. For the rest of patients (i.e., viral breakthrough, relapsers, nonresponders, lost on/for treatment follow-up, and deceased) adverse events and virological data are only registered up to the date of failure. Laboratory values are collected through the end of HCV treatment.

Cumulative incidence rates will be calculated for the occurrence of hepatic decompensation, thromboembolic events, or mortality, as separate events, at multiple time points (4, 8, 12, 24 weeks if available) during the study and at the end of the 12-week follow-up period. The 95% CIs for cumulative incidence will be calculated using the method outlined by Newcombe et al [Newcombe, 1998].Baseline factors potentially related to each event will be identified during exploratory analyses by comparing Kaplan-Meier survival estimates for patients with vs. without the factor and testing for statistical significance using the log-rank test. Cox proportional hazards models will be constructed to evaluate the influence of these identified factors simultaneously.

Kaplan-Meier survival estimates will be calculated for the outcomes of hepatic decompensation, thromboembolic events, and all-cause mortality. Thromboembolic events will be presented as a single category as well as grouped by venous or arterial origin, and by individual event types. Confidence intervals for survival rates will be calculated using the method outlined by Simon et al [Simon, 1986]. These calculations will be performed for two definitions of entry times: i) the time of start of antiviral treatment independently whether eltrombopag was taken before or after DAA treatment start and ii) the time of start of both treatments (i.e., the latest date between starting dates of each treatment).

Patient demographics and characteristics will be described at the time of initiation of antiviral therapy. Virology baseline and distinct follow-up time points (4, 8, 12, 24 weeks on treatment, EOT, 4, 8, 12 weeks after EOT if available). Laboratory information will be described at baseline and distinct follow-up time points points (4, 8, 12, 24 weeks if available) during the study Continuous variables will be reported as mean, standard deviation, median, 25th and 75th quartiles, and range. Categorical variables will be summarized as number and proportion of subjects with observed (non-missing) data, with corresponding 95% confidence intervals (CI) by exact methods.

Descriptive statistics used for summaries of continuous variables (collected from the CRF and derived) will be number of observations, mean, standard deviation, median, 25th and 75th quartiles, and range. Descriptive statistics used for summaries of categorical variables will be frequencies and percentages.

Narratives may be built out for a variety of patient cohorts, e.g., HCV patients on eltrombopag with outcome of hepatic decompensation, patients without eltrombopag with outcome of mortality, etc.

Primary, interim and final analyses will be performed by the HCVT Data Coordinating Center (DCC) which resides at the [redacted]

Statistical analyses and graphical representation will be generated using SAS/STAT software for Windows version 9.4 or higher, and narratives will be generated using JMP Clinical software version 5 or higher ([redacted])

2.1.1 General definitions

Hepatitis C Virus (HCV) is a leading cause of chronic liver disease worldwide.

Study treatment consists of combination therapy with peginterferon and ribavirin (double therapy) or where appropriate, interferon, ribavirin and a direct acting anti-viral agent (triple therapy), although the treatment landscape is changing rapidly with new therapies.

Study drug Eltrombopag (Revolade™/Promacta™) is an oral second generation thrombopoietin receptor agonist which promotes megakaryocyte differentiation and proliferation. Eltrombopag (Promacta) was approved in the U.S. in November 2012 for chronic hepatitis C virus (HCV)-associated thrombocytopenia to allow for the maintenance of interferon-based therapy. Eltrombopag (REVOLADE) was approved by the European Commission in September 2013 for the treatment of thrombocytopenia in adult patients with HCV, where the degree of thrombocytopenia is the main factor preventing or limiting the ability to maintain optimal interferon-based therapy. Eltrombopag allows patients who would otherwise have been poor candidates due to low platelet counts to undergo interferon-based therapy for HCV.

SVR: sustained virological response 12 weeks after therapy (SVR12) defined as HCV RNA below the lower limit of quantification or undetectable at least 64 days after treatment was discontinued.

RVR: rapid virological response defined as HCV RNA below the lower limit of quantification or undetectable at least 22 days after treatment was started.

Cirrhosis status is defined by an algorithm implemented in the HCV-TARGETdata collection process, as previously described (REF). The primary indicator of cirrhosis is a liver biopsy with a METAVIR score of F4. When liver biopsy shows a METAVIR score of F3, patients must have one secondary measure. Secondary indicators include serum fibrosis measures (FibroSure/FibroTest, FibroSpect, and Hepascore); Transient Elastography (Fibroscan) ≥14kPa; signs of portal hypertension (esophageal/gastric varices, portal gastropathy, or serum platelet count <140,000/µL)

Decompensated cirrhosis was defined as presence of current or past ascites, hepatic encephalopathy, spontaneous bacterial peritonitis, hepatic hydrothorax or variceal hemorrhage or concomitant medications with a specific indication for the before mentioned indications

Relative Study Day: The date of the first dose of interferon-based therapy is Day 1. This will be footnoted on any table or listing for which study days are given. (-) sign indicates days prior to the start of study drug (e.g. Day -5 means 5 days prior to administration of study drug; there will be no day '0').

The calculations for the relative study day are as follows:

- Post therapy: (Visit Date) - (Day 1) + 1
- Prior to therapy: (Visit Date) - (Day 1)

Baseline is defined as the last measurement taken prior to the study drug administration, unless otherwise specified.

2.2 Analysis sets

The study population will consist all eligible subjects with recorded EOT date.

The efficacy population will include a subset of safety population with available treatment outcomes.

2.2.1 Subgroup of interest –n/a

2.3 Patient disposition, demographics and other baseline characteristics

The disposition of all eligible subjects will be summarized. The number and percentage of subjects who are included in safety population, complete the study, withdraw from the study prematurely, withdraw consent and lost on treatment follow-up will be displayed. For subjects who withdraw prematurely, the number and percentage withdrawing by reason (adverse event, death, withdrawal of consent, protocol violation, and other reasons) will be displayed.

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

HCV treatment consists of combination therapy with peginterferon and ribavirin (double therapy) or where appropriate, interferon, ribavirin and a direct acting anti-viral agent (triple therapy), although the treatment landscape is changing rapidly with new therapies. Thrombocytopenia as a treatment related adverse event or a complication of chronic liver disease often necessitates dose reduction and discontinuation in these patients.

Eltrombopag (Revolade/Promacta) is an oral second generation thrombopoietin receptor agonist which promotes megakaryocyte differentiation and proliferation. Eltrombopag allows patients who would otherwise have been poor candidates due to low platelet counts to undergo interferon-based therapy for HCV.

2.4.1 Study treatment / compliance – n/a as data is not collected in HCVT

2.4.2 Prior, concomitant and post medications

Concomitant medications are medications other than DAA, PEG , RBV and Eltrombopag which are taken prior to the program therapy first dose day and continued to be taken on and after the program therapy first dose day or medications which are started on or after the program therapy first dose day and before the program therapy last dose day. Concomitant medications will be summarized by frequencies and percentages for treated patients for program therapy treatment period. Concomitant medications will be reported alphabetically by anatomic class, therapeutic class and generic name assigned by the WHO dictionary. For each specific concomitant medication, the number and percentage of patients who took at least 1 dose of the medication will be reported

2.5 Statistical analysis

2.5.1 Statistical hypothesis, model, and method of analysis

Although there is no defined research hypothesis, the safety and efficacy data will be collected. These data may comprise the number of clinical and outcome endpoints. It should be noted that not all endpoints will be necessarily available because the collection of some data is optional in this study.

Variables included in the analysis of the primary and secondary objectives are summarized below:

The main ***outcomes*** of this study are:

1. Hepatic decompensation, defined as new onset or worsening of baseline of any of the following:

-Ascites

-Hepatic encephalopathy

-Variceal Bleeding

-Hepatopulmonary syndrome

-Hepatorenal syndrome,

-Hepatic hydrothorax

-Spontaneous Bacterial Peritonitis

2. Thromboembolic events:

-Myocardial infarction (MI)

-Ischemic Stroke (IS)

-Portal vein thrombosis (PVT)

-Deep vein thrombosis (DVT)

-Pulmonary embolism (PE)

3. Mortality (all cause and cause-specific)

4. Treatment effectiveness among eltrombopag users, assessed as

-Percentage of eltrombopag users reaching early virologic response, defined as clinically significant reduction in HCV RNA (≥2 log10 drop or undetectable) after 12 weeks of antiviral treatment

-Percentage of eltrombopag users achieve SVR, defined by HCV RNA negative 12 weeks after cessation of treatment or later

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

***Exposure*:**

The main exposure variable is treatment with eltrombopag, in combination with peginterferon, ribavirin, and direct acting antiviral agents (triple therapy). Dose, duration of treatment, and drug discontinuation are available only for the HCV treatment regimen and not for Elthrombopag.

***Other Covariates*:**

Demographics:

Continuous variables:

• Age

Categorical variables:

• Age (<65 years and ≥ 65 years);

• Gender (Male, Female);

• Race (White, Black or African American, or Other);

• Ethnicity (Hispanic or Latino, Not Hispanic or Latino);

Virology data:

Continuous variables:

• HCV RNA value (log10 IU/mL).

Categorical variables:

• HCV Genotype (1, 2, 3, 4, 5, 6, Mixed, Unknown);

• HCV Genotype 1 subtype (1a, 1b, Others/Unknown);

• Previous HCV Treatment: (Naive, Experienced);

• Previous PI failure- patients with PI-containing regimens as prior HCV therapy who had virological failure: (Yes, No).

Disease History will be summarized for treated patients (see table shells DEMOGRAPHIC and LABS attached)

Duration of treatment in categories (<6, 6-10, 10-14, 14-20, 20-28, >28 Weeks);

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

Concomitant Medications. Concomitant medications are medications other than DAA, PEG, RBV and Eltrombopag which are taken prior to the program therapy first dose day and continued to be taken on and after the program therapy first dose day or medications which are started on or after the program therapy first dose day and before the program therap y last dose day. Concomitant medications will be summarized by frequencies and percentages for treated patients for program therapy treatment period. Concomitant medications will be reported alphabetically by anatomic class, therapeutic class and generic n ame assigned by the WHO dictionary. For each specific concomitant medication, the number and percentage of patients who took at least 1 dose of the medication will be reported.

2.5.2 Handling of missing values/censoring/discontinuations

No imputation algorithms will be used to estimate missing data.

2.6 Safety analyses

Simple descriptive statistics will be used to summarize results.

The assessment of safety will be based on frequency of AEs, frequency of SAEs, frequency of discontinuations of treatment due to AE, deaths, and the results of vital sign measurements, physical examinations and clinical laboratory tests.

2.6.1 Adverse events (AEs)

Adverse events will be collected during on-treatment and Follow-up period. Additional information collected for each AE will be whether or not the adverse event was serious. Adverse experiences, including intercurrent events, will be summarized according to the numbers and percentages of patients reporting one or more occurrences during the study period. The adverse experiences contained in the summary tables will include all experiences that began on or after the day of first dose of study drug. The actual terms used by the investigator to identify adverse experiences in the Case Report Forms will be coded using the MedDRA Dictionary (version 15.1). Adverse experiences (individual and grouped by System Organ Class) will be tabulated for the treatment period regardless of relationship to study drug and by reported relationship to study drug as judged by the investigator.

2.6.1.1 Adverse events of special interest / grouping of AEs – n/a

2.6.2 Deaths

Causes of Death will be collected during on-treatment and Follow-up period. The Causes of Death contained in the summary tables will include all experiences that began on or after the day of first dose of study drug. The actual terms used by the investigator to identify Cause of Death in the Case Report Forms will be coded using the MedDRA Dictionary (version 15.1). Causes of Death (individual and grouped by System Organ Class) will be tabulated for the treatment and follow up period regardless of relationship to study drug and by reported relationship to study drug as judged by the investigator.

2.6.3 Laboratory data

Laboratory values are collected from baseline through the end of HCV treatment: MELD, albumin (g/dl), platelet count (1000/ul), creatinine clearance, total bilirubin (mg/dl), hemoglobin (g/dl), and international normalized ratio (INR), HCV RNA. virology, and laboratory information will be described at baseline. Baseline laboratory values as well as changes in laboratory values from baseline to the end of treatment will be described. Continuous variables will be reported as mean, standard deviation, median, 25th and 75th quartiles, and range. Categorical variables will be summarized as number and proportion of subjects with observed (nonmissing) data, with corresponding 95% confidence intervals (CI) by exact methods.

2.6.4 Other safety data

2.6.4.1 ECG and cardiac imaging data – n/a

2.6.4.2 Vital signs – n/a

2.7 Pharmacokinetic endpoints – n/a

2.8 PD and PK/PD analyses– n/a

2.9 Patient-reported outcomes– n/a

2.10 Biomarkers– n/a

2.11 Other Exploratory analyses

Proposed statistical approaches may at times require modifications due to unanticipated features of the data. Any deviations from the planned analyses will be documented in prospective amendments to the statistical analysis plan.

2.12 Interim analysis

An interim analysis will be conducted in 2016 by the HCVT Data Coordinating Center (DCC) which resides at the [redacted]

Outputs to be provided in the interim analysis:

Baseline demographics, for *all patients with EOT date (by regimen and by Event of interest (Decompensation, Thromboembolic events)*

Baseline Labs, for *all patients with EOT date (by regimen and by Event of interest (Decompensation, Thromboembolic events)*

Table listing of Pts with new Decomp events

Table listing of Pts with new Thromboembolic events

Frequency of Deaths

Predictors of Decompensation

Predictors of Thromboembolic events

Predictors of Mortality

Patient disposition and completion rate

AEs causing discontinuation, for *all patients with EOT date (by regimen and by Event of interest (Decompensation, Thromboembolic events)*

SVR rates (EP and PP)

All AEs , for *all patients with EOT date (by regimen and by Event of interest (Decompensation, Thromboembolic events)*

All SAEs, for *all patients with EOT date (by regimen and by Event of interest (Decompensation, Thromboembolic events)*

HCV RNA plots at 4, 8, 12 and 24 weeks as BLOQ or Quantifiable, for *all patients with available treatment outcome (by regimen and by Event of interest (Decompensation, Thromboembolic events)*

Kaplan-Meier plots for Decomp events, Thromboembolic events and Mortality, for *all patients with EOT date (by regimen and by Event of interest (Decompensation, Thromboembolic events)*

- From start of antiviral therapy
- From date when both therapies initiated

Delta platelets start to treatment stop, for *all patients with available laboratory values (by regimen)*

3 Sample size calculation

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

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

The event rate of hepatic decompensation in this specific population is unknown. The rate that occurred among eltrombopag users in the combined ENABLE trials, which was 10% (Afdhal, 2014), , is used as an estimate, and for sample size calculation this rate is varied from 8% to 12% .

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

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

A similar figure is presented for the event rate for thromboembolic events, using the ENABLE trials event rate of 3% (Afdhal, 2014) as the mid-point and varying the rate from 1% to 5% (Figure 2).

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

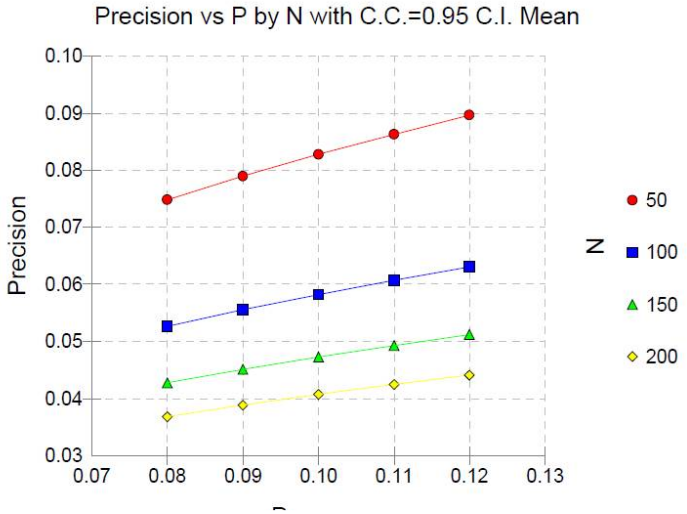
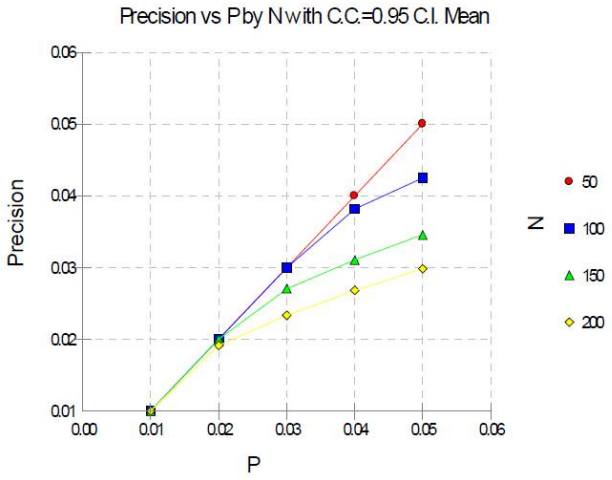


Figure 2 Precision (y-axis) for event rates (x-axis) ranging from 1%-5% for the outcome of thromboembolic events for 4 potential sample sizes of eltrombopag users



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

The study is not designed to compare hepatic decompensation rates in eltrombopag users with rates in a control group of HCV-TARGET patients not using eltrombopag due to insufficiency of the sample size to draw statistical inferences. Based on the enrolment rate of 2.1%, it is estimated that 105 eltrombopag patients will comprise the nested HCV-TARGET cohort study when all 5000 HCV-TARGET patients have been enrolled.

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

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

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

Additionally, the study is not be powered to detect a difference in hepatic decompensation or in mortality comparing patients who achieve SVR to patients who do not achieve SVR.

4 Change to protocol specified analyses

1. A part of secondary objective 'The study will also report the 3-year incidence of hepatic decompensation and mortality, comparing patients who achieve sustained virologic response to patients who do not achieve SVR among eltrombopag patients treated with interferon-based therapy and direct acting agents, which has not yet been studied' corresponds to the current protocol. However, per HCV Target protocol cannot be done as the subjects are from Target 1.0 and 3 year follow up is not feasible. Protocol amendment needed.

2 . Treatment effectiveness examine effectiveness of eltrombopag users to initiate HCV therapy could not be assessed since history of medications is collected only on patients who started antiviral therapy.

5 Reference

1. *SAS®, Version 9.4.* SAS Institute, inc., 2014.
2. Afdhal N, Dusheiko G, Giannini E, Chen P,Han K, Mohsin A, Rodriguez-Torres M, Rugina S, Bakulin I , Lawitz E, Shiffman M, Tayyab G, Poordad F, Kamel Y, Brainsky A, Geib J, Vasey S, Patwardhan R, Campbell F, Theodore D. Eltrombopag increases platelet numbers in thrombocytopenic patients with HCV infections and cirrhosis, allowing for effective antiviral therapy. Gastroenterology 2014; 146 (2): 442-452.
3. Newcombe RG. Two-sided confidence intervals for the single proportion: comparison of seven methods. Stat Med 1998; 17(8):857-872.
4. Simon R. Confidence intervals for reporting results of clinical trials. Ann Intern Med 1986; 105(3):429-435.

