Eltrombopag (Promacta®) for Use for Hepatitis C Related Thrombocytopenia
National Drug Monograph Addendum
March 2013
VA Pharmacy Benefits Management Services,
Medical Advisory Panel, VISN Pharmacist Executives and Office of Public Health

The purpose of VA PBM Services drug monographs is to provide a comprehensive drug review for making formulary decisions. These documents will be updated when new clinical data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.

Executive Summary [1]

- Eltrombopag is an oral, thrombopoietin receptor agonist FDA approved for the treatment of thrombocytopenia in patients with chronic immune (idiopathic) thrombocytopenia (ITP) who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy.
- In November 2012, the FDA expanded the approved indications for eltrombopag for the treatment of thrombocytopenia in patients with chronic hepatitis C to allow patients to initiate and maintain interferon-based therapy. The approval was based on results from two phase 3, randomized, double-blind, placebo-controlled, multicenter, unpublished trials, ENABLE 1 and ENABLE 2 (Eltrombopag to Initiate and Maintain Interferon Antiviral Treatment to Benefit Subjects with Hepatitis C and Liver Disease).
- In both ENABLE 1 and ENABLE 2, sustained viral response (SVR) rates were significantly higher in patients who were taking eltrombopag as seen in Table 3. In ENABLE 1, 104 (23%) patients treated with eltrombopag achieved SVR as compared to 33 (14%) patients on placebo (p=0.0064). In ENABLE 2, 97 patients (19%) patients treated with eltrombopag achieved SVR as compared to 32 (13%) patients on placebo (p=0.02).
- In both studies, patients receiving eltrombopag had more thromboembolic events incident and progression of cataracts, and hepatobiliary AEs. The package labeling for eltrombopag contains a Box Warning for hepatotoxicity and hepatic decompensation.
- In conclusion, eltrombopag has been shown to significantly improve SVR rates over placebo when used to allow initiation and maintenance of interferon and ribavirin therapy in patients with hepatitis C related thrombocytopenia as shown in 2 randomized, double-blind placebo controlled phase III trials, ENABLE 1 and ENABLE 2. The benefits of treatment must outweigh risks when the decision is made to use eltrombopag in these patients with chronic hepatitis C whose degree of thrombocytopenia prevents the initiation of interferon therapy; there is a box warning of hepatoxicity and liver decompensation as those treated with eltrombopag experienced more of these events. Furthermore, safety and efficacy have not established with the use of eltrombopag with direct-acting antivirals (e.g. boceprevir or telaprevir containing regimens).

Introduction

The purpose of this addendum is to evaluate the available evidence of safety, tolerability, efficacy, cost, and other pharmaceutical issues that would be relevant to evaluating eltrombopag for addition to the VA National Formulary for the indication of thrombocytopenia in patients with chronic hepatitis C planning to initiate interferon-based therapy. Refer to the original

Eltrombopag National Drug Monograph for more complete information on eltrombopag at: https://vaww.cmopnational.va.gov/cmop/PBM/default.aspx

FDA Approved Indication for Hepatitis C [1]

Eltrombopag is FDA-approved for patients with thrombocytopenia with chronic hepatitis C to allow initiation and maintenance of interferon-based therapy.

Dosage and Administration [1]

Initiate eltrombopag at a dose of 25mg once daily. Adjust eltrombopag by 25mg increments every 2 weeks as necessary to achieve target platelet count required to initiate antiviral therapy; target platelet count should be ≥90,000/µL if using peg-interferon alfa-2a and ≥100,000/µL if using peg-interferon alfa-2b.

Use the lowest dose of eltrombopag to achieve and maintain a platelet count necessary to initiate and maintain pegylated interferon and ribavirin. During antiviral therapy, adjust eltrombopag dose to avoid dose reduction of peg-interferon. Do not exceed eltrombopag dose of 100 mg daily. Eltrombopag should be discontinued when antiviral therapy is discontinued.

Monitor platelet count every week prior to initiating antiviral therapy. Monitor CBCs with differentials (including platelet counts) weekly during antiviral therapy until a stable platelet count is achieved. Monitor platelet counts monthly thereafter or sooner as clinically indicated. Eltrombopag should not be used in an attempt to normalize platelet counts. Clinical hematology and liver tests should also be monitored throughout therapy with eltrombopag.

Table 1 describes dose adjustment of eltrombopag in adults with chronic hepatitis C consistent with FDA approved package labeling. Table 2 describes dose adjustment of eltrombopag in adults with chronic hepatitis C based on expert opinion.

