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Eltrombopag Increases Platelet Numbers in Thrombocytopenic Patients With HCV Infection and Cirrhosis, Allowing for Effective Antiviral Therapy

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CLINICAL LIVER

See Covering the Cover synopsis on page 327; see editorial on page 339.

BACKGROUND & AIMS: Thrombocytopenia is common among patients with hepatitis C virus (HCV) infection and advanced fibrosis or cirrhosis, limiting initiation and dose of peginterferon-alfa (PEG) and ribavirin (RBV) therapy. The phase 3 randomized, controlled studies, Eltrombopag to Initiate and Maintain Interferon Antiviral Treatment to Benefit Subjects with Hepatitis C-Related Liver Disease (ENABLE)-1 and ENABLE-2, investigated the ability of eltrombopag to increase the number of platelets in patients, thereby allowing them to receive initiation or maintenance therapy with PEG and RBV. **METHODS:** Patients with HCV infection and thrombocytopenia (platelet count <75,000/μL) who participated in ENABLE-1 (n = 715) or ENABLE-2 (n = 805), from approximately 150 centers in 23 countries, received open-label eltrombopag (25–100 mg/day) for 9 weeks or fewer. Patients whose platelet counts reached the predefined minimal threshold for the initiation of PEG and RBV therapy (95% from ENABLE-1 and 94% from ENABLE-2) entered the antiviral treatment phase, and were assigned randomly (2:1) to groups that received eltrombopag or placebo along with antiviral therapy (24 or 48 weeks, depending on HCV genotype). The primary end point was sustained virologic response (SVR) 24 weeks after completion of antiviral therapy. **RESULTS:** More patients who received eltrombopag than placebo achieved SVRs (ENABLE-1: eltrombopag, 23%; placebo, 14%; $P = .0064$; ENABLE-2: eltrombopag, 19%; placebo, 13%; $P = .0202$). PEG was administered at higher doses, with fewer dose reductions, in the eltrombopag groups of each study compared with the placebo groups. More patients who received eltrombopag than placebo maintained platelet counts of 50,000/μL or higher throughout antiviral treatment (ENABLE-1, 69% vs 15%; ENABLE-2, 81% vs 23%). Adverse events were similar between groups, with the exception of hepatic decompensation (both studies: eltrombopag, 10%; placebo, 5%) and thromboembolic events, which were more common in the eltrombopag group of ENABLE-2. **CONCLUSIONS:** Eltrombopag increases platelet numbers in thrombocytopenic patients with HCV and advanced fibrosis and cirrhosis, allowing otherwise ineligible or marginal patients to begin and maintain antiviral therapy, leading to significantly increased rates of SVR. Clinical trial no: NCT00516321, NCT00529568.

Keywords: Portal Hypertension; Liver Disease; Complication; Blood Clot.

Thrombocytopenia (TCP) is a common complication of chronic liver disease associated with hepatitis C virus (HCV) infection and correlates with disease severity and portal hypertension.[1–3] Antiviral therapy with peginterferon-α (PEG) and ribavirin (RBV) further reduces platelet counts through bone marrow suppression.[4] Initiation of PEG-based antiviral therapy is recommended if platelets exceed 90,000/μL (PEG-2a) or 100,000/μL (PEG-2b), and dose reduction is recommended if platelet counts decrease to less

Abbreviations used in this paper: **AE, adverse event; CI, confidence interval; ENABLE, Eltrombopag to Initiate and Maintain Interferon Antiviral Treatment to Benefit Subjects with Hepatitis C-Related Liver Disease; ETR, end-of-treatment response; EVR, early virologic response; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; PEG, peginterferon alfa; PVT, portal vein thrombosis; PY, patient-year; RBV, ribavirin; RVR, rapid virologic response; SAE, serious adverse event; SVR, sustained virologic response; TCP, thrombocytopenia; TEE, thromboembolic event.**

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than 50,000/μL.[5,6] PEG dose reductions, particularly during the initial weeks of treatment, diminish the likelihood of sustained virologic response (SVR).[7–9]