6 Appendix

1 List of Tables

Disposition and Demography

Efficacy

Safety

Adverse Events

Concomitant medications

2. Figures

Table 1. Disposition of patients

Variable		Treatment Group Regimen 1 (N=xxx)	Regimen 2 (N=xxx)	Regimen 3 (N=xxx)	Total (N=xxx)
All	Yes	xxx (xxx.x%)	xxx (xxx.x%)	xxx (xxx.x%)	xxx (xxx.x%)
- Started treatment	Yes	xxx (xxx.x%)	xxx (xxx.x%)	xxx (xxx.x%)	xxx (xxx.x%)
- Discontinued Prematurely	Yes	xxx (xxx.x%)	xxx (xxx.x%)	xxx (xxx.x%)	xxx (xxx.x%)
- AE	Yes	xxx (xxx.x%)	xxx (xxx.x%)	xxx (xxx.x%)	xxx (xxx.x%)
- Lack of efficacy	Yes	xxx (xxx.x%)	xxx (xxx.x%)	xxx (xxx.x%)	xxx (xxx.x%)
- Withdrawal by subject	Yes	xxx (xxx.x%)	xxx (xxx.x%)	xxx (xxx.x%)	xxx (xxx.x%)
- Non-compliance	Yes	xxx (xxx.x%)	xxx (xxx.x%)	xxx (xxx.x%)	xxx (xxx.x%)
- Other	Yes	xxx (xxx.x%)	xxx (xxx.x%)	xxx (xxx.x%)	xxx (xxx.x%)
- Completed treatment	Yes	xxx (xxx.x%)	xxx (xxx.x%)	xxx (xxx.x%)	xxx (xxx.x%)
- <=12 weeks	Yes	xxx (xxx.x%)	xxx (xxx.x%)	xxx (xxx.x%)	xxx (xxx.x%)
- >12 and <= 16 weeks	Yes	xxx (xxx.x%)	xxx (xxx.x%)	xxx (xxx.x%)	xxx (xxx.x%)
- 16+ weeks	Yes	xxx (xxx.x%)	xxx (xxx.x%)	xxx (xxx.x%)	xxx (xxx.x%)
- Success	Yes	xxx	xxx	xxx	xxx
- Relapser	Yes	xxx	xxx	xxx	xxx
- Viral Breakthrough	Yes	xxx	xxx	xxx	xxx
- Non-Responder	Yes	xxx	xxx	xxx	xxx
- Lost to post Tx followup	Yes	xxx	xxx	xxx	xxx
- Hepatic decompensation	Yes	xxx (xxx.x%)	xxx (xxx.x%)	xxx (xxx.x%)	xxx (xxx.x%)
- Thromboembolic events	Yes	xxx (xxx.x%)	xxx (xxx.x%)	xxx (xxx.x%)	xxx (xxx.x%)
- Died	Yes	xxx (xxx.x%)	xxx (xxx.x%)	xxx (xxx.x%)	xxx (xxx.x%)

WEUSKOP7135 patients
Run Date: mm/dd/yy

Table 2. DEMOGRAPHICS

Variable	Treatment Group Regimen 1 (N=xxx)	Regimen 2 (N=xxx)	Total (N=xxx)
SEX			
Female	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Male	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x %)
AGE			
18-39	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
40-64	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
65+	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Patient age at the start of treatments	xxx	xxx	xxx
Mean	xx.x	xx.x	xx.x
S.D.	xx.x	xx.x	xx.x
Median	xx.x	xx.x	xx.x
Min Max	xx.x xx.x	xx.x xx.x	xx.x xx.x
Q1 Q3	xx.x xx.x	xx.x xx.x	xx.x xx.x
RACE			
White	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Black or African American	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Other or Pending	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
ETHNICITY			
Hispanic	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Non Hispanic	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Not Reported	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Pending	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
HCV GENOTYPES			
1	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
2	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
3	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
4-x	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Pending	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
SUBTYPES OF HCV 1 GENOTYPE			
1 a	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
1 b	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
1 c	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
1 e	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
1 nos	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
1 pending	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
PRIOR HCV TREATMENT EXPERIENCE			
Naive	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Experienced	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
CIRRHOSIS			
Not Cirrhotic	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Cirrhotic	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
EVIDENCE OF PRIOR DECOMPENSATION			
Yes	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
No	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
HIV			
Yes	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
No	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)

WEUSKOP7135 patients
Run Date: mm/dd/yy

Table 2. DEMOGRAPHICS (continuation)

Variable	Treatment Group: Regimen 1 (N=xxx)	Regimen 2 (N=xxx)	Regimen 3 (N=xxx)
LIVER TRANSPLANT			
Yes	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
No	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
LIVER CANCER			
Yes	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
No	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
KIDNEY TRANSPLANT			
Yes	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
No	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
DIABETES			
Yes	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
No	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
TAC use			
Yes	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
No	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
CSA use			
Yes	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
No	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
EVEROLIMUS/SIROLIMUS use			
Yes	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
No	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
MMF/MPA use			
No	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Yes	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
STEROID use after baseline			
No	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Yes	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Was taking any antiacids?			
No	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Yes	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Was taking proton pump inibitors?			
Yes	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
No	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)

WEUSKOP7135
Run Date: mm/dd/yy

Table 3. BASELINE LABORATORY VALUES

Variable	Treatment Group Regimen 1 (N=xxx)	Regimen 2 (N=xxx)	Total (N=xxx)
ALT (IU/L)	xxx	xxx	xxx
Mean	xx.x	xx.x	xx.x
S.D.	xx.x	xx.x	xx.x
Median	xx.x	xx.x	xx.x
Min Max	xx.x xx.x	xx.x xx.x	xx.x xx.x
Q1 Q3	xx.x xx.x	xx.x xx.x	xx.x xx.x
AST (IU/L)	xxx	xxx	xxx
Mean	xx.x	xx.x	xx.x
S.D.	xx.x	xx.x	xx.x
Median	xx.x	xx.x	xx.x
Min Max	xx.x xx.x	xx.x xx.x	xx.x xx.x
Q1 Q3	xx.x xx.x	xx.x xx.x	xx.x xx.x
TOTAL BILIRUBIN (mg/dL)	xxx	xxx	xxx
Mean	xx.x	xx.x	xx.x
S.D.	xx.x	xx.x	xx.x
Median	xx.x	xx.x	xx.x
Min Max	xx.x xx.x	xx.x xx.x	xx.x xx.x
Q1 Q3	xx.x xx.x	xx.x xx.x	xx.x xx.x
TOTAL BILIRUBIN cat			
<=3	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
>3	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Pending	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
PLATELETS (x10E3/uL)	xxx	xxx	xxx
Mean	xx.x	xx.x	xx.x
S.D.	xx.x	xx.x	xx.x
Median	xx.x	xx.x	xx.x
Min Max	xx.x xx.x	xx.x xx.x	xx.x xx.x
Q1 Q3	xx.x xx.x	xx.x xx.x	xx.x xx.x
ALBUMIN (g/dL)	xxx	xxx	xxx
Mean	xx.x	xx.x	xx.x
S.D.	xx.x	xx.x	xx.x
Median	xx.x	xx.x	xx.x
Min Max	xx.x xx.x	xx.x xx.x	xx.x xx.x
Q1 Q3	xx.x xx.x	xx.x xx.x	xx.x xx.x
CREATININ (mg/dL)	xxx	xxx	xxx
Mean	xx.x	xx.x	xx.x
S.D.	xx.x	xx.x	xx.x
Median	xx.x	xx.x	xx.x
Min Max	xx.x xx.x	xx.x xx.x	xx.x xx.x
Q1 Q3	xx.x xx.x	xx.x xx.x	xx.x xx.x
CREATININE cat (mg/dL)			
<=1.5	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
>1.5-2.0	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Pending	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
CREATININE CLEARANCE	256	37	293
Mean	xx.x	xx.x	xx.x
S.D.	xx.x	xx.x	xx.x
Median	xx.x	xx.x	xx.x
Min Max	xx.x xx.x	xx.x xx.x	xx.x xx.x
Q1 Q3	xx.x xx.x	xx.x xx.x	xx.x xx.x
CREATININE CLEARANCE cat			
<=30	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
>30	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Pending	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

To be continued

Table 3. BASELINE LABORATORY VALUES (continuation)

	Treatment Group		
Variable	Regimen 1 (N=283)	Regimen 2 (N=38)	Total (N=321)
eGFR cat			
30-59	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
60-89	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
90+	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Less than 30	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Pending	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
MELD cat			
0-9	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
10-15	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
16-21	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Pending	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
BASELINE_MELD_CIRR_10			
10+	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
<10	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Pending	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
MELD_ AMONG CIRRHOTICS	xxx	xxx	xxx
Mean	xx.x	xx.x	xx.x
S.D.	xx.x	xx.x	xx.x
Median	xx.x	xx.x	xx.x
Min Max	xx.x xx.x	xx.x xx.x	xx.x xx.x
Q1 Q3	xx.x xx.x	xx.x xx.x	xx.x xx.x
HEMOGLOBIN (g/dL)	xxx	xxx	xxx
Mean	xx.x	xx.x	xx.x
S.D.	xx.x	xx.x	xx.x
Median	xx.x	xx.x	xx.x
Min Max	xx.x xx.x	xx.x xx.x	xx.x xx.x
Q1 Q3	xx.x xx.x	xx.x xx.x	xx.x xx.x
INR	xxx	xxx	xxx
Mean	xx.x	xx.x	xx.x
S.D.	xx.x	xx.x	xx.x
Median	xx.x	xx.x	xx.x
Min Max	xx.x xx.x	xx.x xx.x	xx.x xx.x
Q1 Q3	xx.x xx.x	xx.x xx.x	xx.x xx.x
HCV RNA (IU/mL)	xxx	xxx	xxx
Mean	xx.x	xx.x	xx.x
S.D.	xx.x	xx.x	xx.x
Median	xx.x	xx.x	xx.x
Min Max	xx.x xx.x	xx.x xx.x	xx.x xx.x
Q1 Q3	xx.x xx.x	xx.x xx.x	xx.x xx.x
HCV RNA (IU/mL, log10)	xxx	xxx	xxx
Mean	xx.x	xx.x	xx.x
S.D.	xx.x	xx.x	xx.x
Median	xx.x	xx.x	xx.x
Min Max	xx.x xx.x	xx.x xx.x	xx.x xx.x
Q1 Q3	xx.x xx.x	xx.x xx.x	xx.x xx.x
HCV RNA (cat)			
BLOQ	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Pending	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Quant	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

To be continued

Table 3. BASELINE LABORATORY VALUES (continuation)

Variable	Treatment Group Regimen 1 (N=xxx)	Regimen 2 (N=xxx)	Total (N=xxx)
delta HGB [Ad1]	xxx	xxx	xxx
Mean	xx.x	xx.x	xx.x
S.D.	xx.x	xx.x	xx.x
Median	xx.x	xx.x	xx.x
Min Max	xx.x xx.x	xx.x xx.x	xx.x xx.x
Q1 Q3	xx.x xx.x	xx.x xx.x	xx.x xx.x
delta PLT [Ad1]	xxx	xxx	xxx
Mean	xx.x	xx.x	xx.x
S.D.	xx.x	xx.x	xx.x
Median	xx.x	xx.x	xx.x
Min Max	xx.x xx.x	xx.x xx.x	xx.x xx.x
Q1 Q3	xx.x xx.x	xx.x xx.x	xx.x xx.x
delta CRCL [Ad1]	xxx	xxx	xxx
Mean	xx.x	xx.x	xx.x
S.D.	xx.x	xx.x	xx.x
Median	xx.x	xx.x	xx.x
Min Max	xx.x xx.x	xx.x xx.x	xx.x xx.x
Q1 Q3	xx.x xx.x	xx.x xx.x	xx.x xx.x
DELTA_TBIL	xxx	xxx	xxx
Mean	xx.x	xx.x	xx.x
S.D.	xx.x	xx.x	xx.x
Median	xx.x	xx.x	xx.x
Min Max	xx.x xx.x	xx.x xx.x	xx.x xx.x
Q1 Q3	xx.x xx.x	xx.x xx.x	xx.x xx.x
DELTA_CRE	xxx	xxx	xxx
Mean	xx.x	xx.x	xx.x
S.D.	xx.x	xx.x	xx.x
Median	xx.x	xx.x	xx.x
Min Max	xx.x xx.x	xx.x xx.x	xx.x xx.x
Q1 Q3	xx.x xx.x	xx.x xx.x	xx.x xx.x
DELTA_MELD	xxx	xxx	xxx
Mean	xx.x	xx.x	xx.x
S.D.	xx.x	xx.x	xx.x
Median	xx.x	xx.x	xx.x
Min Max	xx.x xx.x	xx.x xx.x	xx.x xx.x
Q1 Q3	xx.x xx.x	xx.x xx.x	xx.x xx.x
DELTA_MELD_cat			
MELD decreased	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
MELD held	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
MELD increased	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Pending	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

WEUSKOP7135
Run Date: mm/dd/yy

NOVARTIS

Clinical Development

ETB115A (eltrombopag)

Study No. CETB115A2408

A prospective observational cohort study nested within the Hepatitis C Therapeutic Registry and Research Network (HCV-TARGET) to evaluate real world use of eltrombopag in adult patients with chronic hepatitis C virus infection who are unable to initiate or maintain optimal interferon-based therapy due to thrombocytopenia

Document type:	Clinical Study Report Signatures
Report type:	Interim Clinical Study Report
Referring to:	CSR released on 29-Aug-2016

Signatures of the principal or coordinating investigator(s)

1 Signatures of the report authors

[redacted]	Signature	Date
[redacted]	Signature	Date

2 Signature of the sponsor's responsible medical officer

I certify that this report accurately describes the conduct and the results of this clinical study.

[redacted]	Signature	Date

Outcomes Part 1

Contents

Introduction

The Interim Report was prepared in adherence with Study Protocol dated 12 August 2014 and Statistical Analysis Plan dated 1 December 2015. Due to small number of patients and low incidence of Events if Interest in this cohort several analyses are not feasible as indicated below

- "Explore factors associated with risk of hepatic decompensation and risk of thromboembolic events among patients receiving eltrombopag with interferon- based therapy and direct acting anti-viral agents" -Due to insufficient number of events thee analyses are not feasible
- "Determine the incidence rate ratio of hepatic decompensation and mortality at 3 years, comparing eltrombopag patients achieving sustained virologic response to eltrombopag patients who did not achieve SVR in the setting of treatment with interferon-based therapy and direct acting anti-viral agents"- This timepoint is not reached at the time of interim analyses. Due to majority of patients in the cohort being from the time of the study when 3 year follow up was not collected, only 3 patients may have sufficient data at the end of the study
- Incidence of thromboembolic events and mortality will also be determined. Thromboembolic events include myocardial infarction, ischemic stroke, pulmonary embolism, deep vein thrombosis, portal vein thrombosis, and other events.- There were no thromboembolic events and only one death recorded in this cohort therefore any analyses are not feasible
- SOF- Sofosbuvir
- BOC- Boceprevir
- TVR- Telaprevir
- PEG- Peg-Interferon
- RBV- Ribavirin

Table 1. TREATMENT STATUS BY REGIMEN

Variable	Treatment Group SOF PEG RBV (N=3)	BOC PEG RBV (N=18)	TEL PEG RBV (N=40)	Total (N=61)
All	3 (100.0%)	18 (100.0%)	40 (100.0%)	61 (100.0%)
- Started treatment	3 (100.0%)	17 (94.4%)	40 (100.0%)	60 (98.4%)
- Discontinued Prematurely	1 (33.3%)	9 (50.0%)	24 (60.0%)	34 (55.7%)
- AE	1 (33.3%)	4 (22.2%)	16 (40.0%)	21 (34.4%)
- Lack of efficacy	0 (0.0%)	4 (22.2%)	7 (17.5%)	11 (18.0%)
- Lost to follow-up	0 (0.0%)	0 (0.0%)	1 (2.5%)	1 (1.6%)
- Other	0 (0.0%)	1 (5.6%)	0 (0.0%)	1 (1.6%)
- Completed treatment	2 (66.7%)	8 (44.4%)	16 (40.0%)	26 (42.6%)
- Lost to post Tx followup	1	0	0	1
- Results not provided by site	0	4	8	12
†- Died	0 (0.0%)	0 (0.0%)	1 (2.5%)	1 (1.6%)

Run Date: 05/10/16

Table 1a. TREATMENT STATUS: Patients who developed Hepatic Decompensation vs Patients without decompensation

Variable	Treatment Group: Developed Hepatic Decompensation (N=4)	No Hepatic Decompensation (N=57)	Total (N=61)
All	4 (100.0%)	57 (100.0%)	61 (100.0%)
- Started treatment	3 (75.0%)	57 (100.0%)	60 (98.4%)
- Discontinued Prematurely	2 (50.0%)	32 (56.1%)	34 (55.7%)
- AE	1 (25.0%)	20 (35.1%)	21 (34.4%)
- Lack of efficacy	1 (25.0%)	10 (17.5%)	11 (18.0%)
- Lost to follow-up	0 (0.0%)	1 (1.8%)	1 (1.6%)
- Other	0 (0.0%)	1 (1.8%)	1 (1.6%)
- Completed treatment	1 (25.0%)	25 (43.9%)	26 (42.6%)
- Lost to post Tx followup	1	0	1
- - Results not provided by site	1	11	12
†- Died	0 (0.0%)	1 (1.8%)	1 (1.6%)

Run Date: 05/10/16

Supplement 1.1 AEs causing discontinuation

Variable	Treatment regimen: SOF PEG RBV (N=1) N	BOC PEG RBV (N=4) N	TEL PEG RBV (N=16) N	Total (N=21) N
AE leaded to discontinuation [AdI]				
AE NOS	0	1	2	3
Abdominal pain	0	0	1	1
Anasarca	0	0	1	1
Ascites	0	1	0	1
Rash	0	0	1	1
Death NOS	0	0	1	1
Hepatic Encephalopathy	0	0	1	1
Cerebral Hemorrhage	0	0	1	1
Pneumonia	0	1	0	1
Neutropenia	0	1	0	1
Conjunctival Haemorrhage	0	0	1	1
Colitis	0	0	1	1
Pyrexia	0	0	1	1
Syncope	1	0	0	1
Thrombocytopenia	0	0	5	5

Run Date: 05/10/16

Supplement 1.1a AEs causing discontinuation: Patients who developed Hepatic Decompensation vs Patients without decompensation

	Treatment regimen		
Variable	Hepatic Decompensation (N=1) N	No Hepatic Decompensation (N=20) N	Total (N=21) N
AE leaded to discontinuation [Ad1]			
AE NOS	0	3	3
Abdominal pain	0	1	1
Anasarca	0	1	1
Ascites	1	0	1
DRESS syndrome (rash)	0	1	1
Death NOS	0	1	1
Encephalopathy	0	1	1
Interacerebral Hemorrhage	0	1	1
Lung infection	0	1	1
Neutropenia	0	1	1
Ocular hematoma	0	1	1
Pancolitis	0	1	1
Prolonged Fever	0	1	1
Syncope	0	1	1
Thrombocytopenia	0	5	5

Run Date: 05/10/16

Supplement 1.2 Reasons for discontinuation other than ae and lack of efficacy

Variable	Treatment regimen		
	BOC PEG RBV (N=1)	TEL PEG RBV (N=1)	Total (N=2)
	N	N	N
Reason for discontinuation			
DISC | Insurance dropped	0	1	1
DISC | Refused treatment/Did not cooperate	1	0	1

Run Date: 05/10/16

Supplement 1.3 Reasons for discontinuation other than ae and lack of efficacy: patients who developed hepatic decompensation vs patients without decompensation

	Treatment regimen	
	No Hepatic Decompensation (N=2)	Total (N=2)
Variable	N	N
Reason for discontinuation		
DISC | Insurance dropped	1	1
DISC | Refused treatment/Did not cooperate	1	1

Run Date: 05/10/16

Supplement 1.3 Causes of death

Variable	Treatment regimen: TEL PEG RBV (N=1) N	Total (N=1) N
If the patient died, how? [Ac1]		
| FUNGAL SEPSIS	1	1

Run Date: 05/10/16

Supplement 1.3 Causes of death: Patients who developed Hepatic Decompensation vs Patients without decompensation

Variable	Treatment regimen: No Hepatic Decompensation (N=1) N	Total (N=1) N
If the patient died, how? [Ac1]		
| FUNGAL SEPSIS	1	1

Run Date: 05/10/16

Table 2. DEMOGRAPHICS

Variable	Treatment Group: SOF PEG RBV (N=3)	BOC PEG RBV (N=18)	TEL PEG RBV (N=40)	Total (N=61)
SEX				
Female	2 (66.7%)	3 (16.7%)	12 (30.0%)	17 (27.9%)
Male	1 (33.3%)	15 (83.3%)	28 (70.0%)	44 (72.1%)
AGE				
40-64	3 (100.0%)	18 (100.0%)	33 (82.5%)	54 (88.5%)
65+	0 (0.0%)	0 (0.0%)	7 (17.5%)	7 (11.5%)
Patient age at the start of IFN treatments.	3	18	40	61
Mean	59.3	56.8	57.7	57.5
Median	59.0	58.0	56.8	57.6
Std	4.51	5.79	6.96	6.48
Min Max	55.0 - 64.0	40.6 - 64.9	43.6 - 74.9	40.6 - 74.9
Q1 Q3	55.0 - 64.0	54.3 - 60.7	53.8 - 63.1	54.0 - 62.3
RACE				
White	3 (100.0%)	18 (100.0%)	32 (80.0%)	53 (86.9%)
Black or African American	0 (0.0%)	0 (0.0%)	6 (15.0%)	6 (9.8%)
Other or Pending	0 (0.0%)	0 (0.0%)	2 (5.0%)	2 (3.3%)
ETHNICITY				
Hispanic	0 (0.0%)	0 (0.0%)	2 (5.0%)	2 (3.3%)
Non Hispanic	2 (66.7%)	16 (88.9%)	37 (92.5%)	55 (90.2%)
Not Reported	1 (33.3%)	0 (0.0%)	0 (0.0%)	1 (1.6%)
Pending	0 (0.0%)	2 (11.1%)	1 (2.5%)	3 (4.9%)
HCV GENOTYPES				
1	3 (100.0%)	18 (100.0%)	40 (100.0%)	61 (100.0%)
SUBTYPES OF HCV GENOTYPES				
1 NOS	1 (33.3%)	2 (11.1%)	11 (27.5%)	14 (22.9%)
1 a	1 (33.3%)	10 (55.6%)	21 (52.5%)	32 (52.5%)
1 b	1 (33.3%)	6 (33.3%)	8 (20.0%)	15 (24.6%)
PRIOR HCV TREATMENT EXPERIENCE				
Naive	2 (66.7%)	9 (50.0%)	11 (27.5%)	22 (36.1%)
Experienced	1 (33.3%)	9 (50.0%)	29 (72.5%)	39 (63.9%)
CIRRHOSIS				
Not Cirrhotic	0 (0.0%)	4 (22.2%)	6 (15.0%)	10 (16.4%)
Cirrhotic	3 (100.0%)	14 (77.8%)	33 (82.5%)	50 (82.0%)
Not reported	0 (0.0%)	0 (0.0%)	1 (2.5%)	1 (1.6%)
EVIDENCE OF PRIOR DECOMPENSATION				
Yes	1 (33.3%)	4 (22.2%)	7 (17.5%)	12 (19.7%)
No	2 (66.7%)	14 (77.8%)	33 (82.5%)	49 (80.3%)
HIV				
Yes	0 (0.0%)	0 (0.0%)	1 (2.5%)	1 (1.6%)
No	3 (100.0%)	18 (100.0%)	39 (97.5%)	60 (98.4%)
LIVER TRANSPLANT				
No	3 (100.0%)	18 (100.0%)	40 (100.0%)	61 (100.0%)