Table 1. Dose Adjustment of Eltrombopag in Adults with Chronic Hepatitis C

Initial dose of eltrombopag	25 mg orally once daily
Dose Adjustment based on platelet count	
<50,000/µL following at least 2 weeks of eltrombopag	Increase daily dose by 25 mg; wait 2 weeks to assess the effects of this and any subsequent dose adjustments. Please note that maximum dose is 100 mg/day.
≥200,000/µL to ≤400,000/µL at any time	Decrease daily dose by 25 mg; wait 2 weeks to assess the effects of this and any subsequent dose adjustments
>400,000/µL	**Stop eltrombopag**; increase the frequency of platelet monitoring to twice weekly. Once platelet count is <150,000/µL, reinitiate therapy at daily dose reduced by 25 mg. For patients taking 25 mg once daily, reinitiate therapy at a daily dose of 12.5 mg.
Maximum dose	100 mg/day
Discontinuation	Eltrombopag should be discontinued when antiviral therapy is discontinued.

Table 2. PBM Recommendations for Initial and Adjustments of Eltrombopag in Adult with Chronic Hepatitis C (*recommendations based on expert opinion)*

Initial dose of eltrombopag	25 mg orally once daily
Dose Adjustment based on platelet count *Please note that the dosage adjustment recommended below differs from FDA prescribing information. The below recommendations are based upon hepatology experts in the VA that recommend to maintain target platelet counts between 50,000/µL to 150,000/µL to reduce potential thrombotic complications.*	
<50,000/µL following at least 2 weeks of eltrombopag	Increase daily dose by 25 mg; wait 2 weeks to assess the effects of this and any subsequent dose adjustments. Please note that maximum dose is 100 mg/day.
≥150,000/µL to 200,000/µL at any time	Decrease daily dose by 25 mg; wait 2 weeks to assess the effects of this and any subsequent dose adjustments
>200,000/µL at any time	**Stop eltrombopag**; increase the frequency of platelet monitoring to twice weekly. Once platelet count is <100,000/µL, reinitiate therapy at daily dose reduced by 25 mg. For patients taking 25mg once daily, reinitiate therapy at a daily dose of 12.5 mg.
Maximum dose	100 mg/day
Discontinuation	Eltrombopag should be discontinued when antiviral therapy is discontinued.

Administration [1]
Eltrombopag should be taken on an empty stomach (1 hour before or 2 hours after a meal). Allow at least a 4-hour interval between eltrombopag and other medications (e.g., antacids), calcium-rich foods, or supplements containing polyvalent cations such as iron, calcium, aluminum, magnesium, selenium, and zinc.

Efficacy [1,4,5]

Efficacy Measures
The purpose of eltrombopag is to increase platelets to a threshold in which antiviral therapy is able to be initiated and maintained at full doses in order to achieve the greatest benefit of a sustained virologic response (SVR).

Eltrombopag has been evaluated for the treatment of thrombocytopenia in patients with chronic hepatitis C virus (HCV) infection to initiate and maintain antiviral therapy with peg-interferon and ribavirin in 2 unpublished, randomized, double-blind, placebo-controlled trials (ENABLE 1 and ENABLE 2). Approximately 90% of patients had bridging fibrosis or cirrhosis at baseline with 95% of patients with Child-Pugh level A (score 5-6). Patients with a platelet count of <75,000/µL were enrolled. Sixty-nine percent of patients had HCV genotype 1, 4, and 6 while the remainder had genotypes 2 and 3. Approximately 30 percent of patients were previously treated with interferon and ribavirin with failure to achieve SVR for reasons due to

thrombocytopenia. Patients who had a non-response to previous treatment with interferon and ribavirin for reasons other than thrombocytopenia were excluded.

Each trial included an open-label phase, where all patients received eltrombopag up to 9 weeks to reach platelet counts of ≥90,000/μL in ENABLE 1 and ≥100,000/μL in ENABLE 2 prior to randomization. In ENABLE 1, 95% of patients achieved platelet levels ≥90,000/μL and were randomized to the antiviral treatment phase (n= 682). In ENABLE 2, 945 of patient achieved platelet levels ≥100,000/μL and were randomized to the antiviral treatment phase (n= 759).

The primary endpoint for ENABLE 1 and ENABLE 2 was SVR rate, defined as the percentage of patients with non-detectable HCV RNA 24 weeks after completion of planned treatment with peg-interferon and ribavirin.

Secondary endpoints include the proportion of patients with a shift in platelet count from <75,000 to ≥90,000/μL during the pre-antiviral phase; assessment of platelet counts throughout the trial; proportion of patients achieving outcomes relative to early virologic response (EVR), rapid virologic response (RVR), end-of-treatment response (ETR); requirements of antiviral dose reductions or discontinuation, and adverse effects (AEs).

Summary of efficacy findings

Primary Endpoint

In both ENABLE 1 and ENABLE 2, SVR rates were significantly higher in patients who were taking eltrombopag as seen in Table 3. In ENABLE 1, 104 (23%) patients treated with eltrombopag achieved SVR as compared to 33 (14%) patients on placebo (p=0.0064). In ENABLE 2, 97 patients (19%) patients treated with eltrombopag achieved SVR as compared to 32 (13%) patients on placebo (p=0.02).