Eltrombopag (Promacta; GlaxoSmithKline, Research Triangle Park, NC) is an oral, nonpeptide, thrombopoietin receptor agonist recently approved in the United States for treatment of thrombocytopenia in patients with chronic hepatitis C to allow the initiation and maintenance of interferon-based therapy. In a phase 2 study of patients with HCV-related cirrhosis and TCP, eltrombopag 30–75 mg once daily increased platelet counts to a level sufficient to initiate PEG-based therapy in 71%–91% of patients.[10]

Few studies of HCV antiviral therapy have been conducted in patients with cirrhosis, TCP, and presumed portal hypertension because of the risk of aggravated TCP. The objective of the Eltrombopag to Initiate and Maintain Interferon Antiviral Treatment to Benefit Subjects with Hepatitis C-Related Liver Disease (ENABLE) studies was to assess the ability of supportive eltrombopag therapy to increase platelets to levels sufficient to initiate and maintain PEG+RBV antiviral therapy, avoiding dose reductions/discontinuations, and potentially improving SVR rates in this population.

Patients and Methods

Design and Treatment

The ENABLE-1 (PEG-2a) and ENABLE-2 (PEG-2b) studies were designed similarly (Figure 1), differing only in the PEG used and their corresponding platelet thresholds for initiating antiviral therapy (ENABLE-1, 90,000/μL; ENABLE-2, 100,000/μL). The protocols for both studies (ClinicalTrials.gov numbers: NCT00516321 and NCT00529568) were reviewed and approved by the applicable ethics committee or institutional review boards at each center, in accordance with the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use Good Clinical Practice and applicable country-specific requirements. All authors had access to the study data and reviewed and approved the final manuscript. Each patient provided written informed consent before performing any study-specific procedures. The ENABLE-1 study was conducted between October 30, 2007, and March 31, 2011. ENABLE-2 was conducted between November 15, 2007, and August 23, 2011.

Both studies comprised 2 parts. During the initiation phase, thrombocytopenic patients with chronic HCV received open-label eltrombopag in a dose-escalating fashion dependent on platelet response (25 mg, 50 mg, 75 mg, or 100 mg once daily) for 2–9 weeks. Patients whose platelet counts reached the predefined minimal threshold for initiating antiviral therapy were randomized 2:1 to eltrombopag or placebo in the subsequent double-blind, antiviral phase and treated for 24 or 48 weeks according to the HCV genotype. Patients receiving eltrombopag 100 mg/day for 3 weeks who failed to meet the platelet count threshold were entered into the follow-up period of the study. The trial ended when the last patient completed the last follow-up visit.

Patients successfully randomized into the antiviral phase in ENABLE-1 received PEG-2a 180 μg weekly subcutaneously and oral RBV as per the package insert; for ENABLE-2, patients received PEG-2b 1.5 μg/kg weekly subcutaneously plus oral RBV as per the package insert (Figure 1). Standardized stopping and futility rules were applied for PEG-interferon according to the American Association for the Study of Liver Diseases guidelines.[11]

A centralized computer-generated randomization list was generated through a validated system (RandALL) by the study sponsor, using the predefined strata (HCV genotype, baseline