Run Date: 05/10/16

Table 2. DEMOGRAPHICS (continued)

Variable	Treatment Group			
	SOF PEG RBV (N=3)	BOC PEG RBV (N=18)	TEL PEG RBV (N=40)	Total (N=61)
LIVER CANCER				
No	3 (100.0%)	0 (0.0%)	0 (0.0%)	3 (4.9%)
Not reported	0 (0.0%)	18 (100.0%)	40 (100.0%)	58 (95.1%)
KIDNEY TRANSPLANT				
No	3 (100.0%)	0 (0.0%)	0 (0.0%)	3 (4.9%)
Not reported	0 (0.0%)	18 (100.0%)	40 (100.0%)	58 (95.1%)
DIABETES				
Yes	0 (0.0%)	3 (16.7%)	7 (17.5%)	10 (16.4%)
No	3 (100.0%)	15 (83.3%)	33 (82.5%)	51 (83.6%)

Run Date: 05/10/16

Table 2a. DEMOGRAPHICS: Patients who developed Hepatic Decompensation vs Patients without decompensation

Variable	Treatment Group: Hepatic Decompensation (N=4)	No Hepatic Decompensation (N=57)	Total (N=61)
SEX			
Female	0 (0.0%)	17 (29.8%)	17 (27.9%)
Male	4 (100.0%)	40 (70.2%)	44 (72.1%)
AGE			
40-64	4 (100.0%)	50 (87.7%)	54 (88.5%)
65+	0 (0.0%)	7 (12.3%)	7 (11.5%)
Patient age at the start of IFN treatments. [Ad1]	4	57	61
Mean	55.8	57.6	57.5
Median	56.9	57.6	57.6
Std	5.40	6.58	6.48
Min Max	48.5 - 60.8	40.6 - 74.9	40.6 - 74.9
Q1 Q3	50.1 - 60.3	54.0 - 62.6	54.0 - 62.3
RACE			
White	4 (100.0%)	49 (86.0%)	53 (86.9%)
Black or African American	0 (0.0%)	6 (10.5%)	6 (9.8%)
Other or Pending	0 (0.0%)	2 (3.5%)	2 (3.3%)
ETHNICITY			
Hispanic	0 (0.0%)	2 (3.5%)	2 (3.3%)
Non Hispanic	3 (75.0%)	52 (91.2%)	55 (90.2%)
Not Reported	1 (25.0%)	0 (0.0%)	1 (1.6%)
Pending	0 (0.0%)	3 (5.3%)	3 (4.9%)
SUBTYPES OF HCV GENOTYPES			
1 NOS	0 (0.0%)	14 (24.6%)	14 (22.9%)
1 a	2 (50.0%)	30 (52.6%)	32 (52.5%)
1 b	2 (50.0%)	13 (22.8%)	15 (24.6%)
PRIOR HCV TREATMENT EXPERIENCE			
Naive	2 (50.0%)	20 (35.1%)	22 (36.1%)
Experienced	2 (50.0%)	37 (64.9%)	39 (63.9%)
CIRRHOSIS			
Not Cirrhotic	1 (25.0%)	9 (15.8%)	10 (16.4%)
Cirrhotic	3 (75.0%)	47 (82.5%)	50 (82.0%)
Not reported	0 (0.0%)	1 (1.8%)	1 (1.6%)
EVIDENCE OF PRIOR DECOMPENSATION			
Yes	1 (25.0%)	11 (19.3%)	12 (19.7%)
No	3 (75.0%)	46 (80.7%)	49 (80.3%)

Table 2a. DEMOGRAPHICS: Patients who developed Hepatic Decompensation vs Patients without decompensation (continued)

Variable	Treatment Group: Hepatic Decompensation (N=4)	Treatment Group: No Hepatic Decompensation (N=57)	Total (N=61)
HIV			
Yes	0 (0.0%)	1 (1.8%)	1 (1.6%)
No	4 (100.0%)	56 (98.2%)	60 (98.4%)
LIVER TRANSPLANT			
No	4 (100.0%)	57 (100.0%)	61 (100.0%)
LIVER CANCER			
No	1 (25.0%)	2 (3.5%)	3 (4.9%)
Not reported	3 (75.0%)	55 (96.5%)	58 (95.1%)
KIDNEY TRANSPLANT			
No	1 (25.0%)	2 (3.5%)	3 (4.9%)
Not reported	3 (75.0%)	55 (96.5%)	58 (95.1%)
DIABETES			
Yes	1 (25.0%)	9 (15.8%)	10 (16.4%)
No	3 (75.0%)	48 (84.2%)	51 (83.6%)

Run Date: 05/10/16

Table 3. BASELINE LABORATORY VALUES

Variable	Treatment Group: SOF PEG RBV (N=3)	BOC PEG RBV (N=18)	TEL PEG RBV (N=40)	Total (N=61)
ALT (IU/L)	3	17	39	59
Mean	93.0	92.0	117.7	109.1
Median	62.0	79.0	88.0	85.0
Std	71.71	55.85	78.88	72.55
Min Max	42.0 - 175.0	32.0 - 205.0	24.0 - 392.0	24.0 - 392.0
Q1 Q3	42.0 - 175.0	48.5 - 135.0	63.0 - 158.0	53.0 - 146.0
AST (IU/L)	3	17	39	59
Mean	138.0	110.1	112.6	113.2
Median	161.0	86.0	108.0	96.0
Std	73.26	89.19	63.77	71.26
Min Max	56.0 - 197.0	30.0 - 354.0	21.0 - 328.0	21.0 - 354.0
Q1 Q3	56.0 - 197.0	53.5 - 110.5	64.0 - 142.0	60.0 - 142.0
TOTAL BILIRUBIN (mg/dL)	3	16	37	56
Mean	1.9	1.2	1.2	1.2
Median	1.5	1.2	1.1	1.1
Std	1.21	0.62	0.62	0.66
Min Max	1.0 - 3.3	0.4 - 2.9	0.5 - 3.5	0.4 - 3.5
Q1 Q3	1.0 - 3.3	0.6 - 1.4	0.8 - 1.5	0.8 - 1.5
TOTAL BILIRUBIN cat				
<=3	2 (66.7%)	16 (88.9%)	36 (90.0%)	54 (88.5%)
>3	1 (33.3%)	0 (0.0%)	1 (2.5%)	2 (3.3%)
Not reported	0 (0.0%)	2 (11.1%)	3 (7.5%)	5 (8.2%)
PLATELETS (x10E3/uL)	3	16	39	58
Mean	67.0	96.8	75.0	80.6
Median	69.0	86.0	63.0	69.0
Std	6.24	46.63	44.52	44.71
Min Max	60.0 - 72.0	33.0 - 198.0	28.0 - 260.0	28.0 - 260.0
Q1 Q3	60.0 - 72.0	60.3 - 136.3	48.0 - 89.0	55.8 - 96.5
baseline PLT (cat)				
100,000+	0 (0.0%)	7 (38.9%)	6 (15.0%)	13 (21.3%)
<100,000	3 (100.0%)	9 (50.0%)	33 (82.5%)	45 (73.8%)
Not reported	0 (0.0%)	2 (11.1%)	1 (2.5%)	3 (4.9%)
ALBUMIN (g/dL)	3	16	38	57
Mean	3.1	3.8	3.6	3.7
Median	3.0	3.6	3.7	3.6
Std	0.42	0.39	0.54	0.51
Min Max	2.8 - 3.6	3.1 - 4.4	2.2 - 4.7	2.2 - 4.7
Q1 Q3	2.8 - 3.6	3.6 - 4.3	3.4 - 4.0	3.4 - 4.0
baseline ALB (cat)				
3.2+	1 (33.3%)	15 (83.3%)	33 (82.5%)	49 (80.3%)
<3.2	2 (66.7%)	1 (5.6%)	5 (12.5%)	8 (13.1%)
Not reported	0 (0.0%)	2 (11.1%)	2 (5.0%)	4 (6.6%)

Run Date: 05/10/16

Table 3. BASELINE LABORATORY VALUES (continued)

Variable	Treatment Group SOF PEG RBV (N=3)	BOC PEG RBV (N=18)	TEL PEG RBV (N=40)	Total (N=61)
CREATININ (mg/dL)	3	17	38	58
Mean	0.5	0.8	0.9	0.9
Median	0.5	0.8	0.8	0.8
Std	0.02	0.15	0.37	0.32
Min Max	0.5 - 0.5	0.6 - 1.1	0.5 - 2.9	0.5 - 2.9
Q1 Q3	0.5 - 0.5	0.7 - 1.0	0.7 - 1.0	0.7 - 1.0
CREATININ cat (mg/dL)				
<=1.5	3 (100.0%)	17 (94.4%)	37 (92.5%)	57 (93.4%)
>2.0	0 (0.0%)	0 (0.0%)	1 (2.5%)	1 (1.6%)
Not reported	0 (0.0%)	1 (5.6%)	2 (5.0%)	3 (4.9%)
CREATININE CLEARANCE	3	17	36	56
Mean	169.5	131.6	113.1	121.7
Median	173.0	126.1	108.8	117.5
Std	6.49	40.13	44.00	43.65
Min Max	162.0 - 173.5	57.8 - 199.1	31.5 - 237.6	31.5 - 237.6
Q1 Q3	162.0 - 173.5	107.5 - 162.8	83.8 - 129.7	92.1 - 160.6
CREATININE CLEARANCE cat				
>30	3 (100.0%)	17 (94.4%)	36 (90.0%)	56 (91.8%)
Not reported	0 (0.0%)	1 (5.6%)	4 (10.0%)	5 (8.2%)
eGFR cat				
90+	3 (100.0%)	0 (0.0%)	0 (0.0%)	3 (4.9%)
Not reported	0 (0.0%)	18 (100.0%)	40 (100.0%)	58 (95.1%)
MELD CIRRHOTIC cat				
0-9	1 (33.3%)	6 (33.3%)	12 (30.0%)	19 (31.1%)
10-15	1 (33.3%)	2 (11.1%)	3 (7.5%)	6 (9.8%)
16-21	0 (0.0%)	0 (0.0%)	1 (2.5%)	1 (1.6%)
Not reported	1 (33.3%)	6 (33.3%)	17 (42.5%)	24 (39.3%)
_Not cirrh	0 (0.0%)	4 (22.2%)	6 (15.0%)	10 (16.4%)
_Unknown c	0 (0.0%)	0 (0.0%)	1 (2.5%)	1 (1.6%)
BASELINE_MELD_CIRR_10				
10+	1 (33.3%)	2 (11.1%)	4 (10.0%)	7 (11.5%)
<10	1 (33.3%)	6 (33.3%)	12 (30.0%)	19 (31.1%)
Not reported	1 (33.3%)	6 (33.3%)	17 (42.5%)	24 (39.3%)
_Not cirrhotic	0 (0.0%)	4 (22.2%)	6 (15.0%)	10 (16.4%)
_Unknown cirr s	0 (0.0%)	0 (0.0%)	1 (2.5%)	1 (1.6%)
MELD_ AMONG CIRRHOTICS	2	8	16	26
Mean	11.5	8.5	9.0	9.0
Median	11.5	8.5	8.0	8.0
Std	4.95	1.20	3.46	3.03
Min Max	8.0 - 15.0	7.0 - 10.0	6.0 - 20.0	6.0 - 20.0
Q1 Q3	8.0 - 15.0	7.3 - 9.8	7.0 - 9.8	7.0 - 10.0
HEMOGLOBIN (g/dL)	3	17	39	59
Mean	12.7	14.4	14.1	14.1
Median	12.6	14.4	13.9	14.0
Std	0.60	0.89	1.72	1.52
Min Max	12.1 - 13.3	12.7 - 16.1	10.6 - 17.9	10.6 - 17.9
Q1 Q3	12.1 - 13.3	13.9 - 15.0	13.2 - 15.3	13.3 - 15.2

Run Date: 05/10/16

Table 3. BASELINE LABORATORY VALUES (continued)

Variable	Treatment Group			
	SOF PEG RBV (N=3)	BOC PEG RBV (N=18)	TEL PEG RBV (N=40)	Total (N=61)
INR	3	0	0	3
Mean	1.3			1.3
Median	1.4			1.4
Std	0.11			0.11
Min Max	1.2 - 1.4			1.2 - 1.4
Q1 Q3	1.2 - 1.4	- -	- -	1.2 - 1.4
HCV RNA (IU/mL)	3	17	39	59
Mean	1660333.3	3799076.5	2395970.3	2762849.9
Median	1880000.0	1964703.0	1389139.0	1682740.0
Std	1234248.89	4477937.90	2595342.05	3235013.37
Min Max	331000 - 2770000	59419 - 17600000	3147 - 12200000	3147 - 17600000
Q1 Q3	331000 - 2770000	308008 - 6130000	540863 - 2960000	535000 - 4143279
HCV RNA (IU/mL, log10)	3	17	39	59
Mean	6.1	6.1	6.1	6.1
Median	6.3	6.3	6.1	6.2
Std	0.49	0.79	0.69	0.71
Min Max	5.5 - 6.4	4.8 - 7.2	3.5 - 7.1	3.5 - 7.2
Q1 Q3	5.5 - 6.4	5.4 - 6.8	5.7 - 6.5	5.7 - 6.6
HCV RNA (cat)				
Not reported	0 (0.0%)	1 (5.6%)	1 (2.5%)	2 (3.3%)
Quant	3 (100.0%)	17 (94.4%)	39 (97.5%)	59 (96.7%)

Run Date: 05/10/16

Table 3a. BASELINE LABORATORY VALUES: Patients who developed Hepatic Decompensation vs Patients

Variable	Treatment Group: Hepatic Decompensation (N=4)	No Hepatic Decompensation (N=57)	Total (N=61)
ALT (IU/L)	4	55	59
Mean	101.8	109.6	109.1
Median	86.5	81.0	85.0
Std	48.25	74.29	72.55
Min Max	62.0 - 172.0	24.0 - 392.0	24.0 - 392.0
Q1 Q3	67.8 - 151.0	51.0 - 146.0	53.0 - 146.0
AST (IU/L)	4	55	59
Mean	169.5	109.1	113.2
Median	156.0	96.0	96.0
Std	73.64	70.01	71.26
Min Max	95.0 - 271.0	21.0 - 354.0	21.0 - 354.0
Q1 Q3	109.0 - 243.5	59.0 - 125.0	60.0 - 142.0
TOTAL BILIRUBIN (mg/dL)	3	53	56
Mean	2.1	1.2	1.2
Median	2.1	1.1	1.1
Std	1.26	0.60	0.66
Min Max	0.8 - 3.3	0.4 - 3.5	0.4 - 3.5
Q1 Q3	0.8 - 3.3	0.8 - 1.4	0.8 - 1.5
TOTAL BILIRUBIN cat			
<=3	2 (50.0%)	52 (91.2%)	54 (88.5%)
>3	1 (25.0%)	1 (1.8%)	2 (3.3%)
Not reported	1 (25.0%)	4 (7.0%)	5 (8.2%)
PLATELETS (x10E3/uL)	3	55	58
Mean	64.0	81.5	80.6
Median	63.0	69.0	69.0
Std	4.58	45.76	44.71
Min Max	60.0 - 69.0	28.0 - 260.0	28.0 - 260.0
Q1 Q3	60.0 - 69.0	55.0 - 98.0	55.8 - 96.5
baseline PLT (cat)			
100,000+	0 (0.0%)	13 (22.8%)	13 (21.3%)
<100,000	3 (75.0%)	42 (73.7%)	45 (73.8%)
Not reported	1 (25.0%)	2 (3.5%)	3 (4.9%)
ALBUMIN (g/dL)	3	54	57
Mean	3.1	3.7	3.7
Median	2.9	3.7	3.6
Std	0.44	0.50	0.51
Min Max	2.8 - 3.6	2.2 - 4.7	2.2 - 4.7
Q1 Q3	2.8 - 3.6	3.5 - 4.0	3.4 - 4.0
baseline ALB (cat)			
3.2+	1 (25.0%)	48 (84.2%)	49 (80.3%)
<3.2	2 (50.0%)	6 (10.5%)	8 (13.1%)
Not reported	1 (25.0%)	3 (5.3%)	4 (6.6%)

Run Date: 05/10/16

Table 3a. BASELINE LABORATORY VALUES: Patients who developed Hepatic Decompensation vs Patients (continued)

Variable	Treatment Group: Hepatic Decompensation (N=4)	Treatment Group: No Hepatic Decompensation (N=57)	Treatment Group: Total (N=61)
CREATININ (mg/dL)	4	54	58
Mean	0.8	0.9	0.9
Median	0.9	0.8	0.8
Std	0.24	0.33	0.32
Min Max	0.5 - 1.0	0.5 - 2.9	0.5 - 2.9
Q1 Q3	0.6 - 1.0	0.7 - 1.0	0.7 - 1.0
CREATININE CLEARANCE	4	52	56
Mean	144.4	120.0	121.7
Median	141.1	117.1	117.5
Std	24.76	44.44	43.65
Min Max	121.7 - 173.5	31.5 - 237.6	31.5 - 237.6
Q1 Q3	122.8 - 169.2	89.0 - 157.6	92.1 - 160.6
CREATININE CLEARANCE cat			
>30	4 (100.0%)	52 (91.2%)	56 (91.8%)
Not reported	0 (0.0%)	5 (8.8%)	5 (8.2%)
eGFR cat			
90+	1 (25.0%)	2 (3.5%)	3 (4.9%)
Not reported	3 (75.0%)	55 (96.5%)	58 (95.1%)
MELD CIRRHOTIC cat			
0-9	1 (25.0%)	18 (31.6%)	19 (31.1%)
10-15	2 (50.0%)	4 (7.0%)	6 (9.8%)
16-21	0 (0.0%)	1 (1.8%)	1 (1.6%)
Not reported	0 (0.0%)	24 (42.1%)	24 (39.3%)
_Not cirrh	1 (25.0%)	9 (15.8%)	10 (16.4%)
_Unknown c	0 (0.0%)	1 (1.8%)	1 (1.6%)
BASELINE_MELD_CIRR_10			
10+	2 (50.0%)	5 (8.8%)	7 (11.5%)
<10	1 (25.0%)	18 (31.6%)	19 (31.1%)
Not reported	0 (0.0%)	24 (42.1%)	24 (39.3%)
_Not cirrhotic	1 (25.0%)	9 (15.8%)	10 (16.4%)
_Unknown cirr s	0 (0.0%)	1 (1.8%)	1 (1.6%)
MELD_ AMONG CIRRHOTICS	3	23	26
Mean	12.0	8.7	9.0
Median	12.0	8.0	8.0
Std	3.00	2.87	3.03
Min Max	9.0 - 15.0	6.0 - 20.0	6.0 - 20.0
Q1 Q3	9.0 - 15.0	7.0 - 9.0	7.0 - 10.0
HEMOGLOBIN (g/dL)	4	55	59
Mean	13.9	14.1	14.1
Median	14.3	14.0	14.0
Std	1.26	1.55	1.52
Min Max	12.1 - 14.9	10.6 - 17.9	10.6 - 17.9
Q1 Q3	12.6 - 14.8	13.3 - 15.3	13.3 - 15.2

Table 3a. BASELINE LABORATORY VALUES: Patients who developed Hepatic Decompensation vs Patients (continued)

Variable	Treatment Group: Hepatic Decompensation (N=4)	No Hepatic Decompensation (N=57)	Total (N=61)
INR	1	2	3
Mean	1.4	1.3	1.3
Median	1.4	1.3	1.4
Std		0.13	0.11
Min Max	1.4 - 1.4	1.2 - 1.4	1.2 - 1.4
Q1 Q3	1.4 - 1.4	1.2 - 1.4	1.2 - 1.4
HCV RNA (IU/mL)	3	56	59
Mean	2564473.3	2773477.2	2762849.9
Median	878000.0	1721370.0	1682740.0
Std	3405772.84	3257620.73	3235013.37
Min Max	331000 - 6484420	3147 -17600000	3147 -17600000
Q1 Q3	331000 - 6484420	536466 - 4042459	535000 -4143279
HCV RNA (IU/mL, log10)	3	56	59
Mean	6.1	6.1	6.1
Median	5.9	6.2	6.2
Std	0.66	0.71	0.71
Min Max	5.5 - 6.8	3.5 - 7.2	3.5 - 7.2
Q1 Q3	5.5 - 6.8	5.7 - 6.6	5.7 - 6.6