Table 3. Primary Outcome – Sustained Virologic Response (ITT Population)

	ENABLE 1			**ENABLE 2**		
	Placebo (n = 232)	Eltrombopag (n= 450)	P-value	Placebo (n=253)	Eltrombopag (n= 506)	P-value
Overall SVR, n (%)	33 (14)	104 (23)	0.0064	32 (13)	97 (19)	0.02
SVR, Genotype 2,3	18 (24)	50 (35)	ns	19 (25)	52 (34)	ns
SVR Genotype 1,4,6	15 (10)	54 (18)	ns	13 (7)	45 (13)	ns

Secondary Endpoints

In ENABLE 1, 95% of patients successfully completed the open-label phase achieving a platelet count ≥90,000/μL and were randomized to double-blinded antiviral treatment.

In ENABLE 2, 94% of patients successfully completed the open-label phase and achieved a platelet count ≥100,000/μL and were randomized to the double-blind antiviral treatment phase.

The threshold for dose reduction of peg-interferon is 50,000/μL per package labeling; therefore, it is important to maintain platelets counts above 50,000/μL in order to maintain peg-interferon dose. In ENABLE 1, more patients receiving eltrombopag were able to maintain platelet counts >50,000/μL compared to those receiving placebo, 69% and 15%, respectively. In ENABLE 2 more patients receiving eltrombopag were able to maintain platelet counts >50,000/μL compared to those receiving placebo, 81% and 23%, respectively.

Adverse Events (Safety Data) [1,4,5]

During the open-label antiviral phase for both ENABLE 1 and ENABLE 2, AEs occurring ≥3% were headache, nausea, and diarrhea. The overall summary of adverse events which occurred during the antiviral phase are summarized in Table 4.

The most common adverse events (≥10%) during the double-blind antiviral phase and 30 days follow-up for both ENABLE studies were anemia, pyrexia, fatigue, headache, nausea, diarrhea, insomnia, decreased appetite, cough, influenza-like illness, pruritus, chills, myalgia and asthenia.

In both studies, patients receiving eltrombopag had more thromboembolic events incident and progression of cataracts, and hepatobiliary AEs (Table 5). The most commonly reported adverse event consistent with hepatic decompensation was ascites. In ENABLE 1, hepatic encephalopathy and variceal hemorrhage were more prominent in subjects taking eltrombopag compared to placebo. In ENABLE 2, hepatic encephalopathy and death were more prominent in subjects taking eltrombopag compared to placebo.

Table 4. Overall Summary of AEs during Antiviral Phase, On-Treatment+30 days Follow-Up (Safety Double-Blind Population)

	ENABLE 1		ENABLE 2	
AE Type n (%)	**Placebo (n=232)**	**Eltrombopag (n= 449)**	**Placebo (n= 252)**	**Eltrombopag (n=506)**
Any AE	226 (97)	430 (96)	235 (93)	475 (94)
Any serious AE (SAE)	35 (15)	90 (20)	37 (15)	99 (20)
Any fatal SE*	6 (3)	10 (2)	4 (2)	19 (4)
Any drug-related AE	217 (94)	420 (94)	225 (89)	453 (90)
Any AE leading to study withdrawal	7 (3)	11 (2)	9 (4)	23 (5)
Any ongoing AE at the end of study withdrawal	133 (57)	272 (61)	127 (50)	268 (53)

* Antiviral phase + 6 months follow-up

Table 5. Adverse Events On-Treatment during the Double-Blind Phase + 30 days follow-up (Safety Population)

	ENABLE 1		ENABLE 2	
AE Type	**Placebo (n=232) n (%)**	**Eltrombopag (n=449) N (%)**	**Placebo (n=252) n (%)**	**Eltrombopag (n=506) n (%)**
Thromboembolic Events - PVT	4 (1.7) 2 (0.9)	11 (2.5) 5 (1.1)	1 (<1) 0	20 (4) 7(1)
Hepatobiliary Events -Hepatic decompensation -ALT >3x ULN	 19 (8) 34 (15)	 59 (13) 67 (15)	 16 (6) 49 (19)	 66 (13) 76 (15)
Deaths	6 (3)	10 (2)	4 (2)	19 (4)
Ocular Events - Progression of pre-existing cataract -Incident cataract	 4 (2) 4 (2)	 21 (5) 17 (4)	 8 (3) 8 (3)	 15 (3) 21 (4)
Malignancies -Hepatocellular carcinoma -Other	5 (2) 3 (1) 2 (<1)	13 (3) 13 (3) 0	 11 (4) 1 (<1)	 28 (6) 3 (<1)
Bleeding -Variceal hemorrhage -Gastrointestinal bleeding -Non-variceal bleeding	59 (25) 2 (<1) 0	83 (18) 8 (2) 9 (2)	 45 (18)	 80 (16)