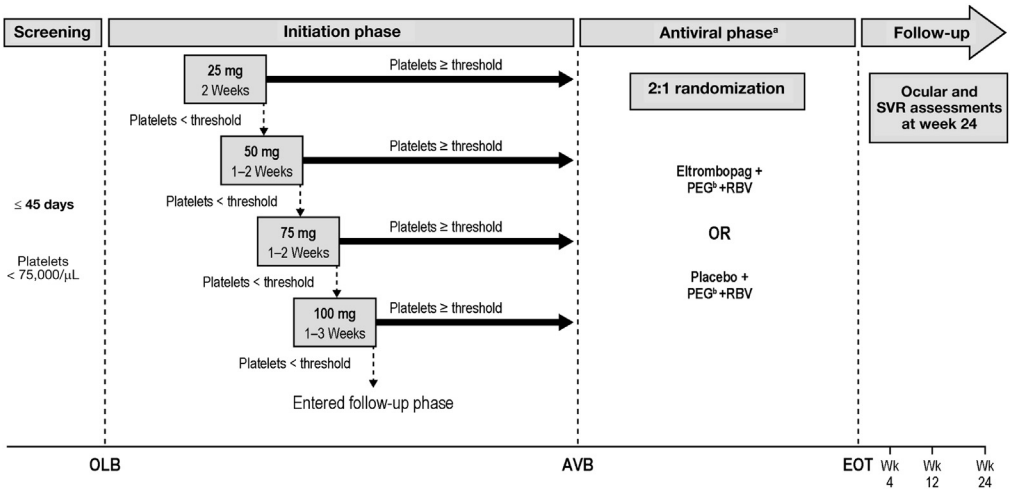

Figure 1. Study design for ENABLE-1 and ENABLE-2. During the open-label initiation phase, patients received eltrombopag for up to 9 weeks until platelet count increased to the prespecified threshold to initiate antiviral therapy (ENABLE-1, 90,000/μL; ENABLE-2, 100,000/μL). At randomization, patients received either the same dose of eltrombopag from the initiation phase or matching placebo. Doppler ultrasound of the abdomen was performed at any time between screening and baseline and every 6 months thereafter to assess for hepatocellular carcinoma and portal vein thrombosis. In ENABLE-1, PEG-2a was dosed at 180 μg/wk with RBV 800 mg/day for genotype 2/3 or 1000 mg/day for patients weighing less than 75 kg or 1200 mg/day for patients weighing 75 kg or more for genotypes other than 2/3. In ENABLE-2, PEG-2b was dosed at 1.5 μg/kg weekly, and RBV was dosed at 800 mg/day, 1000 mg/day, 1200 mg/day, or 1400 mg/day based on body weights of 65 kg or less, 65–80 kg, 81–105 kg, or more than 105 kg, respectively. AVB, antiviral baseline; EOT, end of treatment; OLB, open-label baseline. [a]Twenty-four weeks for hepatitis C virus genotype 2/3 and 48 weeks for other genotypes. [b]PEG-2a in ENABLE-1 and PEG-2b in ENABLE-2.

platelet count, and baseline HCV-RNA level). The study centers registered and randomized patients by telephone using an interactive voice response system.

Patients were stratified at randomization to the antiviral phase by HCV genotype (2/3 vs non-2/3), baseline platelet counts (<50,000 vs ≥50,000/μL), and baseline HCV-RNA level (<800,000 vs ≥800,000 IU/mL). The interactive voice response system was available 24 hours a day, 7 days a week. The patients and all study personnel were blinded to the treatment assignment.

Investigators were instructed to follow the current local product labels for PEG dose reductions and discontinuations. Eltrombopag dose was reduced if platelets exceeded 200,000/μL, and treatment was both interrupted and the dose was reduced if platelets exceeded 400,000/μL.

Patient Population

Patients were enrolled into each study from approximately 150 centers across 23 countries. Eligible patients were 18 years and older, with confirmed HCV infection, baseline platelet count less than 75,000/μL, and otherwise adequate hepatic, renal, and hematologic function to receive antiviral therapy. Patients were eligible if, in the investigator's opinion, they were appropriate candidates for PEG+RBV therapy and could have received prior treatment with PEG+RBV if the reason for stopping treatment was documented thrombocytopenia. Key study exclusion criteria included nonresponders to previous PEG+RBV for reasons other than thrombocytopenia; decompensated liver disease; serious cardiac, cerebrovascular, or pulmonary disease that would preclude PEG+RBV therapy; history of thromboembolic events (evidence of portal vein thrombosis, or arterial or venous thrombosis, and any additional 2 risk factors); hepatitis B virus or human immunodeficiency virus infection; any condition involving active bleeding or need for anticoagulation with heparin or coumadin; and a history of clinically significant bleeding from esophageal or gastric varices.

End Points and Assessments

The primary objective of both studies was to evaluate the effect of eltrombopag treatment on SVR, defined as the proportion of patients with undetectable serum HCV-RNA levels 24 weeks after completing antiviral therapy (Supplementary Appendix). HCV-RNA level was assessed at screening, antiviral baseline, weeks 4 and 12, completion of antiviral therapy, and post-therapy weeks 12 and 24.