Run Date: 05/10/16

Table 4. ALL ADVERSE EVENTS TO DATE BY TREATMENT REGIMEN BY SYSTEM/ORGAN CLASS

	Treatment Group											
	SOF PEG RBV (N=3)			BOC PEG RBV (N=18)			TEL PEG RBV (N=40)			Overall (N=61)		
TXT_AEDECOD	nPt	nPt/N	nAE	nPt	nPt/N	nAE	nPt	nPt/N	nAE	nPt	nPt/N	nAE
TOTAL PATIENT WITH AE	3	(100.0)		18	(100.0)		40	(100.0)		61	(100.0)	
BLOOD AND LYMPHATIC SYSTEM DISORDERS	2	(66.7)	4	18	(100.0)	45	38	(95.0)	76	58	(95.1)	125
Thrombocytopenia	2	(66.7)	2	17	(94.4)	17	28	(70.0)	28	47	(77.0)	47
Anaemia	2	(66.7)	2	13	(72.2)	14	31	(77.5)	32	46	(75.4)	48
Neutropenia	0	(0.0)	0	9	(50.0)	9	10	(25.0)	12	19	(31.1)	21
Leukopenia	0	(0.0)	0	4	(22.2)	4	1	(2.5)	1	5	(8.2)	5
Disseminated Intravascular Coagulation	0	(0.0)	0	0	(0.0)	0	1	(2.5)	1	1	(1.6)	1
Leukocytosis	0	(0.0)	0	0	(0.0)	0	1	(2.5)	1	1	(1.6)	1
Lymphadenitis	0	(0.0)	0	1	(5.6)	1	0	(0.0)	0	1	(1.6)	1
Pancytopenia	0	(0.0)	0	0	(0.0)	0	1	(2.5)	1	1	(1.6)	1
CARDIAC DISORDERS	0	(0.0)	0	0	(0.0)	0	1	(2.5)	1	1	(1.6)	1
Supraventricular Tachycardia	0	(0.0)	0	0	(0.0)	0	1	(2.5)	1	1	(1.6)	1
EAR AND LABYRINTH DISORDERS	0	(0.0)	0	1	(5.6)	1	1	(2.5)	1	2	(3.3)	2
Ear Pain	0	(0.0)	0	1	(5.6)	1	0	(0.0)	0	1	(1.6)	1
Vertigo	0	(0.0)	0	0	(0.0)	0	1	(2.5)	1	1	(1.6)	1
ENDOCRINE DISORDERS	0	(0.0)	0	0	(0.0)	0	3	(7.5)	3	3	(4.9)	3
Hypothyroidism	0	(0.0)	0	0	(0.0)	0	3	(7.5)	3	3	(4.9)	3
EYE DISORDERS	0	(0.0)	0	0	(0.0)	0	2	(5.0)	2	2	(3.3)	2
Conjunctival Haemorrhage	0	(0.0)	0	0	(0.0)	0	1	(2.5)	1	1	(1.6)	1
Retinopathy	0	(0.0)	0	0	(0.0)	0	1	(2.5)	1	1	(1.6)	1
GASTROINTESTINAL DISORDERS	1	(33.3)	2	6	(33.3)	10	21	(52.5)	34	28	(45.9)	46
Anorectal Discomfort	0	(0.0)	0	4	(22.2)	4	13	(32.5)	13	17	(27.9)	17
Nausea	0	(0.0)	0	2	(11.1)	2	6	(15.0)	6	8	(13.1)	8
Diarrhoea	1	(33.3)	1	1	(5.6)	1	2	(5.0)	2	4	(6.6)	4
Ascites	1	(33.3)	1	1	(5.6)	1	0	(0.0)	0	2	(3.3)	2
Chelitis	0	(0.0)	0	0	(0.0)	0	2	(5.0)	2	2	(3.3)	2
Gastrooesophageal Reflux	0	(0.0)	0	0	(0.0)	0	2	(5.0)	2	2	(3.3)	2
Haemorrhoids	0	(0.0)	0	0	(0.0)	0	2	(5.0)	2	2	(3.3)	2
Vomiting	0	(0.0)	0	0	(0.0)	0	2	(5.0)	2	2	(3.3)	2
Abdominal Pain	0	(0.0)	0	0	(0.0)	0	1	(2.5)	1	1	(1.6)	1
Abdominal Pain Lower	0	(0.0)	0	0	(0.0)	0	1	(2.5)	1	1	(1.6)	1
Anal Fissures	0	(0.0)	0	0	(0.0)	0	1	(2.5)	1	1	(1.6)	1
Colitis	0	(0.0)	0	0	(0.0)	0	1	(2.5)	1	1	(1.6)	1
Dysphagia	0	(0.0)	0	1	(5.6)	1	0	(0.0)	0	1	(1.6)	1
Haematemesis	0	(0.0)	0	0	(0.0)	0	1	(2.5)	1	1	(1.6)	1
Oral Pain	0	(0.0)	0	1	(5.6)	1	0	(0.0)	0	1	(1.6)	1

Table 4. ALL ADVERSE EVENTS TO DATE BY TREATMENT REGIMEN BY SYSTEM/ORGAN CLASS (continued)

	Treatment Group											
	SOF PEG RBV (N=3)			BOC PEG RBV (N=18)			TEL PEG RBV (N=40)			Overall (N=61)		
TXT_AEDECOD	nPt	nPt/N	nAE	nPt	nPt/N	nAE	nPt	nPt/N	nAE	nPt	nPt/N	nAE
GENERAL DISORDERS AND ADMINISTRATION S	2	(66.7)	5	7	(38.9)	8	11	(27.5)	19	20	(32.8)	32
Oedema Peripheral	1	(33.3)	1	4	(22.2)	4	3	(7.5)	3	8	(13.1)	8
Fatigue	1	(33.3)	1	2	(11.1)	2	4	(10.0)	4	7	(11.5)	7
Pyrexia	1	(33.3)	1	1	(5.6)	1	3	(7.5)	3	5	(8.2)	5
Influenza Like Illness	1	(33.3)	1	1	(5.6)	1	2	(5.0)	2	4	(6.6)	4
Asthenia	0	(0.0)	0	0	(0.0)	0	1	(2.5)	1	1	(1.6)	1
Chest Pain	0	(0.0)	0	0	(0.0)	0	1	(2.5)	1	1	(1.6)	1
Chills	0	(0.0)	0	0	(0.0)	0	1	(2.5)	1	1	(1.6)	1
Injection Site Bruising	0	(0.0)	0	0	(0.0)	0	1	(2.5)	1	1	(1.6)	1
Irritability	1	(33.3)	1	0	(0.0)	0	0	(0.0)	0	1	(1.6)	1
Local Swelling	0	(0.0)	0	0	(0.0)	0	1	(2.5)	2	1	(1.6)	2
Anasarca	0	(0.0)	0	0	(0.0)	0	1	(2.5)	1	1	(1.6)	1
HEPATOBILIARY DISORDERS	0	(0.0)	0	0	(0.0)	0	2	(5.0)	3	2	(3.3)	3
Hyperbilirubinaemia	0	(0.0)	0	0	(0.0)	0	2	(5.0)	2	2	(3.3)	2
Aspartate Aminotransferases Increased	0	(0.0)	0	0	(0.0)	0	1	(2.5)	1	1	(1.6)	1
INFECTIONS AND INFESTATIONS	0	(0.0)	0	4	(22.2)	5	6	(15.0)	11	10	(16.4)	16
Upper Respiratory Tract	0	(0.0)	0	1	(5.6)	1	2	(5.0)	2	3	(4.9)	3
Oral Candidiasis	0	(0.0)	0	0	(0.0)	0	2	(5.0)	2	2	(3.3)	2
Pneumonia	0	(0.0)	0	1	(5.6)	1	1	(2.5)	1	2	(3.3)	2
Cellulitis	0	(0.0)	0	0	(0.0)	0	1	(2.5)	1	1	(1.6)	1
E. Cloacae Infection	0	(0.0)	0	1	(5.6)	1	0	(0.0)	0	1	(1.6)	1
Fungal Sepsis	0	(0.0)	0	0	(0.0)	0	1	(2.5)	2	1	(1.6)	2
Parotitis	0	(0.0)	0	0	(0.0)	0	1	(2.5)	1	1	(1.6)	1
Pharyngitis	0	(0.0)	0	0	(0.0)	0	1	(2.5)	1	1	(1.6)	1
Septic Shock	0	(0.0)	0	0	(0.0)	0	1	(2.5)	1	1	(1.6)	1
Streptococcus Viridans	0	(0.0)	0	1	(5.6)	1	0	(0.0)	0	1	(1.6)	1
Urinary Tract Infection	0	(0.0)	0	1	(5.6)	1	0	(0.0)	0	1	(1.6)	1
INVESTIGATIONS	0	(0.0)	0	2	(11.1)	2	1	(2.5)	1	3	(4.9)	3
Blood Bilirubin Increased	0	(0.0)	0	1	(5.6)	1	0	(0.0)	0	1	(1.6)	1
Blood thyroid Stimulating Hormone Increased	0	(0.0)	0	1	(5.6)	1	0	(0.0)	0	1	(1.6)	1
Troponin Increased	0	(0.0)	0	0	(0.0)	0	1	(2.5)	1	1	(1.6)	1

Table 4. ALL ADVERSE EVENTS TO DATE BY TREATMENT REGIMEN BY SYSTEM/ORGAN CLASS (continued)

	Treatment Group											
	SOF PEG RBV (N=3)			BOC PEG RBV (N=18)			TEL PEG RBV (N=40)			Overall (N=61)		
TXT_AEDECOD	nPt	nPt/N	nAE	nPt	nPt/N	nAE	nPt	nPt/N	nAE	nPt	nPt/N	nAE
METABOLISM AND NUTRITION DISORDERS	0	(0.0)	0	3	(16.7)	3	7	(17.5)	16	10	(16.4)	19
Hypokalaemia	0	(0.0)	0	1	(5.6)	1	2	(5.0)	2	3	(4.9)	3
Decreased Appetite	0	(0.0)	0	2	(11.1)	2	2	(5.0)	2	4	(6.6)	4
Hyponatraemia	0	(0.0)	0	0	(0.0)	0	2	(5.0)	2	2	(3.3)	2
Hyperglycaemia	0	(0.0)	0	0	(0.0)	0	2	(5.0)	2	2	(3.3)	2
Blood Albumin Decreased	0	(0.0)	0	0	(0.0)	0	1	(2.5)	1	1	(1.6)	1
Blood Creatinine Increased	0	(0.0)	0	0	(0.0)	0	1	(2.5)	1	1	(1.6)	1
Blood Uric Acid Increased	0	(0.0)	0	0	(0.0)	0	1	(2.5)	1	1	(1.6)	1
Dehydration	0	(0.0)	0	0	(0.0)	0	1	(2.5)	1	1	(1.6)	1
Hyperglycaemia	0	(0.0)	0	0	(0.0)	0	1	(2.5)	1	1	(1.6)	1
Hyperkalaemia	0	(0.0)	0	0	(0.0)	0	1	(2.5)	1	1	(1.6)	1
Hypocalcaemia	0	(0.0)	0	0	(0.0)	0	1	(2.5)	1	1	(1.6)	1
Metabolic Acidosis	0	(0.0)	0	0	(0.0)	0	1	(2.5)	1	1	(1.6)	1
MUSCULOSKELETAL AND CONNECTIVE TISSUE	1	(33.3)	2	0	(0.0)	0	4	(10.0)	6	5	(8.2)	8
Arthralgia	1	(33.3)	1	0	(0.0)	0	3	(7.5)	3	4	(6.6)	4
Myalgia	0	(0.0)	0	0	(0.0)	0	2	(5.0)	2	2	(3.3)	2
Joint Effusion	1	(33.3)	1	0	(0.0)	0	0	(0.0)	0	1	(1.6)	1
Rhabdomyolysis	0	(0.0)	0	0	(0.0)	0	1	(2.5)	1	1	(1.6)	1
NEOPLASMS BENIGN, MALIGNANT AND UNSPEC	0	(0.0)	0	1	(5.6)	1	2	(5.0)	2	3	(4.9)	3
Hepatocellular Carcinoma	0	(0.0)	0	0	(0.0)	0	2	(5.0)	2	2	(3.3)	2
Nasopharyngeal Cancer	0	(0.0)	0	1	(5.6)	1	0	(0.0)	0	1	(1.6)	1
NERVOUS SYSTEM DISORDERS	1	(33.3)	2	4	(22.2)	4	8	(20.0)	10	13	(21.3)	16
Hepatic Encephalopathy	0	(0.0)	0	2	(11.1)	2	3	(7.5)	3	5	(8.2)	5
Dizziness	1	(33.3)	1	0	(0.0)	0	2	(5.0)	2	3	(4.9)	3
Dysgeusia	0	(0.0)	0	2	(11.1)	2	0	(0.0)	0	2	(3.3)	2
Headache	0	(0.0)	0	0	(0.0)	0	2	(5.0)	2	2	(3.3)	2
Cerebral Haemorrhage	0	(0.0)	0	0	(0.0)	0	1	(2.5)	1	1	(1.6)	1
Lethargy	0	(0.0)	0	0	(0.0)	0	1	(2.5)	1	1	(1.6)	1
Syncope	1	(33.3)	1	0	(0.0)	0	0	(0.0)	0	1	(1.6)	1
Trigeminal Neuralgia	0	(0.0)	0	0	(0.0)	0	1	(2.5)	1	1	(1.6)	1
PSYCHIATRIC DISORDERS	1	(33.3)	1	2	(11.1)	2	9	(22.5)	10	12	(19.7)	13
Depression	0	(0.0)	0	1	(5.6)	1	4	(10.0)	4	5	(8.2)	5
Insomnia	0	(0.0)	0	1	(5.6)	1	4	(10.0)	4	5	(8.2)	5
Anxiety	0	(0.0)	0	0	(0.0)	0	1	(2.5)	1	1	(1.6)	1
Confusion	0	(0.0)	0	0	(0.0)	0	1	(2.5)	1	1	(1.6)	1
Mood Swings	1	(33.3)	1	0	(0.0)	0	0	(0.0)	0	1	(1.6)	1

Table 4. ALL ADVERSE EVENTS TO DATE BY TREATMENT REGIMEN BY SYSTEM/ORGAN CLASS (continued)

	Treatment Group											
	SOF PEG RBV (N=3)			BOC PEG RBV (N=18)			TEL PEG RBV (N=40)			Overall (N=61)		
TXT_AEDECOD	nPt	nPt/N	nAE	nPt	nPt/N	nAE	nPt	nPt/N	nAE	nPt	nPt/N	nAE
RENAL AND URINARY DISORDERS	0	(0.0)	0	1	(5.6)	1	2	(5.0)	2	3	(4.9)	3
Hematuria	0	(0.0)	0	1	(5.6)	1	0	(0.0)	0	1	(1.6)	1
Renal Failure	0	(0.0)	0	0	(0.0)	0	1	(2.5)	1	1	(1.6)	1
Renal Failure Acute	0	(0.0)	0	0	(0.0)	0	1	(2.5)	1	1	(1.6)	1
REPRODUCTIVE SYSTEM AND BREAST DISORDE	0	(0.0)	0	0	(0.0)	0	1	(2.5)	1	1	(1.6)	1
Scrotal Oedema	0	(0.0)	0	0	(0.0)	0	1	(2.5)	1	1	(1.6)	1
RESPIRATORY, THORACIC AND MEDIASTINAL	1	(33.3)	1	1	(5.6)	1	5	(12.5)	5	7	(11.5)	7
Cough	0	(0.0)	0	0	(0.0)	0	3	(7.5)	3	3	(4.9)	3
Congestion Nasal	0	(0.0)	0	1	(5.6)	1	0	(0.0)	0	1	(1.6)	1
Dyspnoea Exertional	1	(33.3)	1	0	(0.0)	0	0	(0.0)	0	1	(1.6)	1
Oropharyngeal Pain	0	(0.0)	0	0	(0.0)	0	1	(2.5)	1	1	(1.6)	1
Respiratory Failure	0	(0.0)	0	0	(0.0)	0	1	(2.5)	1	1	(1.6)	1
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	0	(0.0)	0	7	(38.9)	7	26	(65.0)	35	33	(54.1)	42
Rash	0	(0.0)	0	7	(38.9)	7	25	(62.5)	28	32	(52.5)	35
Pruritus	0	(0.0)	0	0	(0.0)	0	3	(7.5)	3	3	(4.9)	3
Blisters	0	(0.0)	0	0	(0.0)	0	1	(2.5)	1	1	(1.6)	1
Erythema	0	(0.0)	0	0	(0.0)	0	1	(2.5)	1	1	(1.6)	1
Lichen Planus	0	(0.0)	0	0	(0.0)	0	1	(2.5)	1	1	(1.6)	1
Psoriasis	0	(0.0)	0	0	(0.0)	0	1	(2.5)	1	1	(1.6)	1

Table 5. SERIOUS ADVERSE EVENTS TO DATE BY TREATMENT REGIMEN BY SYSTEM /ORGAN CLASS

	Treatment Group									
	SOF PEG RBV (N=3)			BOC PEG RBV (N=18)			TEL PEG RBV (N=40)		Overall (N=61)	
TXT_AEDECOD	nPt	nPt/N	nSAE	nPt	nPt/N	nSAE	nPt	nPt/N	nPt	nPt/N	nSAE
TOTAL PATIENT WITH SAE	1	(33.3)		1	(5.6)		5	(12.5)	7	(11.5)	
BLOOD AND LYMPHATIC SYSTEM DISORDERS	0	(0.0)	0	1	(5.6)	2	5	(12.5)	14	6	(9.8)	16
Thrombocytopenia	0	(0.0)	0	1	(5.6)	1	4	(10.0)	4	5	(8.2)	5
Anaemia	0	(0.0)	0	0	(0.0)	0	4	(10.0)	4	4	(6.6)	4
Neutropenia	0	(0.0)	0	0	(0.0)	0	2	(5.0)	4	2	(3.3)	4
Disseminated Intravascular Coagulation	0	(0.0)	0	0	(0.0)	0	1	(2.5)	1	1	(1.6)	1
Leukocytosis	0	(0.0)	0	0	(0.0)	0	1	(2.5)	1	1	(1.6)	1
Leukopenia	0	(0.0)	0	1	(5.6)	1	0	(0.0)	0	1	(1.6)	1
CARDIAC DISORDERS	0	(0.0)	0	0	(0.0)	0	1	(2.5)	1	1	(1.6)	1
Supraventricular Tachycardia	0	(0.0)	0	0	(0.0)	0	1	(2.5)	1	1	(1.6)	1
EAR AND LABYRINTH DISORDERS	0	(0.0)	0	0	(0.0)	0	1	(2.5)	1	1	(1.6)	1
Vertigo	0	(0.0)	0	0	(0.0)	0	1	(2.5)	1	1	(1.6)	1
ENDOCRINE DISORDERS	0	(0.0)	0	0	(0.0)	0	1	(2.5)	1	1	(1.6)	1
Hypothyroidism	0	(0.0)	0	0	(0.0)	0	1	(2.5)	1	1	(1.6)	1
GASTROINTESTINAL DISORDERS	0	(0.0)	0	0	(0.0)	0	4	(10.0)	10	4	(6.6)	10
Anorectal Discomfort	0	(0.0)	0	0	(0.0)	0	3	(7.5)	3	3	(4.9)	3
Nausea	0	(0.0)	0	0	(0.0)	0	2	(5.0)	2	2	(3.3)	2
Abdominal Pain	0	(0.0)	0	0	(0.0)	0	1	(2.5)	1	1	(1.6)	1
Chelitis	0	(0.0)	0	0	(0.0)	0	1	(2.5)	1	1	(1.6)	1
Colitis	0	(0.0)	0	0	(0.0)	0	1	(2.5)	1	1	(1.6)	1
Haematemesis	0	(0.0)	0	0	(0.0)	0	1	(2.5)	1	1	(1.6)	1
Vomiting	0	(0.0)	0	0	(0.0)	0	1	(2.5)	1	1	(1.6)	1
GENERAL DISORDERS AND ADMINISTRATION S	1	(33.3)	3	1	(5.6)	1	1	(2.5)	3	3	(4.9)	7
Oedema Peripheral	1	(33.3)	1	1	(5.6)	1	1	(2.5)	1	3	(4.9)	3
Fatigue	1	(33.3)	1	0	(0.0)	0	1	(2.5)	1	2	(3.3)	2
Pyrexia	1	(33.3)	1	0	(0.0)	0	1	(2.5)	1	2	(3.3)	2
HEPATOBILIARY DISORDERS	0	(0.0)	0	0	(0.0)	0	1	(2.5)	1	1	(1.6)	1
Hyperbilirubinaemia	0	(0.0)	0	0	(0.0)	0	1	(2.5)	1	1	(1.6)	1