Warnings and Precautions [1]

Hepatotoxicity and Hepatic Decompensation – Package labeling for eltrombopag contains a Box Warning for hepatotxicity and hepatic decompensation. The risk for hepatic decompensation ascends from studies done in patients with chronic hepatitis C and thrombocytopenia treated with interferon and ribavirin in combination with eltrombopag. Both ENABLE 1 and ENABLE 2 revealed more events suggestive of hepatic decompensation in subjects taking eltrombopag compared to subjects taking placebo, 13% vs 8% in ENABLE 1 and 13 vs 6% in ENABLE 2, respectively. Patients with albumin <3.5g/dL or MELD scores ≥10 at baseline had the greatest risk of hepatic decompensation. Events suggestive of hepatic decompensation are ascites, hepatic encephalopathy, variceal hemorrhage, spontaneous bacterial peritonitis, hepatocellular carcinoma, or death.

Serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), and bilirubin should be measured prior to initiation of eltrombopag, every 2 weeks during the dose adjustment phase, and monthly when on a stable dose of eltrombopag. Eltrombopag inhibits UGT1A1 and OATP1B1 which may lead to indirect hyperbilirubinemia; if bilirubin is elevated, perform fractionation. If liver tests are abnormal, repeat testing within 3-5 days and if abnormalities are confirmed, monitor serum liver tests weekly until abnormal values resolve, stabilize, or return to baseline levels.

Eltrombopag should be discontinued if ALT levels increase to ≥3X the upper limit of normal (ULN) and are:

- progressive, or
- persistent for ≥ 4 weeks, or
- accompanied by increased direct bilirubin, or
- accompanied by clinical symptoms of liver injury or evidence for hepatic decompensation

Thrombotic/thromboembolic events: In ENABLE 1 and ENABLE 2, 3% (31/955) of patients treated with eltrombopag experienced a thrombotic event compared to 1% (5/484) receiving placebo. These events were observed at low and at normal platelet counts and included both venous and arterial events. The majority of events were portal vein thrombosis (1% in patients treated with eltrombopag and <1% in patients treated with placebo). Thrombotic/thromboembolic complications may result from increases in platelet levels with eltrombopag. To minimize risk of thrombotic/thromboembolic complications, eltrombopag should not be used to normalize platelet counts.

Cataracts: In ENABLE1 and 2, cataracts developed or worsened in 8% of patients treated with eltrombopag and 5% of patients treated with placebo. A baseline ocular exam should be performed prior to administration and while on treatment, patients should be regularly monitored for signs and symptoms of cataracts.

Drug Interactions [1,3]

In vitro studies have shown that eltrombopag is metabolized by oxidation by CYP1A2 and CYP2C8. UGT1A1 and UGT1A3 are responsible for the glucuronidation of eltrombopag.

The clinical significance of strong inhibitors of CYP1A2 (ciprofloxacin, fluvoxamine), or CYP2C8 (trimethoprim, gemfibrozil), or inducers of CYP1A2 (omeprazole), or CYP2C8 (rifampin) on the systemic exposure to eltrombopag not been established in clinical studies. Patients should be monitored closely for signs of toxicity if receiving concomitant therapy with strong CYP1A2 or CYP2C8 inhibitors.

In vitro studies have shown that eltrombopag is an inhibitor of the organic anion transporting polypeptide OATP1B1 and can increase serum levels of drugs that are substrates of this transporter (e.g., benzylpenicillin, atorvastatin, fluvastatin, pravastatin, rosuvastatin, methotrexate, nateglinide, repaglinide, rifampin). Use caution when using drugs that are substrates of OATP1B1 and consider dose reductions of those drugs. In clinical trials, rosuvastatin was reduced by 50% when given concomitantly with eltrombopag.

In vitro studies have shown that eltrombopag is an inhibitor of UGT1A1, UGT1A3, UGT1A4, UGT1A6, UGT1A9, UGT2B7, and UGT2B15. Those enzymes are responsible for the metabolism of drugs such as acetaminophen, narcotics, and nonsteroidal anti-inflammatory drugs (NSAIDs). These interactions have not been investigated in clinical studies. Caution and close monitoring is advised when using drugs that are metabolized by the above enzymes in conjunction with eltrombopag.

Potential for a drug-drug interaction may exist if eltrombopag is administered with boceprevir or telaprevir. Subject by the FDA upon approval of eltrombopag for the thrombocytopenia in patients with chronic hepatitis C, the FDA is requiring a pharmacokinetic trial to evaluate the effect of boceprevir and telaprevir on eltrombopag and the effect of eltrombopag on boceprevir and telaprevir PK in healthy subjects. This phase 1 trial is currently active. There are no trials evaluating the safety and efficacy of eltrombopag with direct-acting antivirals in patients with chronic hepatitis C.