Secondary efficacy end points included platelet counts throughout the study; PEG and/or RBV dose reductions or discontinuation; and rates of rapid virologic response (RVR), early virologic response (EVR), complete EVR, and end-of-treatment response (ETR). The RVR, EVR, complete EVR, and ETR were not adjusted and are included as supportive data only. Safety end points included adverse events (AEs) using the Division of AIDS AE grading table.[12] Treatment-emergent AEs were considered to have occurred within 30 days after the last dose of study medication, except for death, malignancies, and cataracts, which were assessed until the last study visit. An independent data monitoring committee reviewed safety data throughout the study and efficacy data at predefined milestones. An independent committee reviewed all ophthalmic evaluations because ocular findings in preclinical studies of immature rodents indicated a risk of cataract formation. After the study, a blinded independent adjudication panel reviewed all events suggestive of hepatic decompensation.

Data Analysis

Sample size was determined assuming an SVR of 10% in the placebo group vs 20% in the eltrombopag group. The power of each study to detect this anticipated treatment effect was 92.5%, with an overall 2-sided level of significance of 5%.

A total of 675 patients (eltrombopag, n = 450 patients; placebo, n = 225 patients) were required to be randomized. We estimated that approximately 10% of patients would not complete the pre-antiviral treatment phase. Therefore, 750 patients were enrolled to randomize 675 patients. However, because the proportion of patients with missing data and how they would be handled in the primary analysis was taken into account in determining the assumed proportions with SVR (placebo, 10%; eltrombopag, 20%), the number randomized was not adjusted to account for missing data.

Efficacy was analyzed using the intent-to-treat population, comprising all randomized patients. Safety analyses were based on the safety population, comprising all patients who received study medication. All statistical comparisons and confidence intervals (CIs) were 2-sided; continuous variables were summarized using descriptive statistics, and categoric variables were summarized using frequency counts and percentages. The proportions of patients achieving SVR and other virologic end points were compared between eltrombopag and placebo using stratified Cochran–Mantel–Haenszel chi-square test statistics, adjusted for stratification factors.

For the primary analysis, if a patient had a missing value between visits, then the previous nonmissing HCV-RNA assessment and associated classification was carried forward to fill in the missing value. If a patient's HCV-RNA value at the 24-week follow-up assessment was missing for any reason, the patient was considered a nonresponder. A patient with missing data owing to premature discontinuation of treatment, or from discontinuation of the study for any reason, was considered a nonresponder for all subsequent visits.

Sensitivity analyses were conducted (6 preplanned and 1 post hoc), including assessment of the overall impact of patients who were missing post-treatment assessments, to determine their impact on the primary efficacy end point (SVR).

Results

Patient Characteristics

Treatment groups were well matched within each study and between studies (Table 1). Patient flow during both studies is shown in Supplementary Figure 1.

Median platelet counts at screening were approximately 59,000/μL in both studies. The study population comprised predominantly genotype 1 (62%–65%) with compensated liver disease (94%–97% Child–Pugh[13,14] A: score, 5–6). A high proportion of patients (78%) had a FibroSURE score equivalent to METAVIR F3 or F4, indicative of bridging fibrosis or cirrhosis (9% patients had a METAVIR score of F0/1/2, 13% patients were missing a score). The interleukin 28B status was balanced across groups and studies.