Run Date: 05/19/16

Table 5. SERIOUS ADVERSE EVENTS TO DATE BY TREATMENT REGIMEN BY SYSTEM /ORGAN CLASS (continued)

	Treatment Group									
	SOF PEG RBV (N=3)			BOC PEG RBV (N=18)			TEL PEG RBV (N=40)			Overall (N=61)	
TXT_AEDECOD	nPt	nPt/N	nSAE	nPt	nPt/N	nSAE	nPt	nPt/N	nSAE	nPt	nPt/N	nSAE
INFECTIONS AND INFESTATIONS	0	(0.0)	0	0	(0.0)	0	2	(5.0)	6	2	(3.3)	6
Fungal Sepsis	0	(0.0)	0	0	(0.0)	0	1	(2.5)	2	1	(1.6)	2
Oral Candidiasis	0	(0.0)	0	0	(0.0)	0	1	(2.5)	1	1	(1.6)	1
Parotitis	0	(0.0)	0	0	(0.0)	0	1	(2.5)	1	1	(1.6)	1
Pneumonia	0	(0.0)	0	0	(0.0)	0	1	(2.5)	1	1	(1.6)	1
Septic Shock	0	(0.0)	0	0	(0.0)	0	1	(2.5)	1	1	(1.6)	1
INVESTIGATIONS	0	(0.0)	0	0	(0.0)	0	1	(2.5)	1	1	(1.6)	1
Troponin Increased	0	(0.0)	0	0	(0.0)	0	1	(2.5)	1	1	(1.6)	1
METABOLISM AND NUTRITION DISORDERS	0	(0.0)	0	0	(0.0)	0	2	(5.0)	9	2	(3.3)	9
Blood Albumin Decreased	0	(0.0)	0	0	(0.0)	0	1	(2.5)	1	1	(1.6)	1
Blood Creatinine Increased	0	(0.0)	0	0	(0.0)	0	1	(2.5)	1	1	(1.6)	1
Decreased Appetite	0	(0.0)	0	0	(0.0)	0	1	(2.5)	1	1	(1.6)	1
Dehydration	0	(0.0)	0	0	(0.0)	0	1	(2.5)	1	1	(1.6)	1
Hyperglycaemia	0	(0.0)	0	0	(0.0)	0	1	(2.5)	1	1	(1.6)	1
Hypocalcaemia	0	(0.0)	0	0	(0.0)	0	1	(2.5)	1	1	(1.6)	1
Hyponatraemia	0	(0.0)	0	0	(0.0)	0	1	(2.5)	1	1	(1.6)	1
Hyperglycaemia	0	(0.0)	0	0	(0.0)	0	1	(2.5)	1	1	(1.6)	1
Metabolic Acidosis	0	(0.0)	0	0	(0.0)	0	1	(2.5)	1	1	(1.6)	1
MUSCULOSKELETAL AND CONNECTIVE TISSUE	1	(33.3)	2	0	(0.0)	0	2	(5.0)	3	3	(4.9)	5
Arthralgia	1	(33.3)	1	0	(0.0)	0	1	(2.5)	1	2	(3.3)	2
Joint Effusion	1	(33.3)	1	0	(0.0)	0	0	(0.0)	0	1	(1.6)	1
Myalgia	0	(0.0)	0	0	(0.0)	0	1	(2.5)	1	1	(1.6)	1
Rhabdomyolysis	0	(0.0)	0	0	(0.0)	0	1	(2.5)	1	1	(1.6)	1
NERVOUS SYSTEM DISORDERS	1	(33.3)	2	1	(5.6)	1	1	(2.5)	1	3	(4.9)	4
Dizziness	1	(33.3)	1	0	(0.0)	0	0	(0.0)	0	1	(1.6)	1
Hepatic Encephalopathy	0	(0.0)	0	1	(5.6)	1	0	(0.0)	0	1	(1.6)	1
Syncope	1	(33.3)	1	0	(0.0)	0	0	(0.0)	0	1	(1.6)	1
Trigeminal Neuralgia	0	(0.0)	0	0	(0.0)	0	1	(2.5)	1	1	(1.6)	1
PSYCHIATRIC DISORDERS	0	(0.0)	0	0	(0.0)	0	1	(2.5)	1	1	(1.6)	1
Depression	0	(0.0)	0	0	(0.0)	0	1	(2.5)	1	1	(1.6)	1

Table 5. SERIOUS ADVERSE EVENTS TO DATE BY TREATMENT REGIMEN BY SYSTEM /ORGAN CLASS (continued)

	Treatment Group									
	SOF PEG RBV (N=3)			BOC PEG RBV (N=18)			TEL PEG RBV (N=40)			Overall (N=61)		
TXT_AEDECOD	nPt	nPt/N	nSAE	nPt	nPt/N	nSAE	nPt	nPt/N	nSAE	nPt	nPt/N	nSAE
RENAL AND URINARY DISORDERS	0	(0.0)	0	0	(0.0)	0	1	(2.5)	1	1	(1.6)	1
Renal Failure Acute	0	(0.0)	0	0	(0.0)	0	1	(2.5)	1	1	(1.6)	1
REPRODUCTIVE SYSTEM AND BREAST DISORDE	0	(0.0)	0	0	(0.0)	0	1	(2.5)	1	1	(1.6)	1
Scrotal Oedema	0	(0.0)	0	0	(0.0)	0	1	(2.5)	1	1	(1.6)	1
RESPIRATORY, THORACIC AND MEDIASTINAL	1	(33.3)	1	0	(0.0)	0	1	(2.5)	1	2	(3.3)	2
Dyspnoea Exertional	1	(33.3)	1	0	(0.0)	0	0	(0.0)	0	1	(1.6)	1
Respiratory Failure	0	(0.0)	0	0	(0.0)	0	1	(2.5)	1	1	(1.6)	1
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	0	(0.0)	0	0	(0.0)	0	2	(5.0)	5	2	(3.3)	5
Rash	0	(0.0)	0	0	(0.0)	0	2	(5.0)	2	2	(3.3)	2
Blisters	0	(0.0)	0	0	(0.0)	0	1	(2.5)	1	1	(1.6)	1
Lichen Planus	0	(0.0)	0	0	(0.0)	0	1	(2.5)	1	1	(1.6)	1
Pruritus	0	(0.0)	0	0	(0.0)	0	1	(2.5)	1	1	(1.6)	1

Table 6. BASELINE CONMEDS BY TREATMENT REGIMEN BY ATC Level 1

Level 1 ATC name for ConMed	SOF PEG RBV (N=3)		BOC PEG RBV (N=18)		TEL PEG RBV (N=40)		Overall (N=61)	
	nPt nPt/N	nCM	nPt nPt/N	nCM	nPt nPt/N	nCM	nPt nPt/N	nCM
TOTAL PATIENT WITH CM	3 (100.00)		18 (100.00)		40 (100.00)		61 (100.00)	
ALIMENTARY TRACT AND METABOLISM	3 (100.00)	10	12 (66.67)	27	24 (60.00)	64	39 (63.93)	101
ANTIBACTERIALS FOR SYSTEMIC USE	0 (0.00)	0	0 (0.00)	0	1 (2.50)	1	1 (1.64)	1
ANTIINFECTIVES FOR SYSTEMIC USE	0 (0.00)	0	7 (38.89)	10	9 (22.50)	16	16 (26.23)	26
ANTINEOPLASTIC AND IMMUNOMODULA	0 (0.00)	0	10 (55.56)	12	10 (25.00)	13	20 (32.79)	25
BLOOD AND BLOOD FORMING ORGANS	3 (100.00)	4	18 (100.00)	25	40 (100.00)	83	61 (100.00)	112
CARDIOVASCULAR SYSTEM	3 (100.00)	5	15 (83.33)	28	24 (60.00)	49	42 (68.85)	82
DERMATOLOGICALS	0 (0.00)	0	8 (44.44)	12	24 (60.00)	40	32 (52.46)	52
GENITO URINARY SYSTEM AND SEX HORMONS	0 (0.00)	0	1 (5.56)	1	1 (2.50)	1	2 (3.28)	2
MUSCULO-SKELETAL SYSTEM	2 (66.67)	4	5 (27.78)	7	5 (12.50)	7	12 (19.67)	18
NERVOUS SYSTEM	3 (100.00)	11	10 (55.56)	30	27 (67.50)	63	40 (65.57)	104
RESPIRATORY SYSTEM	2 (66.67)	2	4 (22.22)	7	12 (30.00)	16	18 (29.51)	25
SENSORY ORGANS	0 (0.00)	0	1 (5.56)	1	0 (0.00)	0	1 (1.64)	1
SYSTEMIC HORMONAL PREPARATIONS	1 (33.33)	1	3 (16.67)	3	3 (7.50)	3	7 (11.48)	7
VARIOUS	0 (0.00)	0	0 (0.00)	0	3 (7.50)	3	3 (4.92)	3

Table 7. ALL CONMEDS PRESCRIBED AFTER THE TREATMENT START TO DATE BY TREATMENT REGIMEN BY ATC Level 1

Level 1 ATC name for ConMed	SOF PEG RBV (N=3)			BOC PEG RBV (N=18)			TEL PEG RBV (N=40)			Overall (N=61)		
	nPt	nPt/N	nCM	nPt	nPt/N	nCM	nPt	nPt/N	nCM	nPt	nPt/N	nCM
TOTAL PATIENT WITH CM	3	(100.00)		18	(100.00)		40	(100.00)		61	(100.00)	
ALIMENTARY TRACT AND METABOLISM	3	(100.00)	6	12	(66.67)	27	24	(60.00)	64	39	(63.93)	97
ANTIBACTERIALS FOR SYSTEMIC USE	0	(0.00)	0	0	(0.00)	0	1	(2.50)	1	1	(1.64)	1
ANTIINFECTIVES FOR SYSTEMIC USE	0	(0.00)	0	7	(38.89)	10	9	(22.50)	16	16	(26.23)	26
ANTINEOPLASTIC AND IMMUNOMODULATORS	0	(0.00)	0	10	(55.56)	12	10	(25.00)	13	20	(32.79)	25
BLOOD AND BLOOD FORMING ORGANS	2	(66.67)	2	18	(100.00)	25	40	(100.00)	83	60	(98.36)	110
CARDIOVASCULAR SYSTEM	2	(66.67)	2	15	(83.33)	28	24	(60.00)	49	41	(67.21)	79
DERMATOLOGICALS	0	(0.00)	0	8	(44.44)	12	24	(60.00)	40	32	(52.46)	52
GENITO URINARY SYSTEM AND SEX HORMONES	0	(0.00)	0	1	(5.56)	1	1	(2.50)	1	2	(3.28)	2
MUSCULO-SKELETAL SYSTEM	2	(66.67)	3	5	(27.78)	7	5	(12.50)	7	12	(19.67)	17
NERVOUS SYSTEM	2	(66.67)	5	10	(55.56)	30	27	(67.50)	63	39	(63.93)	98
RESPIRATORY SYSTEM	1	(33.33)	1	4	(22.22)	7	12	(30.00)	16	17	(27.87)	24
SENSORY ORGANS	0	(0.00)	0	1	(5.56)	1	0	(0.00)	0	1	(1.64)	1
SYSTEMIC HORMONAL PREPARATIONS	1	(33.33)	1	3	(16.67)	3	3	(7.50)	3	7	(11.48)	7
VARIOUS	0	(0.00)	0	0	(0.00)	0	3	(7.50)	3	3	(4.92)	3

Table 8a. SVR STATUS AVAILABILITY AMONG PATIENTS WHO STARTED TREATMENT BY PREVIOUS EXPERIENCE STATUS

			Prior Tx experience		
			Exper	Naive	All
Treatment drug					
SOF PEG RBV	Started Tx		1	2	3
	Ended Tx (N)	Sum	1	2	3
	Ended Tx	%of those who started Tx	100.00	100.00	100.00
	Outcome available (N)	Sum	1	2	3
	Outcome available	%of those who started Tx	100.00	100.00	100.00
	Achieved SVR (N)	Sum	1	1	2
	Achieved SVR	% of those with available SVR status	100.00	50.00	66.67
	Outcomes detailed (SVR12)				
	Success	N	1	1	2
	Lost to post-treatment follow-up	N		1	1

			Prior Tx experience		
			Exper	Naive	All
BOC PEG RBV	Started Tx		9	9	18
	Ended Tx (N)	Sum	9	9	18
	Ended Tx	%of those who started Tx	100.00	100.00	100.00
	Outcome available (N)	Sum	7	7	14
	Outcome available	%of those who started Tx	77.78	77.78	77.78
	Achieved SVR (N)	Sum	2	4	6
	Achieved SVR	% of those with available SVR status	28.57	57.14	42.86
	Outcomes detailed (SVR12)				
	Pending / No treatment stop date	N	2	2	4
	Non-Responder	N	1	1	2
	Viral Breakthrough	N		1	1
	Relapser	N	4		4
	Success	N	2	4	6
	Lost to followup | Withdrew | Insurance	N		1	1
TEL PEG RBV	Started Tx		29	11	40
	Ended Tx (N)	Sum	29	11	40
	Ended Tx	%of those who started Tx	100.00	100.00	100.00
	Outcome available (N)	Sum	26	5	31
	Outcome available	%of those who started Tx	89.66	45.45	77.50
	Achieved SVR (N)	Sum	10	2	12
	Achieved SVR	% of those with available SVR status	38.46	40.00	38.71
	Outcomes detailed (SVR12)				
	Pending / No treatment stop date	N	3	5	8
	Non-Responder	N	3	1	4
	Viral Breakthrough	N	3		3
	Relapser	N	6	2	8
	Success	N	10	2	12
	Lost to followup | Withdrew | Insurance	N	4		4
	Physician reported failure (last HCV RNA is BLOQ but not UND)	N		1	1

			Prior Tx experience		
			Exper	Naive	All
All	Started Tx		39	22	61
	Ended Tx (N)	Sum	39	22	61
	Ended Tx	%of those who started Tx	100.00	100.00	100.00
	Outcome available (N)	Sum	34	14	48
	Outcome available	%of those who started Tx	87.18	63.64	78.69
	Achieved SVR (N)	Sum	13	7	20
	Achieved SVR	% of those with available SVR status	38.24	50.00	41.67
	Outcomes detailed (SVR12)				
	Pending / No treatment stop date	N	5	7	12
	Non-Responder	N	4	2	6
	Viral Breakthrough	N	3	1	4
	Relapser	N	10	2	12
	Success	N	13	7	20
	Lost to followup | Withdrew | Insurance	N	4	1	5
	Lost to post-treatment follow-up	N		1	1
	Physician reported failure (last HCV RNA is BLOQ but not UND)	N		1	1

Table 8b. SVR STATUS AVAILABILITY AMONG PATIENTS WHO STARTED TREATMENT BY CIRRHOSIS STATUS

			Cirrhosis status			All
				Cirrh	non-Cirrh	
Treatment drug						
SOF PEG RBV	Started Tx			3		3
	Ended Tx (N)	Sum		3		3
	Ended Tx	%of those who started Tx		100.00		100.00
	Outcome available (N)	Sum		3		3
	Outcome available	%of those who started Tx		100.00		100.00
	Achieved SVR (N)	Sum		2		2
	Achieved SVR	% of those with available SVR status		66.67		66.67
	Outcomes detailed (SVR12)					
	Success	N		2		2
	Lost to post-treatment follow-up	N		1		1

				Cirrhosis status		
				Cirrh	non-Cirrh	All
BOC PEG RBV	Started Tx			14	4	18
	Ended Tx (N)	Sum		14	4	18
	Ended Tx	%of those who started Tx		100.00	100.00	100.00
	Outcome available (N)	Sum		13	1	14
	Outcome available	%of those who started Tx		92.86	25.00	77.78
	Achieved SVR (N)	Sum		5	1	6
	Achieved SVR	% of those with available SVR status		38.46	100.00	42.86
	Outcomes detailed (SVR12)					
	Pending / No treatment stop date	N		1	3	4
	Non-Responder	N		2		2
	Viral Breakthrough	N		1		1
	Relapser	N		4		4
	Success	N		5	1	6
	Lost to followup | Withdrew | Insurance	N		1		1

			Cirrhosis status			
				Cirrh	non-Cirrh	All
TEL PEG RBV	Started Tx		1	33	6	40
	Ended Tx (N)	Sum	1	33	6	40
	Ended Tx	%of those who started Tx	100.00	100.00	100.00	100.00
	Outcome available (N)	Sum		26	5	31
	Outcome available	%of those who started Tx		78.79	83.33	77.50
	Achieved SVR (N)	Sum		11	1	12
	Achieved SVR	% of those with available SVR status		42.31	20.00	38.71
	Outcomes detailed (SVR12)					
	Pending / No treatment stop date	N	1	6	1	8
	Non-Responder	N		3	1	4
	Viral Breakthrough	N		3		3
	Relapser	N		6	2	8
	Success	N		11	1	12
	Lost to followup | Withdrew | Insurance	N		3	1	4
	Physician reported failure (last HCV RNA is BLOQ but not UND)	N		1		1

			Cirrhosis status			
				Cirrh	non-Cirrh	All
All	Started Tx		1	50	10	61
	Ended Tx (N)	Sum	1	50	10	61
	Ended Tx	%of those who started Tx	100.00	100.00	100.00	100.00
	Outcome available (N)	Sum		42	6	48
	Outcome available	%of those who started Tx		84.00	60.00	78.69
	Achieved SVR (N)	Sum		18	2	20
	Achieved SVR	% of those with available SVR status		42.86	33.33	41.67
	Outcomes detailed (SVR12)					
	Pending / No treatment stop date	N	1	7	4	12
	Non-Responder	N		5	1	6
	Viral Breakthrough	N		4		4
	Relapser	N		10	2	12
	Success	N		18	2	20
	Lost to followup | Withdrew | Insurance	N		4	1	5
	Lost to post-treatment follow-up	N		1		1
	Physician reported failure (last HCV RNA is BLOQ but not UND)	N		1		1

Table 9. SVR STATUS AVAILABILITY AMONG PATIENTS WHO STARTED TREATMENT: G1 PATIENTS WITH KNOWN CIRRHOTIC AND PREVIOUS EXPERIENCE STATUS

			Genotype 1				
			G1_exper_C	G1_exper_NC	G1_naive_C	G1_naive_NC	All
Treatment drug							
SOF PEG RBV	Started Tx		1		2		3
	Ended Tx (N)	Sum	1		2		3
	Ended Tx	%of those who started Tx	100.00		100.00		100.00
	Outcome available (N)	Sum	1		2		3
	Outcome available	%of those who started Tx	100.00		100.00		100.00
	Achieved SVR (N)	Sum	1		1		2
	Achieved SVR	% of those with available SVR status	100.00		50.00		66.67
	Outcomes detailed (SVR12)						
	Success	N	1		1		2
	Lost to post-treatment follow-up	N			1		1
BOC PEG RBV	Started Tx		6	3	8	1	18
	Ended Tx (N)	Sum	6	3	8	1	18
	Ended Tx	%of those who started Tx	100.00	100.00	100.00	100.00	100.00
	Outcome available (N)	Sum	6	1	7		14
	Outcome available	%of those who started Tx	100.00	33.33	87.50		77.78
	Achieved SVR (N)	Sum	1	1	4		6
	Achieved SVR	% of those with available SVR status	16.67	100.00	57.14		42.86
	Outcomes detailed (SVR12)						
	Pending / No treatment stop date	N		2	1	1	4
	Non-Responder	N	1		1		2
	Viral Breakthrough	N			1		1
	Relapser	N	4				4
	Success	N	1	1	4		6
	Lost to followup | Withdrew | Insurance	N			1		1

			Genotype 1				
			G1_exper_C	G1_exper_NC	G1_naive_C	G1_naive_NC	All
TEL PEG RBV	Started Tx		23	6	10		39
	Ended Tx (N)	Sum	23	6	10		39
	Ended Tx	%of those who started Tx	100.00	100.00	100.00		100.00
	Outcome available (N)	Sum	21	5	5		31
	Outcome available	%of those who started Tx	91.30	83.33	50.00		79.49
	Achieved SVR (N)	Sum	9	1	2		12
	Achieved SVR	% of those with available SVR status	42.86	20.00	40.00		38.71
	Outcomes detailed (SVR12)						
	Pending / No treatment stop date	N	2	1	4		7
	Non-Responder	N	2	1	1		4
	Viral Breakthrough	N	3				3
	Relapser	N	4	2	2		8
	Success	N	9	1	2		12
	Lost to followup | Withdrew | Insurance	N	3	1			4
	Physician reported failure (last HCV RNA is BLOQ but not UND)	N			1		1