Acquisition Costs

Refer to VA pricing sources for updated information.

Pharmacoeconomic Analysis

No pharmacoeconomic analysis for hepatitis C is available in the published literature.

Conclusions

Eltrombopag has been shown to significantly improve SVR rates over placebo when used to allow initiation and maintenance of interferon and ribavirin therapy in patients with hepatitis C related thrombocytopenia as shown in 2 randomized, double-blind placebo controlled phase III trials, ENABLE 1 and ENABLE 2. The benefits of treatment must outweigh risks when the decision is made to use eltrombopag in these patients with chronic hepatitis C whose degree of thrombocytopenia prevents the initiation of interferon therapy; there is a box warning of hepatoxicity and liver decompensation as those treated with eltrombopag experienced more of these events. Furthermore, safety and efficacy have not established with the use of eltrombopag with direct-acting antivirals (e.g. boceprevir or telaprevir containing regimens).

References

1. Promacta (Eltrombopag) package insert. GlaxoSmithKline. Research Triangle Park, NC. November 2012.
2. Eltrombopag (Promacta®) Criteria for Use. Washington, DC; Pharmacy Benefits Management Services, Medical Advisory Panel and VISN Pharmacist Executives, Veterans Health Administration, Department of Veterans Affairs; May 2013.
3. Eltrombopag/Boceprevir and Eltrombopag/Telaprevir Drug-Drug Interaction Study in Healthy Adult Subjects. ClinicalTrials.gov Web site. http://clinicaltrials.gov/ct2/show/NCT01657552?term=eltrombopag+and+boceprevir&rank=1. Accessed February 21, 2013.
4. Afdhal N, et al. Final Results of ENABLE 1, a Phase 3, Multicenter Study of Eltrombopag as an Adjunct for Antiviral Treatment of Hepatitis C Virus-Related Chronic Liver Disease Associated With Thrombocytopenia [abstract]. In: 62nd Annual Meeting of the American Association for the Study of Liver Disease; 2011 Nov 4-8; San Francisco, California (CA): AASLD; 2011. Abstract LB-3.
5. Dusheiko G et al. Results of ENABLE 2, a Phase 3, Placebo-controlled, Multicenter Study of Eltrombopag, Peginterferon Alfa-2b, and Ribavirin Treatment in Patients with Hepatitis C and Thrombocytopenia [abstract]. In: 47th Annual European Association for the Study of Liver; 2012 April 20; Barcelona, Spaon: EASL; 2012. Abstract #279.

Prepared March 2013. Jenna Kawamoto, PharmD, **Contact persons**: Pam Belperio, PharmD, Office of Public Health; Melinda Neuhauser, PharmD, MPH, VA PBM Services

Appendix: Clinical Trials	
Citation	Afdhal N, et al. Final Results of ENABLE 1, a Phase 3, Multicenter Study of Eltrombopag as an Adjunct for Antiviral Treatment of Hepatitis C Virus-Related Chronic Liver Disease Associated With Thrombocytopenia [abstract]. In: 62nd Annual Meeting of the American Association for the Study of Liver Disease; 2011 Nov 4-8; San Francisco, California (CA): AASLD; 2011. Abstract LB-3.
Study Goals	The objectives of this study were to assess the ability of eltrombopag to: • Increase platelet counts in patient with chronic HCV and thrombocytopenia • Enable initiation of antiviral therapy • Allow maintenance of antiviral therapy • Increase SVR Primary efficacy outcome was SVR rate, defined as the percentage of patients with non-detectable HCV RNA 24 weeks post-completion of treatment period. Secondary Endpoints included the proportion of patients with a shift in platelet count from <75,000/μL to ≥90,000/μL during the pre-antiviral phase, assessment of platelet counts throughout the trial, proportions of patients achieving antiviral outcomes relative to EVR, RVR, ETR, requirements of antiviral dose reductions or discontinuation, and adverse events.
	Study Design Phase III, multicenter 2-part trial, consisting of an open-label, pre-antiviral treatment phase (part 1) and a randomized, double-blind, placebo-controlled, antiviral treatment phase (Part 2). Treatment was blinded to patients and all trial sponsor personnel using matching placebo. **Methods:** Patients with platelets <75,000/μL entered an open-label phase (part 1) to receive eltrombopag to increase platelet levels to a threshold of ≥90,000/μL. Eltrombopag was administered at initial dose of 25 mg once daily for 2 weeks and increased by 25 mg increments over 2 to 3 week periods to achieve the optimal platelet count to initiate antiviral therapy. Max time patients could receive eltrombopag was 9 weeks in this open-label phase. Patients who met platelet threshold of ≥90,000/μL were randomized (2:1) to the same dose of eltrombopag or to placebo in combination with pegylated interferon alfa-2a and ribavirin for up to 48 weeks. Randomization was stratified according to platelet count (<50,000/μL and 50,000/μL to <75,000/μL), genotype (genotype 2/3, and genotype non-2/3) and HCV viral load (<800,000 IU/mL and ≥800,000 IU/mL).
Criteria	**Inclusion criteria** • ≥18 years of age

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Evidence of chronic HCV infection
Baseline platelet count <75,000/μL
Appropriate for peg-interferon and ribavirin antiviral therapy
Hemoglobin ≥11.0g/dL for men or ≥10.0 g/dL for women
Absolute Neutrophil Count >750/mm^3
Creatinine clearance ≥50 mL/minute

Exclusion criteria

Treatment with IFN within 30 days of screening visit
Non-responders to previous (optimal) treatment with peg-interferon and ribavirin for reasons other than thrombocytopenia
Decompensated cirrhosis
Serious cardiac, cerebrovascular, or pulmonary disease
Prior history of arterial or venous thrombosis, and ≥2 of the following risk factors (exceptions made for Canada): hereditary thrombophilic disorders (e.g., Factor V Leiden, antithrombin III deficiency, etc.); hormone replacement therapy; systemic contraception therapy (containing estrogen); smoking, diabetes; hypercholesterolemia; medication for hypertension; or cancer
Evidence of portal vein thrombosis on abdominal imaging within 3 months of baseline visit
Any disease condition associated with active bleeding or requiring anticoagulation with heparin or warfarin
Co-infection with HIV or HBV
Known hypersensitivity, intolerance or allergy to PegIFN and RBV, eltrombopag tablets or any of their ingredients.

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<tr><td>Results</td><td>
Demographics and baseline clinical characteristics of the ITT population were well balanced.
Baseline characteristics (ITT Population)
<table>
<tr><th></th><th>Placebo</th><th>Eltrombopag</th></tr>
<tr><td>Age (years)</td><td>51 (23-72)</td><td>52 (19-76)</td></tr>
<tr><td>Male %</td><td>69</td><td>59</td></tr>
<tr><td>Race %</td><td></td><td></td></tr>
<tr><td>- White</td><td>72</td><td>72</td></tr>
<tr><td>IFN Naïve %</td><td>66</td><td>68</td></tr>
<tr><td>HCV Genotype %</td><td></td><td></td></tr>
<tr><td>- 1</td><td>64</td><td>65</td></tr>
<tr><td>- 2</td><td>9</td><td>6</td></tr>
<tr><td>- 3</td><td>23</td><td>26</td></tr>
<tr><td>- 4,6</td><td><1</td><td><1</td></tr>
<tr><td>HCV RNA</td><td></td><td></td></tr>
<tr><td>- <800,000 IU/mL</td><td>48</td><td>52</td></tr>
<tr><td>- ≥800,000 IU/mL</td><td>51</td><td>48</td></tr>
<tr><td>Childs Pugh Score A (score 5-6) %</td><td>94</td><td>94</td></tr>
<tr><td>Platelet count</td><td></td><td></td></tr>
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- <50,000/μL	27	28
- ≥50,000/μL	73	72
FibroSURE 3 / 4	80	79

In this trial, n=715 patients enrolled in the open-label phase whereby 95% of patients successfully completed this phase reaching threshold platelets count of ≥90,000/μL and were randomized to the double-blind, antiviral treatment phase. All randomized patients n= 682.

Primary Endpoint:

ENABLE 1 (ITT Population)			
	Placebo (n = 232)	Eltrombopag (n= 450)	P-value; 95% CI
SVR, n(%)	33 (14)	104 (23)	0.0064; 2.4-13.4

Secondary Endpoints:

ENABLE 1 (ITT Population)			
Response Type*	Placebo, n (%)	Eltrombopag, n (%)	P-value; 95% CI
RVR	33 (14)	104 (23)	0.0064; 2.4-13.4
EVR	115 (50)	297 (66)	<0.0001; 8.6-21.1
cEVR	60 (26)	187 (42)	0.7495; -2.5-4.5
ETR	86 (37)	214 (48)	0.0080; 3.3-18.1

*RVR: rapid virologic respons; EVR: early virologic response; cEVR: complete early virologic response; ETR: end-of-treatment response

In ENABLE 1, more patients receiving eltrombopag were able to maintain platelet counts >50,000/μL compared to those receiving placebo, 69% and 15%, respectively.