			Genotype 1				
			G1_exper_C	G1_exper_NC	G1_naive_C	G1_naive_NC	All
All	Started Tx		30	9	20	1	60
	Ended Tx (N)	Sum	30	9	20	1	60
	Ended Tx	%of those who started Tx	100.00	100.00	100.00	100.00	100.00
	Outcome available (N)	Sum	28	6	14		48
	Outcome available	%of those who started Tx	93.33	66.67	70.00		80.00
	Achieved SVR (N)	Sum	11	2	7		20
	Achieved SVR	% of those with available SVR status	39.29	33.33	50.00		41.67
	Outcomes detailed (SVR12)						
	Pending / No treatment stop date	N	2	3	5	1	11
	Non-Responder	N	3	1	2		6
	Viral Breakthrough	N	3		1		4
	Relapser	N	8	2	2		12
	Success	N	11	2	7		20
	Lost to followup | Withdrew | Insurance	N	3	1	1		5
	Lost to post-treatment follow-up	N			1		1
	Physician reported failure (last HCV RNA is BLOQ but not UND)	N			1		1

Table 10. SVR STATUS AVAILABILITY AMONG GENO1 PATIENTS WHO STARTED TREATMENT BY SUBTYPE

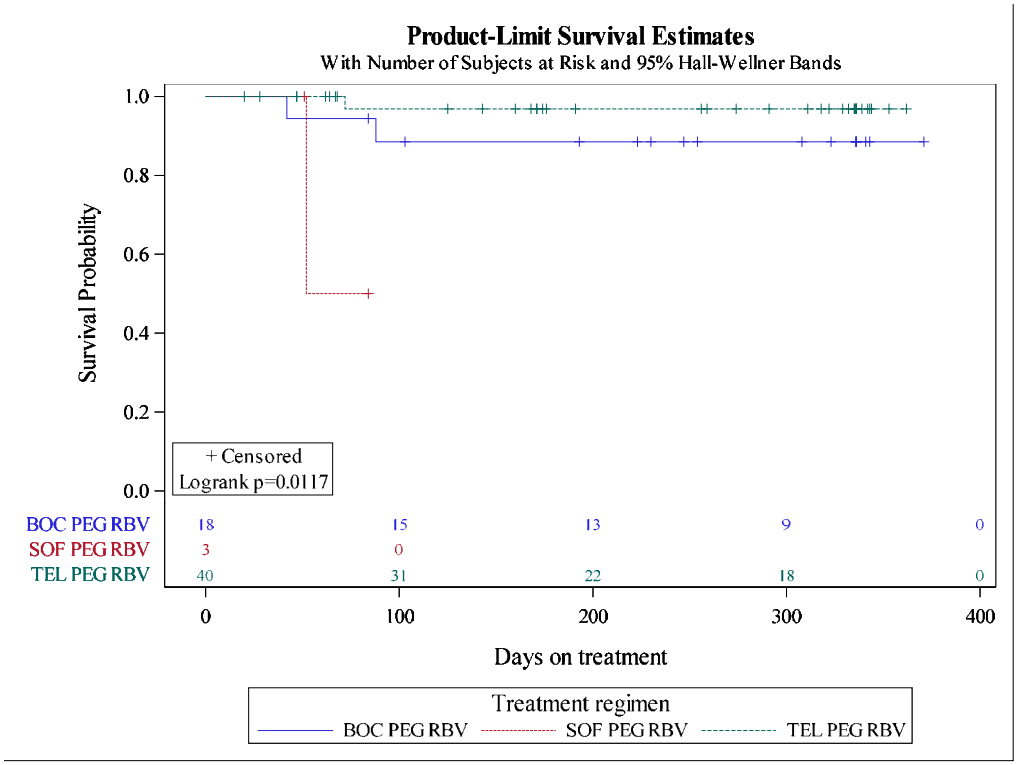
			_hcv_subtype				
				a	b	nos	All
Treatment drug							
SOF PEG RBV	Started Tx			1	1	1	3
	Ended Tx (N)	Sum		1	1	1	3
	Ended Tx	%of those who started Tx		100.00	100.00	100.00	100.00
	Outcome available (N)	Sum		1	1	1	3
	Outcome available	%of those who started Tx		100.00	100.00	100.00	100.00
	Achieved SVR (N)	Sum		1		1	2
	Achieved SVR	% of those with available SVR status		100.00		100.00	66.67
	Outcomes detailed (SVR12)						
	Success	N		1		1	2
	Lost to post-treatment follow-up	N			1		1
BOC PEG RBV	Started Tx			10	6	2	18
	Ended Tx (N)	Sum		10	6	2	18
	Ended Tx	%of those who started Tx		100.00	100.00	100.00	100.00
	Outcome available (N)	Sum		10	2	2	14
	Outcome available	%of those who started Tx		100.00	33.33	100.00	77.78
	Achieved SVR (N)	Sum		4	1	1	6
	Achieved SVR	% of those with available SVR status		40.00	50.00	50.00	42.86
	Outcomes detailed (SVR12)						
	Pending	N			4		4
	Non-Responder	N		1		1	2
	Viral Breakthrough	N		1			1
	Relapser	N		3	1		4
	Success	N		4	1	1	6
	Lost to followup | Withdrew | Insurance	N		1			1

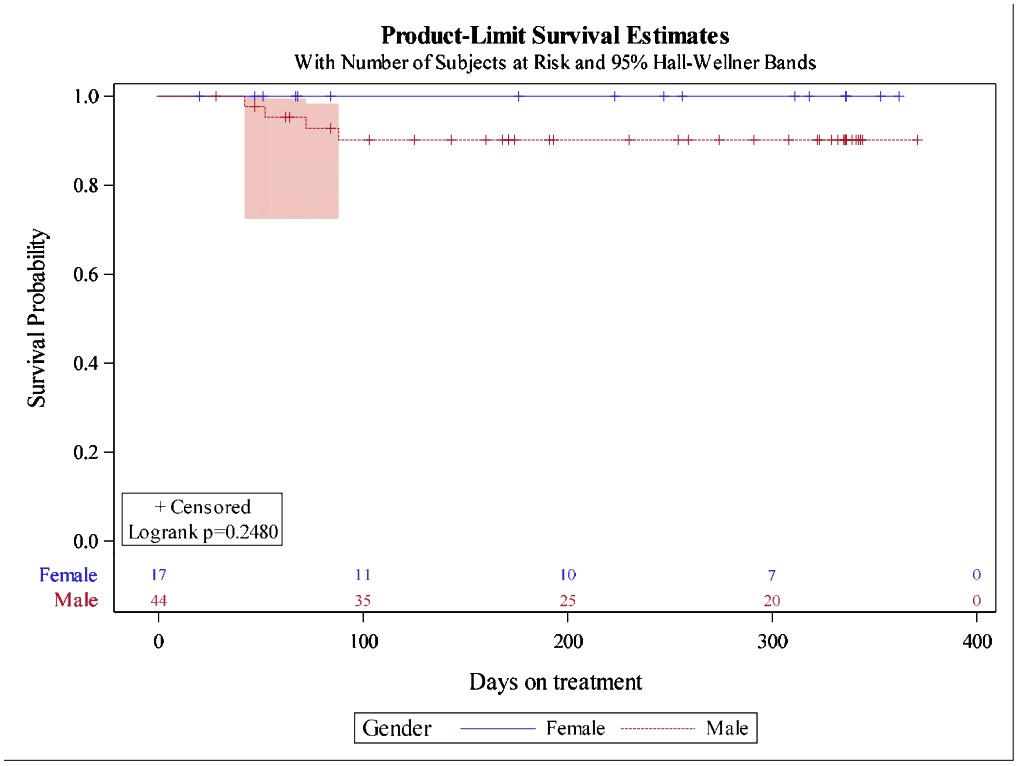
				_hcv_subtype			
				a	b	nos	All
TEL PEG RBV	Started Tx			21	8	11	40
	Ended Tx (N)	Sum		21	8	11	40
	Ended Tx	%of those who started Tx		100.00	100.00	100.00	100.00
	Outcome available (N)	Sum		15	6	10	31
	Outcome available	%of those who started Tx		71.43	75.00	90.91	77.50
	Achieved SVR (N)	Sum		6	4	2	12
	Achieved SVR	% of those with available SVR status		40.00	66.67	20.00	38.71
	Outcomes detailed (SVR12)						
	Pending	N		5	2	1	8
	Non-Responder	N		2		2	4
	Viral Breakthrough	N		1		2	3
	Relapser	N		5	1	2	8
	Success	N		6	4	2	12
	Lost to followup | Withdrew | Insurance	N		1	1	2	4
	Physician reported failure (last HCV RNA is BLOQ but not UND)	N		1			1

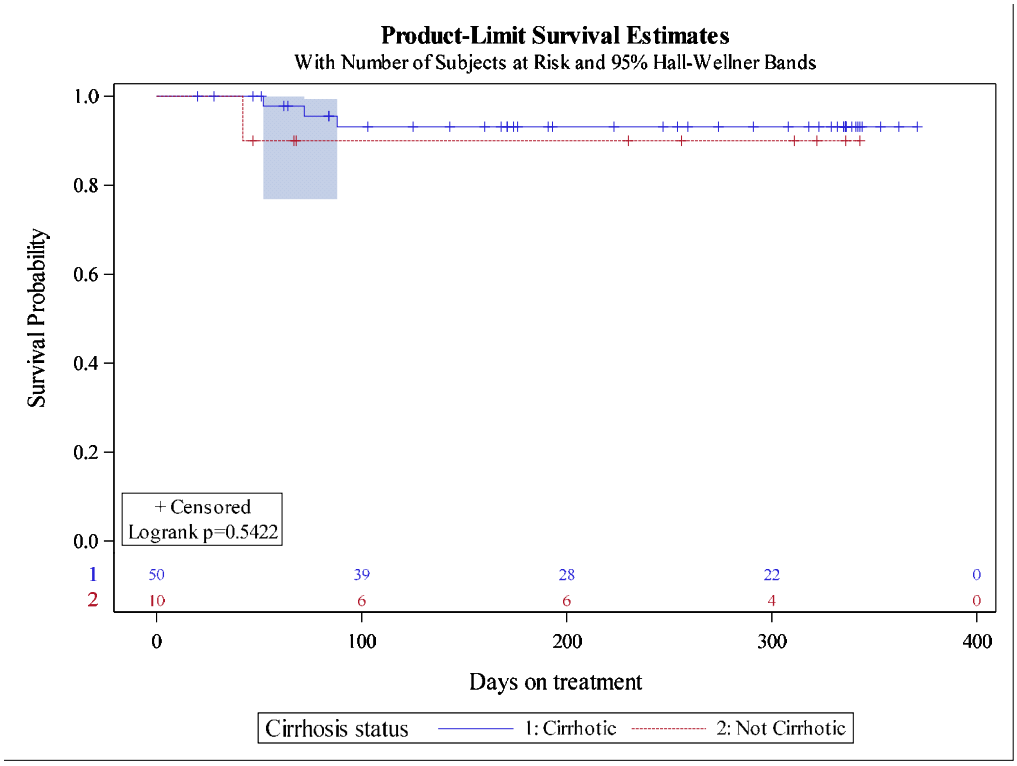
				_hcv_subtype			
				a	b	nos	All
All	Started Tx			32	15	14	61
	Ended Tx (N)	Sum		32	15	14	61
	Ended Tx	%of those who started Tx		100.00	100.00	100.00	100.00
	Outcome available (N)	Sum		26	9	13	48
	Outcome available	%of those who started Tx		81.25	60.00	92.86	78.69
	Achieved SVR (N)	Sum		11	5	4	20
	Achieved SVR	% of those with available SVR status		42.31	55.56	30.77	41.67
	Outcomes detailed (SVR12)						
	Pending	N		5	6	1	12
	Non-Responder	N		3		3	6
	Viral Breakthrough	N		2		2	4
	Relapser	N		8	2	2	12
	Success	N		11	5	4	20
	Lost to followup | Withdrew | Insurance	N		2	1	2	5
	Lost to post-treatment follow-up	N			1		1
	Physician reported failure (last HCV RNA is BLOQ but not UND)	N		1			1

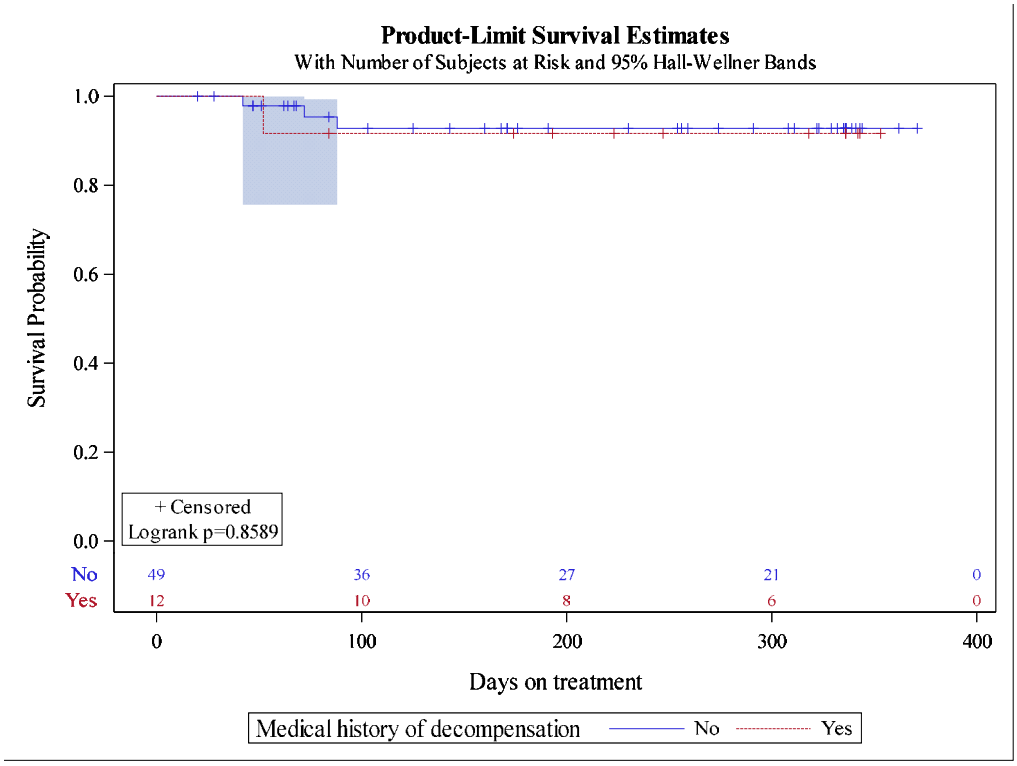
Appendix 1.0

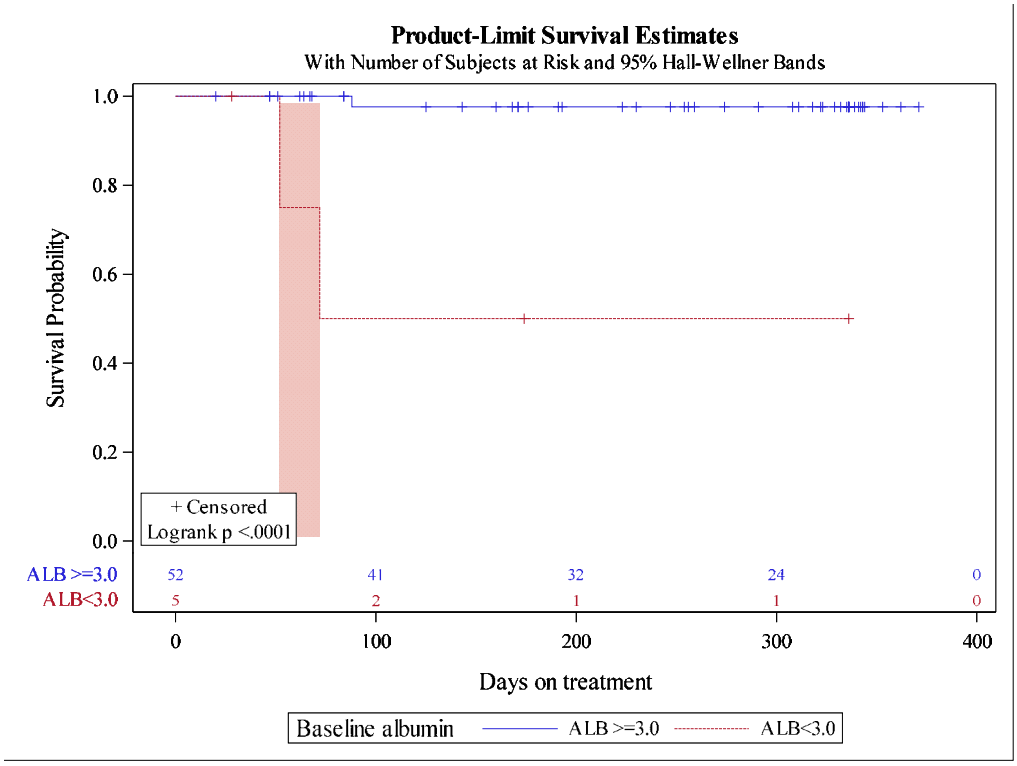
1.1 Kaplan-Meier Plots: Probability to remain free of new decompensating events (calculated from the start day of antiviral therapy)

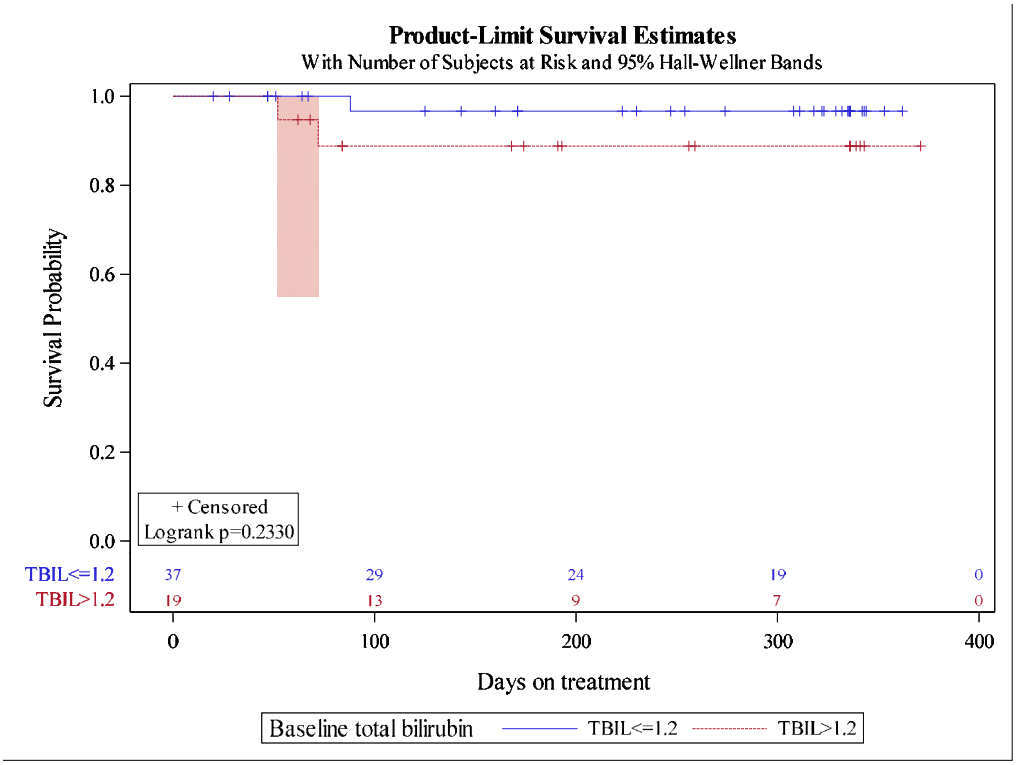








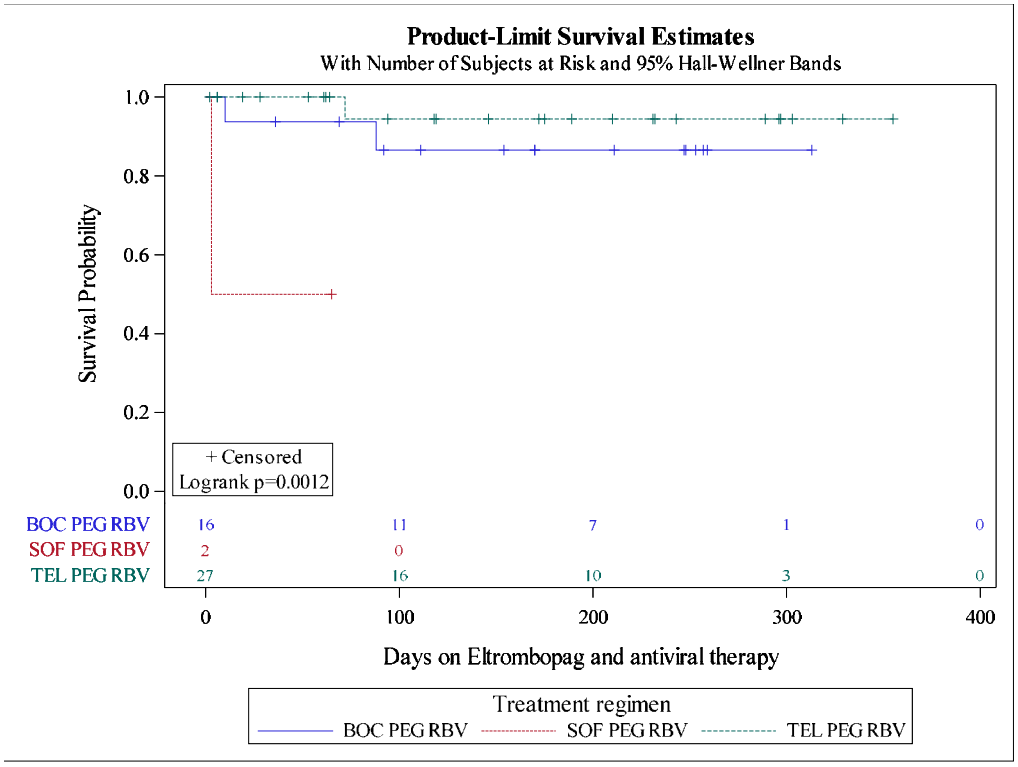


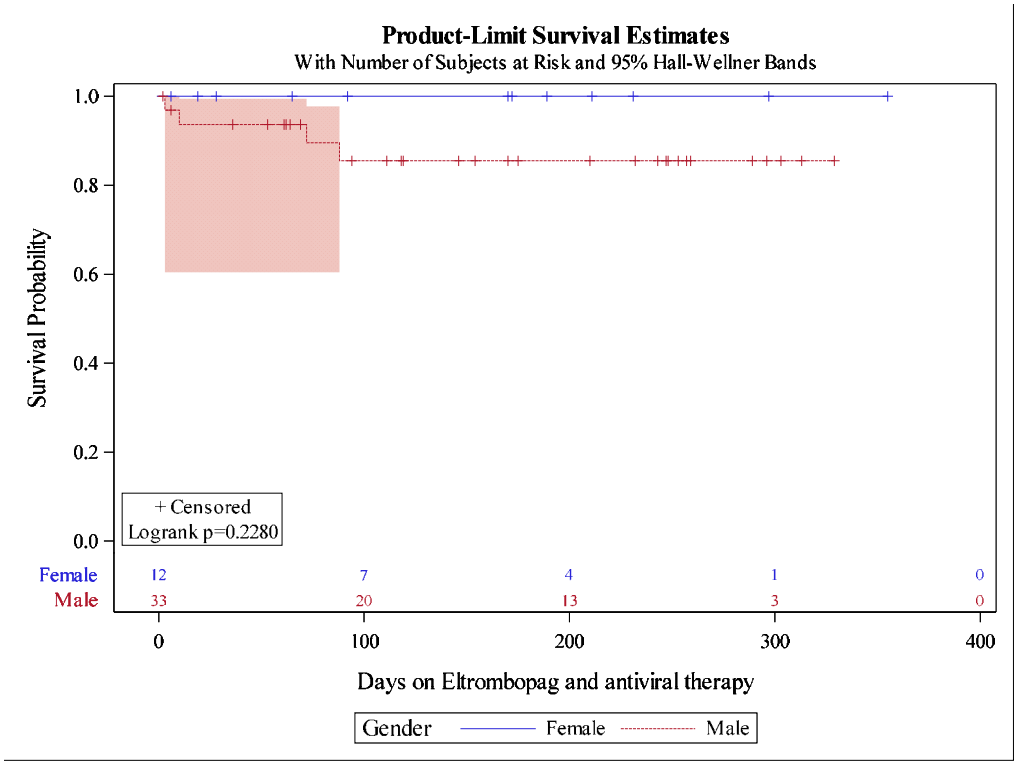


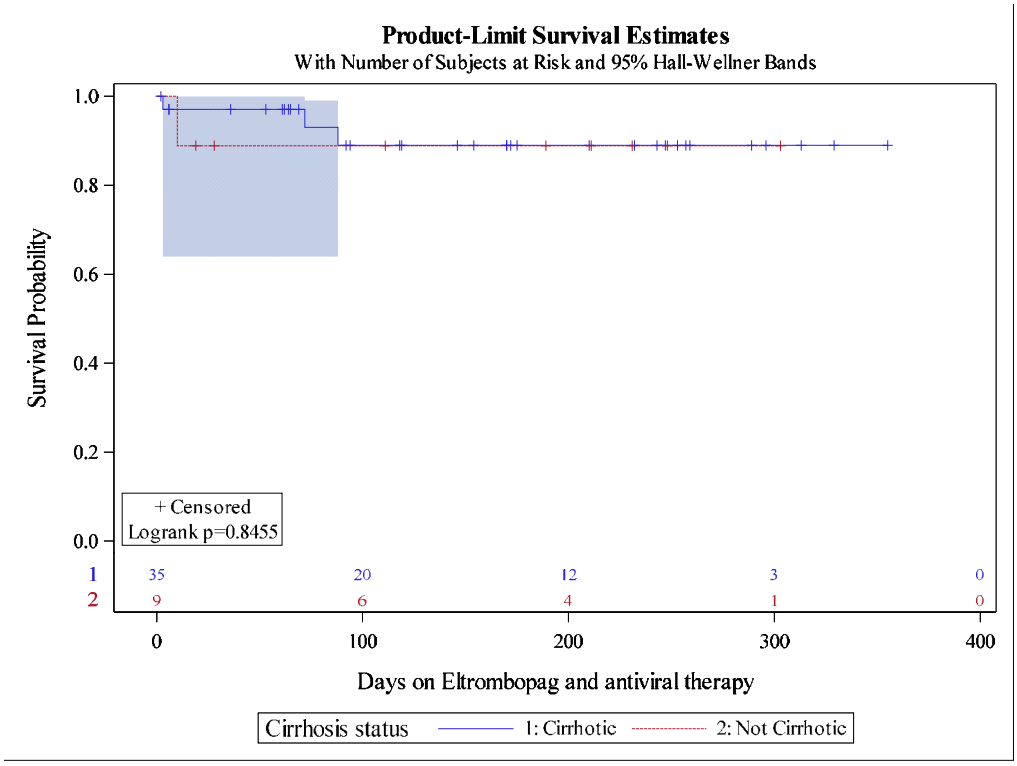
Variable	Estimate	StdErr	ChiSq	ProbChiSq	HazardRatio
Regimen (BOC PEG RBV)	1.38296	1.22502	1.2745	0.2589	3.987
Regimen (SOF PEG RBV)	3.3273	1.48613	5.0127	0.0252	27.863
Gender (Female)	-16.46947	3263	0	0.996	0
Presence of Cirrhosis	-0.69164	1.15731	0.3572	0.5501	0.501
History of Hepatic Decompensation events	-0.20493	1.15485	0.0315	0.8592	0.815
Prior HCV Treatment Experience	-0.574	1.00002	0.3295	0.566	0.563
Age	-0.03596	0.07593	0.2243	0.6358	0.965
Baseline_PLT	-0.0132	0.01977	0.4461	0.5042	0.987
Baseline_ALB	-1.90048	0.92695	4.2035	0.0403	0.149
Baseline_TBIL	1.79988	0.80255	5.0297	0.0249	6.049
Baseline_HGB	-0.16323	0.34471	0.2242	0.6358	0.849

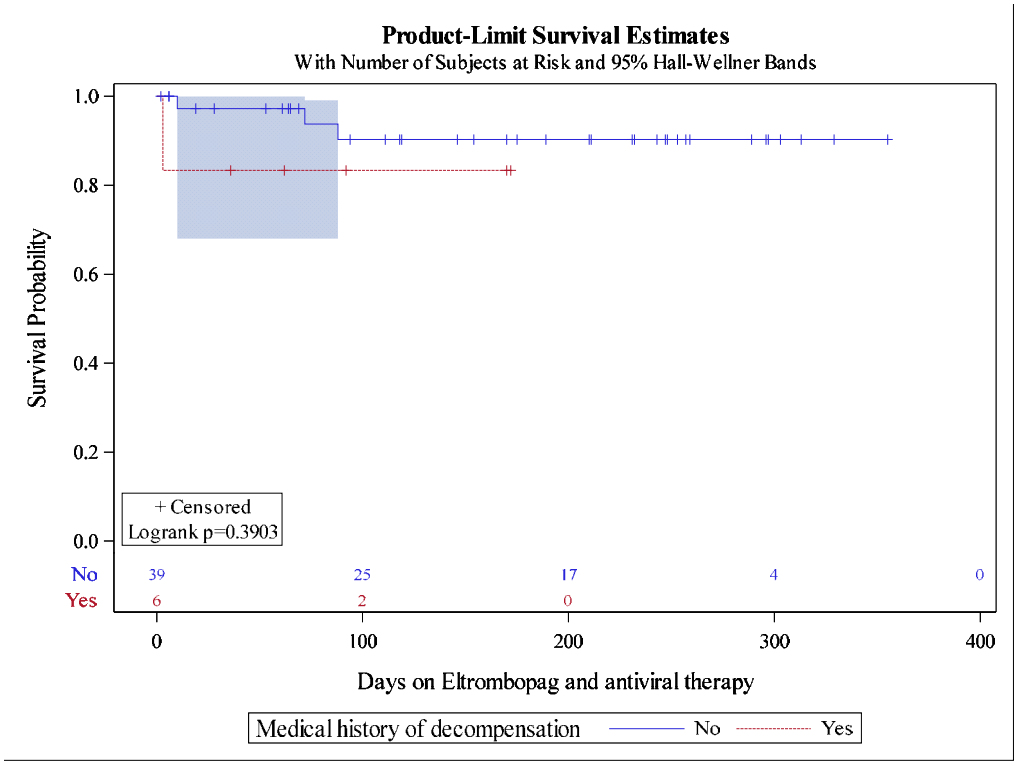
Convergence criterion (GCONV=1E-8) for all models satisfied, but there are only four events, so the results should be interpreted with caution.

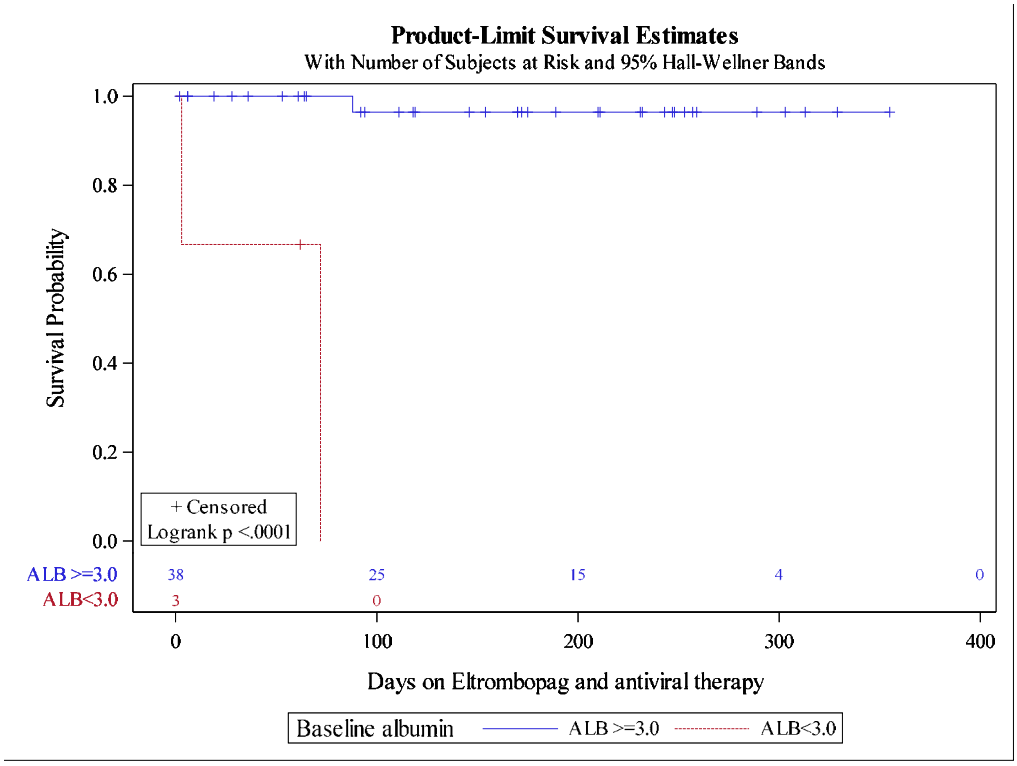
1.2 Kaplan-Meier Plots: Probability to remain free of new decompensating events (calculated from the start day of antiviral therapy in conjunction with Eltrombopag use)

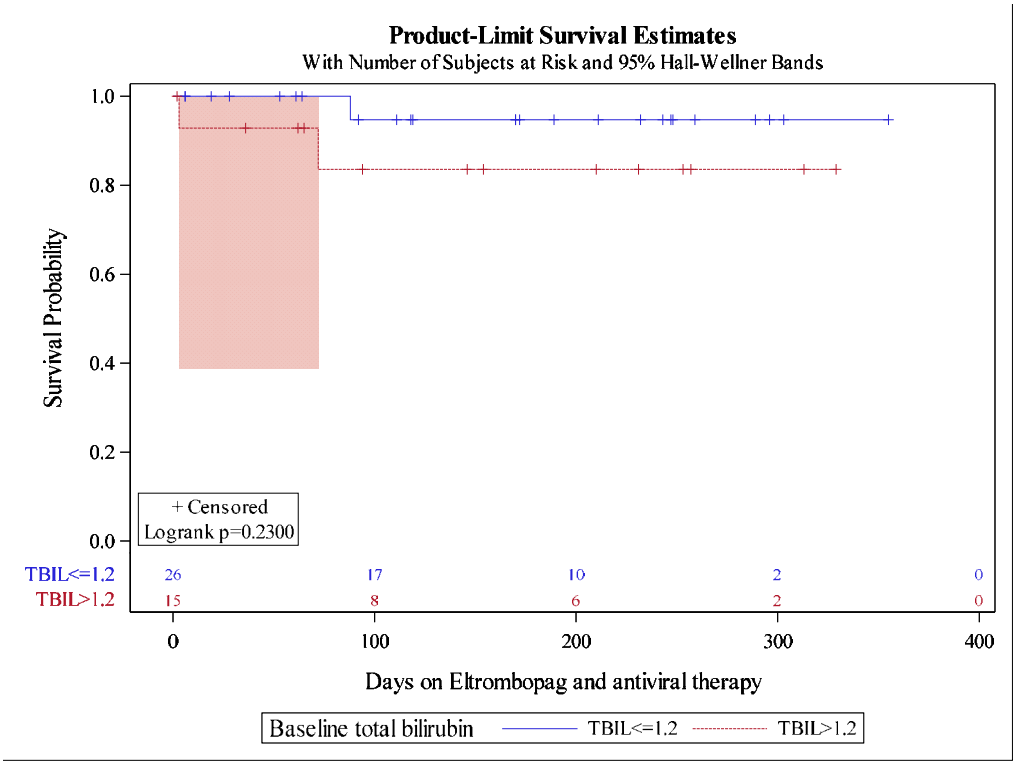












Variable	Estimate	StdErr	ChiSq	ProbChiSq	HazardRatio
Regimen (BOC PEG RBV)	1.03825	1.22547	0.7178	0.3969	2.824
Regimen (SOF PEG RBV)	3.90451	1.6366	5.6917	0.017	49.626
Gender (Female)	-16.50506	3183	0	0.9959	0
Presence of Cirrhosis	-0.22468	1.15501	0.0378	0.8458	0.799
History of Hepatic Decompensation events	-0.95791	1.15744	0.6849	0.4079	0.384
Prior HCV Treatment Experience	-0.48961	1.00099	0.2392	0.6248	0.613
Age	-0.01798	0.07639	0.0554	0.8139	0.982
Baseline_PLT	-0.01565	0.02131	0.5395	0.4626	0.984
Baseline_ALB	-5.23898	2.19391	5.7024	0.0169	0.005
Baseline_TBIL	2.27098	1.01064	5.0493	0.0246	9.689
Baseline_HGB	-0.18153	0.32944	0.3036	0.5816	0.834

Convergence criterion (GCONV=1E-8) for all models satisfied, but there are only four events, so the results should be interpreted with caution.

Outcomes Part 2

Figure 1. ALT values over the course of treatment

		Weeks on concomitant Eltrombopag and antivital therapy								
		0	2	4	8	12	16	32	48	All
ALT (iu/l)	N	59	17	12	12	11	7	2	0	120
	Mean	109.05	63.06	50.42	49.25	69.00	51.43	36.50	.	82.45
	Median	85.00	65.00	42.00	34.50	38.00	27.00	36.50	.	65.50
	Min	24.00	12.00	25.00	22.00	26.00	19.00	35.00	.	12.00
	Max	392.00	139.00	93.00	88.00	144.00	128.00	38.00	.	392.00

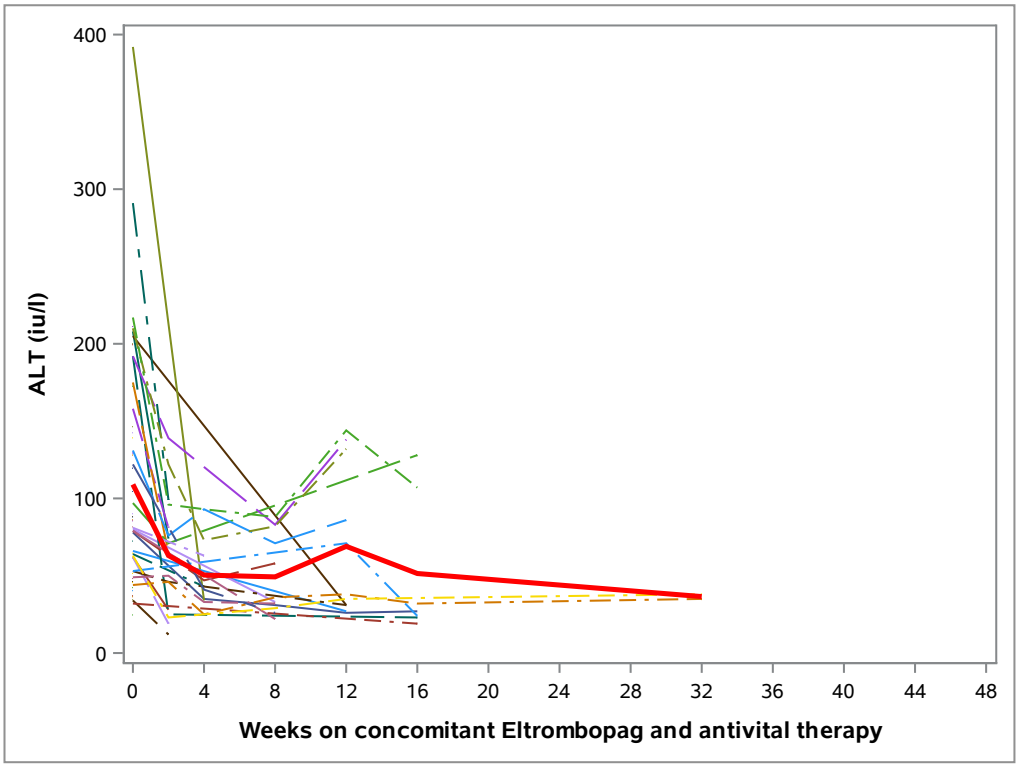


Figure 2. AST values over the course of treatment

		Weeks on concomitant Eltrombopag and antivital therapy								
		0	2	4	8	12	16	32	48	All
AST (iu/l)	N	59	17	12	12	11	7	2	0	120
	Mean	113.17	78.47	63.33	62.17	77.82	70.86	43.00	.	91.29
	Median	96.00	69.00	55.00	47.00	45.00	35.00	43.00	.	76.00
	Min	21.00	16.00	25.00	28.00	30.00	12.00	37.00	.	12.00
	Max	354.00	182.00	145.00	144.00	220.00	214.00	49.00	.	354.00