More patients treated with eltrombopag had no antiviral dose reduction compared with placebo-treated subjects (43% vs 28% respectively). Those taking eltrombopag were associated with a longer interval to first antiviral dose reduction and significantly less antiviral dose reductions (pegIFN and/or ribavirin) in those who were treated with eltrombopag compared to placebo (P= 0.0029).

Adverse Events

AE Type	Placebo (n=232) n (%)	Eltrombopag (n=449) n (%)
Thromboembolic Events - PVT	4 (1.7) 2 (0.9)	11 (2.5) 5 (1.1)
Hepatobiliary Events -Hepatic decompensation -ALT >3x ULN	 19 (8) 34 (15)	 59 (13) 67 (15)
Deaths	6 (3)	10 (2)
Ocular Events - Progression of pre-existing cataract -Incident cataract	 4 (2) 4 (2)	 21 (5) 17 (4)
Malignancies -Hepatocellular carcinoma -Other	5 (2) 3 (1) 2 (<1)	13 (3) 13 (3) 0
Bleeding -Variceal hemorrhage -Gastrointestinal bleeding	59 (25) 2 (<1) 0	83 (18) 8 (2) 9 (2)

AE Type n (%)	Placebo (n=232)	Eltrombopag (n= 449)
Any AE	226 (97)	430 (96)
Any serious AE (SAE)	35 (15)	90 (20)
Any fatal SE*	6 (3)	10 (2)
Any drug-related AE	217 (94)	420 (94)
Any AE leading to IP discontinuation	68 (29)	85 (19)
Any AE leading to study withdrawal	7 (3)	11 (2)
Any ongoing AE at the end of study withdrawal	133 (57)	272 (61)

Conclusions	Patients treated with eltrombopag had significantly higher rates of SVR compared to placebo, 23% vs 14%, respectively. Eltrombopag also enabled the introduction of antiviral therapy in 95% of patients who would otherwise be marginal candidates for pegIFN alfa-2a therapy, delayed and reduced the number of pegIFN alfa-2a dose reduction, and shows an acceptable safety profile in high-risk patients with cirrhosis.
Critique	This study has not been published to fully assess validity.

Citation	Dusheiko G et al. Results of ENABLE 2, a Phase 3, Placebo-controlled, Multicenter Study of Eltrombopag, Peginterferon Alfa-2b, and Ribavirin Treatment in Patients with Hepatitis C and Thrombocytopenia [abstract]. In: 47th Annual European Association for the Study of Liver; 2012 April 20; Barcelona, Spaon: EASL; 2012. Abstract #279.
Study Goals	The objectives of this study were to assess the ability of eltrombopag to: • Increase platelet counts in patient with chronic HCV and thrombocytopenia • Enable initiation of antiviral therapy • Allow maintenance of antiviral therapy • Increase SVR Primary efficacy outcome was SVR rate, defined as the percentage of patients with non-detectable HCV RNA 24 weeks post-completion of treatment period. Secondary Endpoints included the proportion of patients with a shift in platelet count from <75,000/μL to ≥100,000/μL during the pre-antiviral phase, assessment of platelet counts throughout the trial, proportions of patients achieving antiviral outcomes relative to EVR, RVR, ETR, requirements of antiviral dose reductions or discontinuation, and adverse events.
Methods	**Study Design** Phase III, multicenter 2-part trial, consisting of an open-label, pre-antiviral treatment phase (part 1) and a randomized, double-blind, placebo-controlled, antiviral treatment phase (Part 2). Treatment was blinded to patients and all trial sponsor personnel using matching placebo. **Methods:** Patients with platelets <75,000/μL entered an open-label phase (part 1) to receive eltrombopag to increase platelet levels to a threshold of ≥100,000/μL. Eltrombopag was administered at initial dose of 25 mg once daily for 2 weeks and increased by 25 mg increments over 2 to 3 week periods to achieve the optimal platelet count to initiate antiviral therapy. Max time patients could receive eltrombopag was 9 weeks in this open-label phase. Patients who met platelet threshold of ≥100,000/μL were randomized (2:1) to the same dose of eltrombopag or to placebo in combination with pegylated interferon alfa-2b and ribavirin for up to 48 weeks. Randomization was stratified according to platelet count (<50,000/μL and 50,000/μL to <75,000/μL), genotype (genotype 2/3, and genotype non-2/3) and HCV viral load (<800,000 IU/mL and ≥800,000 IU/mL).
Criteria	**Inclusion criteria** • ≥18 years of age • Evidence of chronic HCV infection • Baseline platelet count <75,000/μL