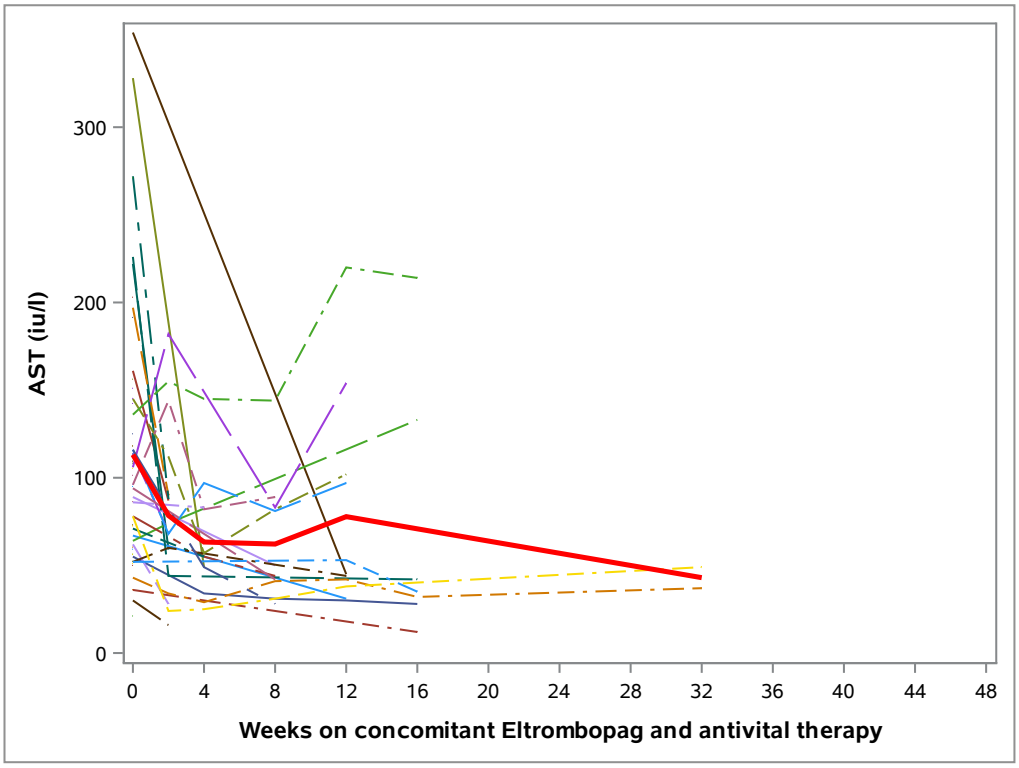


Figure 3. Total Bilirubin values over the course of treatment

		Weeks on concomitant Eltrombopag and antivital therapy								
		0	2	4	8	12	16	32	48	All
Total bilirubin(mg/dl)	N	56	6	6	5	4	3	2	0	82
	Mean	1.22	2.05	1.53	1.76	0.83	1.00	1.10	.	1.31
	Median	1.10	1.50	1.35	0.90	0.80	0.70	1.10	.	1.10
	Min	0.40	0.70	0.60	0.80	0.40	0.70	1.00	.	0.40
	Max	3.50	4.80	3.10	4.40	1.30	1.60	1.20	.	4.80

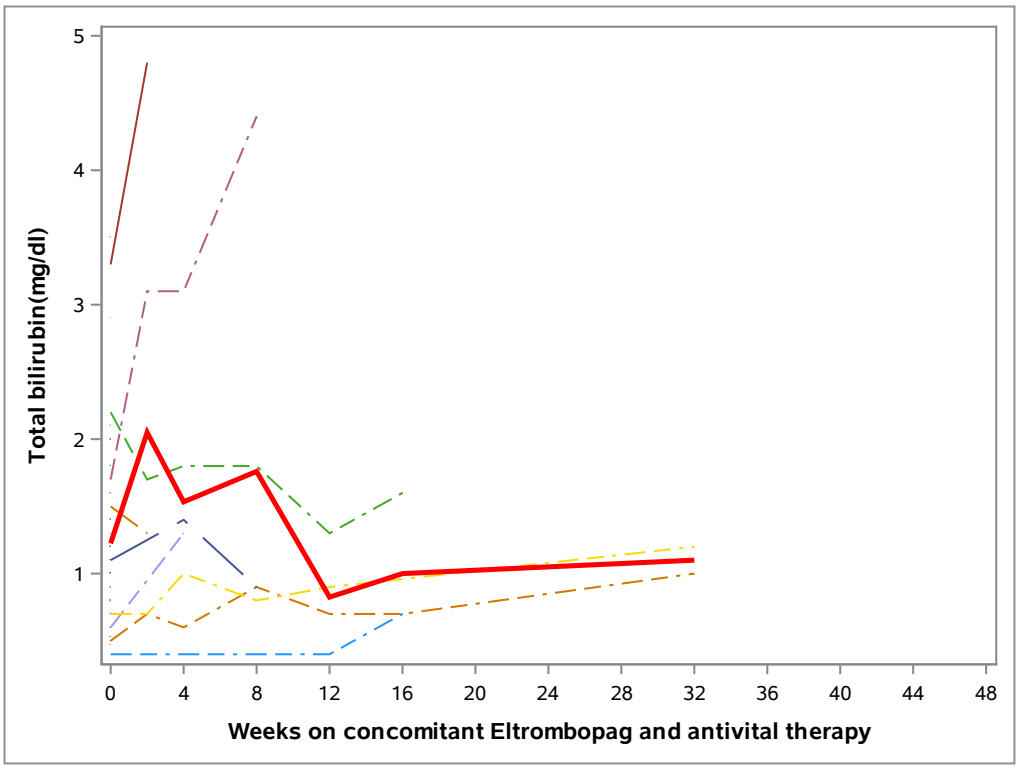


Figure 4. Albumin values over the course of treatment

		Weeks on concomitant Eltrombopag and antivital therapy								
		0	2	4	8	12	16	32	48	All
Albumin (g/dl)	N	57	13	12	11	11	7	2	0	113
	Mean	3.66	3.36	3.24	3.35	3.52	3.83	4.00	.	3.55
	Median	3.60	3.40	3.25	3.40	3.40	3.80	4.00	.	3.60
	Min	2.20	1.70	1.60	1.70	3.10	3.00	3.60	.	1.60
	Max	4.70	4.40	3.90	4.20	4.40	4.40	4.40	.	4.70

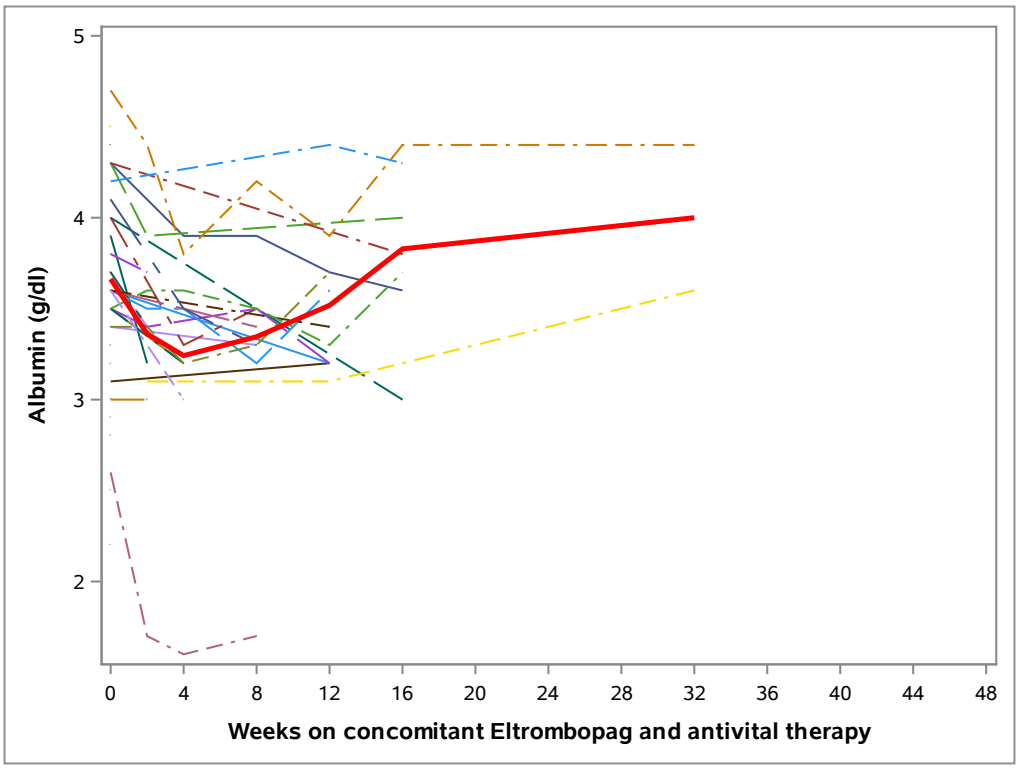


Figure 5. Hemoglobin values over the course of treatment

		Weeks on concomitant Eltrombopag and antivital therapy								
		0	2	4	8	12	16	32	48	All
Hemoglobin (g/dl)	N	59	23	21	18	16	13	8	0	158
	Mean	14.11	11.06	11.23	10.58	10.92	11.21	10.44	.	12.13
	Median	14.00	10.90	11.00	10.55	10.60	10.80	10.60	.	11.60
	Min	10.60	6.60	8.40	5.90	8.70	10.30	8.80	.	5.90
	Max	17.90	14.50	14.10	15.10	15.00	15.10	12.00	.	17.90

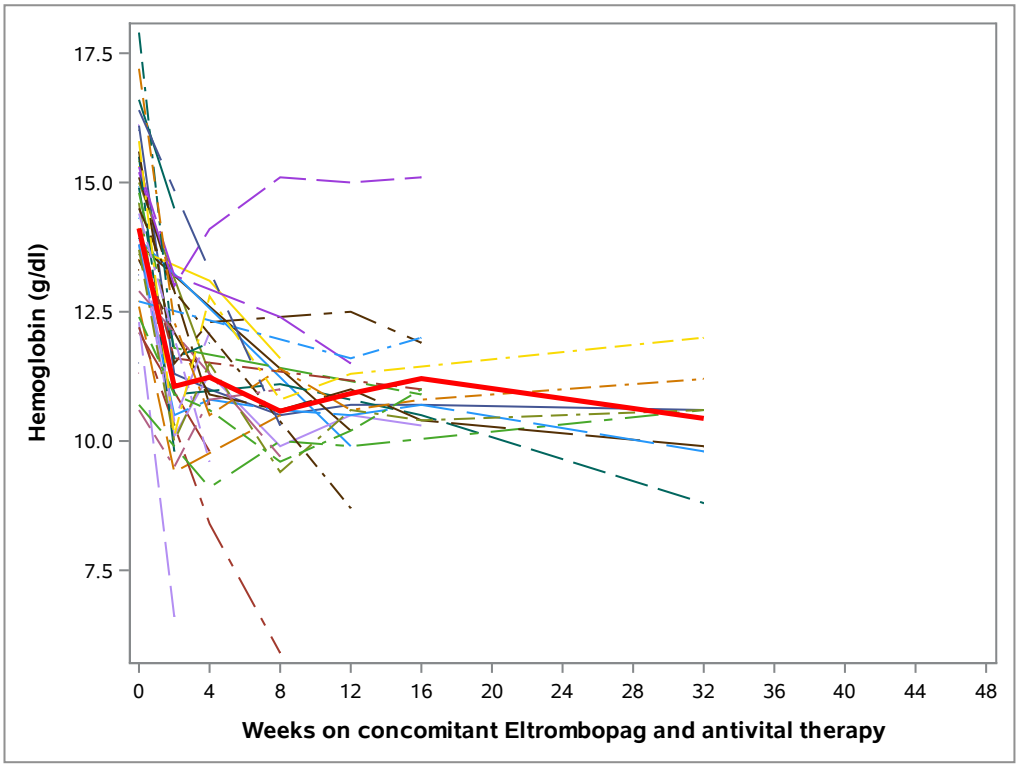


Figure 6. Platelet values over the course of treatment

		Weeks on concomitant Eltrombopag and antivital therapy								All
		0	2	4	8	12	16	32	48	
Platelets (x10E3/uL)	N	58	18	15	13	12	7	3	0	126
	Mean	80.57	43.50	48.00	50.23	47.08	59.86	46.67	.	63.12
	Median	69.00	38.00	39.00	42.00	46.00	61.00	38.00	.	56.00
	Min	28.00	27.00	25.00	26.00	27.00	27.00	25.00	.	25.00
	Max	260.00	110.00	85.00	93.00	72.00	117.00	77.00	.	260.00

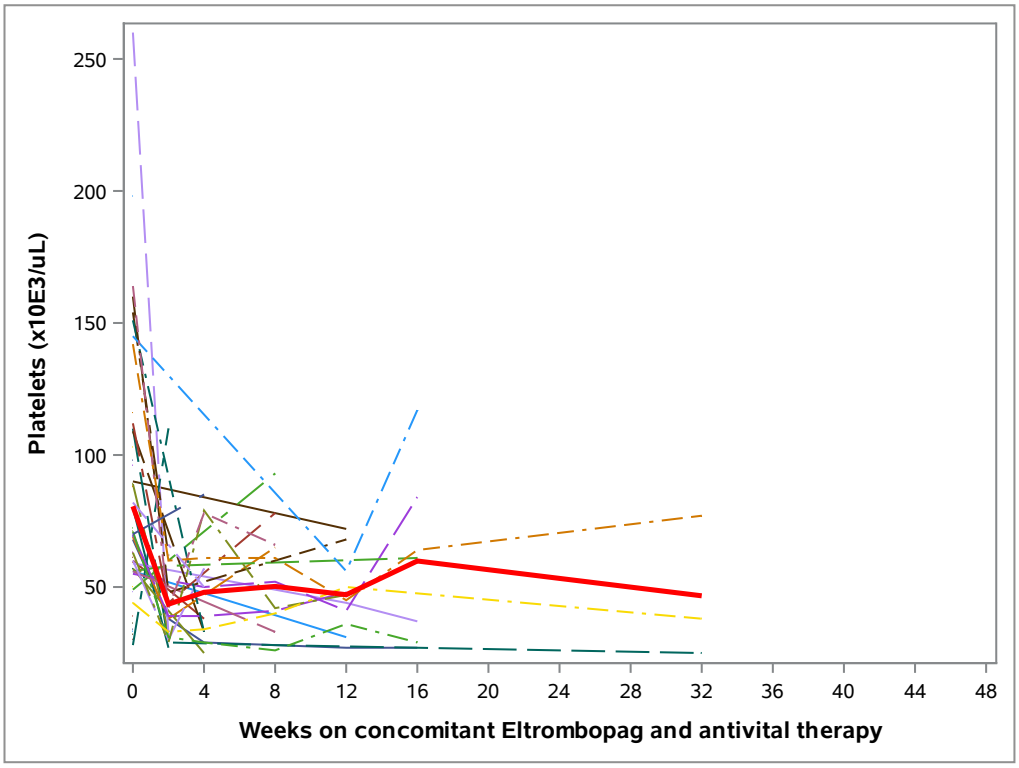


Figure 7. HCV RNA values over the course of treatment

Frequency
Col Pct

Table of HCV_score by week

HCV_score	week 0	2	4	8	12	16	32	48	Total
Detected	0 0.00	4 8.33	11 22.92	3 6.25	7 14.58	0 0.00	0 0.00	0 0.00	25
Missing	2 3.28	35 72.92	8 16.67	23 47.92	21 43.75	42 87.50	45 93.75	48 100.00	224
Not Specifie	0 0.00	0 0.00	1 2.08	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	1
Not detected	0 0.00	1 2.08	16 33.33	17 35.42	16 33.33	6 12.50	2 4.17	0 0.00	58
Quantifiable	59 96.72	8 16.67	12 25.00	5 10.42	4 8.33	0 0.00	1 2.08	0 0.00	89
Total	61	48	48	48	48	48	48	48	397

		Weeks on concomitant Eltrombopag and antivital therapy 0	2	4	8	12	16	32	48	All
HCV RNA	N	59	13	40	25	27	6	3	0	173
	Mean	2762849.88	358656.42	139105.30	938.36	163.30	0.00	1297.33	.	1001541.32
	Median	1682740.00	82.50	2.00	0.00	0.00	0.00	0.00	.	71.00
	Min	3147.00	0.00	0.00	0.00	0.00	0.00	0.00	.	0.00
	Max	17600000.00	4620000.00	4510000.00	15800.00	2728.00	0.00	3892.00	.	17600000.00

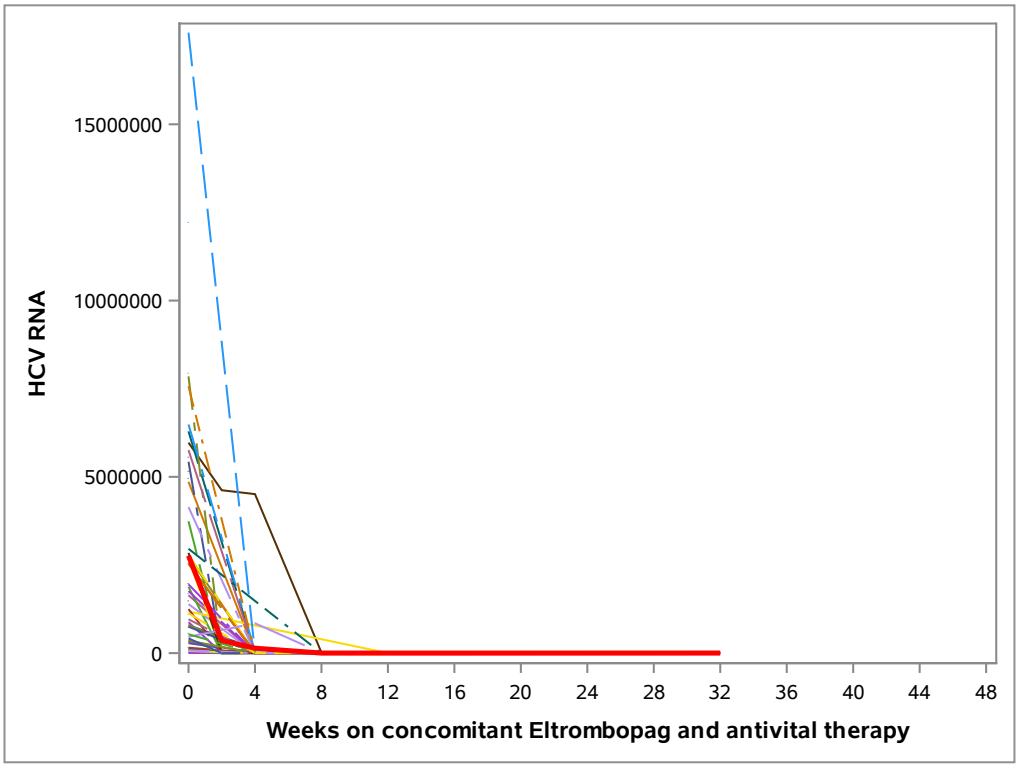
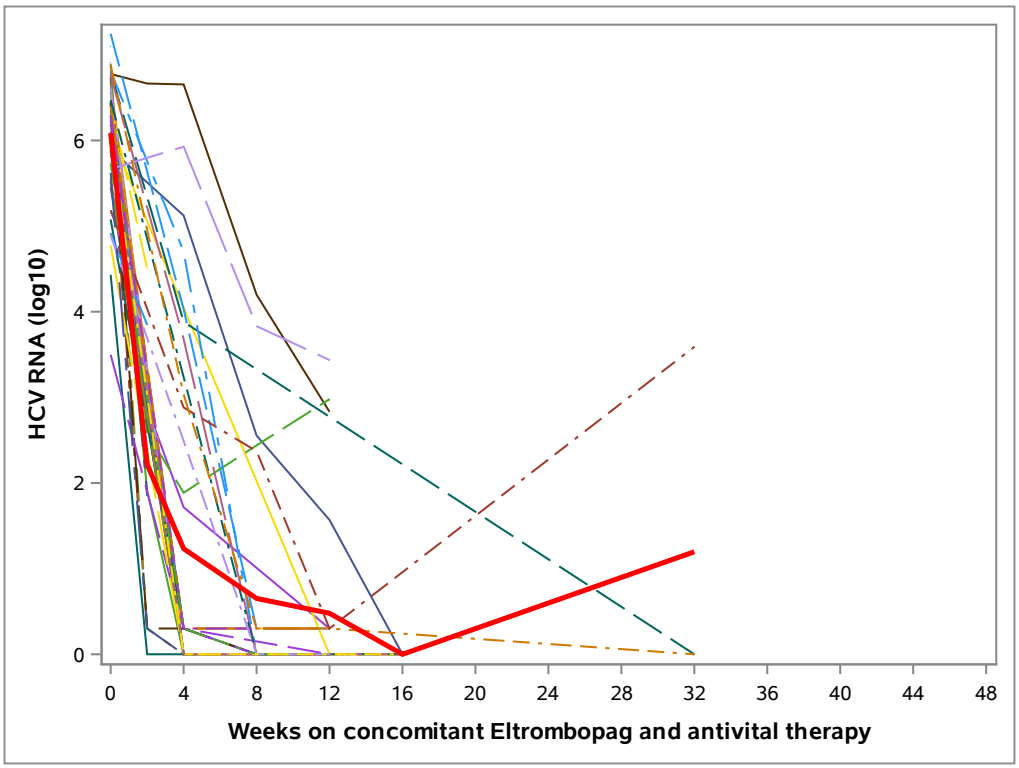


Figure 8. HCV RNA values (log 10) over the course of treatment

		Weeks on concomitant Eltrombopag and antivital therapy								
		0	2	4	8	12	16	32	48	All
HCV RNA (log10)	N	59	13	40	25	27	6	3	0	173
	Mean	6.09	2.22	1.23	0.65	0.48	0.00	1.20	.	2.72
	Median	6.23	1.92	0.30	0.00	0.00	0.00	0.00	.	1.85
	Min	3.50	0.00	0.00	0.00	0.00	0.00	0.00	.	0.00
	Max	7.25	6.66	6.65	4.20	3.44	0.00	3.59	.	7.25



Outcomes Part 3