	• Appropriate for peg-interferon and ribavirin antiviral therapy • Hemoglobin ≥11.0g/dL for men or ≥10.0 g/dL for women • Absolute Neutrophil Count >750/mm^3 • Creatinine clearance ≥50 mL/minute **Exclusion criteria** • Treatment with IFN within 30 days of screening visit • Non-responders to previous (optimal) treatment with peg-interferon and ribavirin for reasons other than thrombocytopenia • Decompensated cirrhosis • Serious cardiac, cerebrovascular, or pulmonary disease • Prior history of arterial or venous thrombosis, and ≥2 of the following risk factors (exceptions made for Canada): hereditary thrombophilic disorders (e.g., Factor V Leiden, antithrombin III deficiency, etc.); hormone replacement therapy; systemic contraception therapy (containing estrogen); smoking, diabetes; hypercholesterolemia; medication for hypertension; or cancer • Evidence of portal vein thrombosis on abdominal imaging within 3 months of baseline visit • Any disease condition associated with active bleeding or requiring anticoagulation with heparin or warfarin • Co-infection with HIV or HBV • Known hypersensitivity, intolerance or allergy to PegIFN and RBV, eltrombopag tablets or any of their ingredients.

Results

Demographics and baseline clinical characteristics of the ITT population were well balanced.

Baseline Characteristics (ITT Population)

	Placebo	**Eltrombopag**
Age (years)	53 (26-74)	52 (22-83)
Male %	63	63
Race %		
- **White**	74	77
IFN Naïve %	72	69
HCV Genotype %		
- **1**	63	63
- **2**	11	8
- **3**	19	22
- **4**	7	6
- **6**	0	<1
HCV RNA		
- **<800,000 IU/mL**	52	53
- **≥800,000 IU/mL**	47	47
Childs Pugh Score A (score 5-6) %	96	97
Platelet count		
- **<50,000/µL**	30	28
- **≥50,000/µL**	70	72
FibroSURE 3 / 4	79	80

In this trial, n=805 patients enrolled in the open-label phase whereby 94% of patients successfully completed this phase reaching threshold platelets count of ≥100,000/µL and were randomized to the double-blind, antiviral treatment phase. All randomized patients n= 759.

Primary Endpoint:

ENABLE 2 (ITT Population)			
	Placebo (n=253)	Eltrombopag (n= 506)	P-value; 95% CI
SVR, n(%)	32 (13)	97 (19)	0.02 1.2-10.9

Secondary Endpoints:

ENABLE 2 (ITT Population)			
Response Type	Placebo, n (%)	Eltrombopag, n (%)	P-value; 95% CI
RVR	34 (13)	78 (15)	-
EVR	103 (41)	313 (62)	<0.0001; 13.6-27.8

cEVR	57 (23)	174 (34)	0.0003; 3.5-14.7
ETR	59 (23)	190 (38)	<0.0001; 6.9-19.4

*RVR: rapid virologic respons; EVR: early virologic response; cEVR: complete early virologic response; ETR: end-of-treatment response

In ENABLE 2, 13 % of patients treated with placebo compared with 4% of patients receiving eltrombopag had a minimum platelet count of <25,000/μL.

More patients treated with eltrombopag had no antiviral dose reduction (46% vs 27% respectively). Those taking eltrombopag were associated with longer interval to first antiviral dose reduction.

Adverse Events

AE Type N (%)	**Placebo (n=252)**	**Eltrombopag (n=506)**
Thromboembolic Events - PVT	1 (<1) 0	20 (4) 7(1)
Hepatobiliary Events -Hepatic decompensation -ALT >3x ULN	 16 (6) 49 (19)	 66 (13) 76 (15)
Deaths	4 (2)	19 (4)
Ocular Events - Progression of pre-existing cataract -Incident cataract	8 (3) 8 (3)	15 (3) 21 (4)
Malignancies -Hepatocellular carcinoma -Other	 11 (4) 1 (<1)	 28 (6) 3 (<1)
Bleeding -Non-variceal bleeding	 45 (18)	 80 (16)

AE Type N (%)	**Placebo (n= 252)**	**Eltrombopag (n=506)**
Any AE	235 (93)	475 (94)
Any serious AE (SAE)	37 (15)	99 (20)
Any fatal SE*	4 (2)	19 (4)
Any drug-related AE	225 (89)	453 (90)
Any AE leading to IP discontinuation	70 (28)	115 (23)
Any AE leading to study withdrawal	9 (4)	23 (5)
Any ongoing AE at the end of study withdrawal	127 (50)	268 (53)

Conclusions	Patients treated with eltrombopag had significantly higher rates of SVR compared to placebo, 19% vs 13%, respectively. Eltrombopag also enabled the introduction of antiviral therapy in 94% of patients who would otherwise be marginal candidates for pegIFN alfa-2a therapy. It also enabled delayed and reduced the number of pegIFN alfa-2a dose reduction. However, this agent requires a risk-benefit evaluation in patients at risk of disease progression due to high rate of thromboembolic events and transient hepatobiliary events in the eltrombopag arm.
Critique	This study has not been published to fully assess validity.