Table 1. Patient Demographics and Baseline Characteristics

	ENABLE-1			ENABLE-2		
	Initiation phase[a]	Antiviral phase[b]		Initiation phase	Antiviral phase[b]	
	Eltrombopag (n = 715)	Placebo (n = 232)	Eltrombopag (n = 450)	Eltrombopag (n = 805)	Placebo (n = 253)	Eltrombopag (n = 506)
Median age, *y* (range)	52 (19–76)	51 (23–72)	52.0 (19–76)	52 (22–83)	53 (26–74)	52 (22–83)
Male, n (%)	446 (62)	159 (69)	264 (59)	510 (63)	160 (63)	321 (63)
Race, n (%)						
White	516 (72)	166 (72)	326 (72)	600 (75)	188 (74)	388 (77)
Asian	172 (24)	57 (25)	107 (24)	189 (23)	61 (24)	107 (21)
Central/South Asian	54 (8)	14 (6)	39 (9)	61 (8)	16 (6)	43 (8)
Japanese/East Asian/ Southeast Asian	118 (17)	43 (19)	68 (15)	127 (16)	45 (18)	64 (13)
African American/African	18 (3)	6 (3)	12 (3)	13 (2)	4 (2)	8 (2)
Other	9 (1)	3 (1)	5 (1)	3 (<1)	0	3 (1)
Bridging fibrosis/cirrhosis[c]						
Patients with measurements, n	715	208	391	805	218	451
n (%)	560 (78)	185 (89)	354 (91)	633 (79)	199 (91)	405 (90)
HCV genotype, n (%)						
N[d]	713	232	449	800	252	504
1	458 (64)	149 (64)	292 (65)	499 (62)	160 (63)	320 (63)
2	54 (8)	22 (9)	27 (6)	72 (9)	28 (11)	40 (8)
3	178 (25)	54 (23)	115 (26)	179 (22)	47 (19)	113 (22)
4	17 (2)	5 (2)	11 (2)	49 (6)	17 (7)	30 (6)
6	6 (<1)	2 (<1)	4 (<1)	1 (<1)	0	1 (<1)
Total 2/3	232 (33)	76 (33)	142 (32)	251 (31)	75 (30)	153 (30)
Total non-2/3	481 (67)	156 (67)	307 (68)	549 (69)	177 (70)	351 (70)
IL28B						
rs12979860		111	204		117	255
CC		26 (23)	56 (27)		34 (29)	86 (34)
CT		69 (62)	112 (55)		62 (53)	129 (51)
TT		16 (14)	36 (18)		21 (18)	40 (16)
ra8099917		111	202		117	255
TT		57 (51)	96 (48)		59 (50)	125 (49)
GT		46 (41)	84 (42)		52 (44)	112 (44)
GG		8 (7)	22 (11)		6 (5)	18 (7)
Child–Pugh score, n (%)						
N[d]	714	232	449	803	253	504
A (score 5–6)	670 (94)	217 (94)	424 (94)	769 (96)	242 (96)	487 (97)
B (score 7–9)	44 (6)	15 (6)	25 (6)	34 (4)	11 (4)	17 (3)
Platelet count, n (%)[e,f]						
<50,000/μL	-	62 (27)	124 (28)	-	77 (30)	140 (28)
≥50,000/μL	-	170 (73)	326 (72)	-	176 (70)	366 (72)
HCV titer, n (%)[f,g]						
<800,000 IU/mL	-	112 (48)	236 (52)	-	132 (52)	266 (53)
≥800,000 IU/mL	-	119 (51)	214 (48)	-	120 (47)	238 (47)

[a]Safety population.
[b]Intent-to-treat population.
[c]FibroSURE score equivalent to METAVIR F3/F4. Proportions are based on the number of patients with measurements.
[d]Platelet count used for randomization into the appropriate strata at the start of the antiviral phase was the platelet value obtained at the screening/initiation phase baseline visit (ie, platelet count before treatment with open-label eltrombopag).
[e]Platelet count at screening/initiation phase baseline.
[f]The stratification for platelet counts and HCV titers was not performed until randomization to the antiviral phase. Therefore, these data are not applicable to the initiation phase of the study.
[g]One patient in the placebo group had a missing HCV titer at baseline.

Initiation Phase: Efficacy

During the initiation phase of ENABLE-1 and ENABLE-2, 97% and 96% of patients, respectively, achieved the required platelet thresholds. The median time to achieve these thresholds was 2 weeks; 85% and 78% of patients in ENABLE-1 and ENABLE-2, respectively, achieved this

platelet threshold within the first 4 weeks of treatment. Eighty-six percent received either 25 mg or 50 mg of eltrombopag daily (Supplementary Appendix).

Initiation Phase: Safety

During the initiation phase, the most common AEs (Table 2) were headache (ENABLE-1, 7%; ENABLE-2, 4%), nausea, and diarrhea (3% each in both studies). No thromboembolic events (TEEs) were reported during the initiation phase, and less than 1% of patients experienced hepatic decompensation. In the initiation phase, 8 patients (1%) experienced 9 serious AEs (SAEs) in ENABLE-1, and 9 patients (1%) experienced 9 SAEs in ENABLE-2, none of which were considered related to eltrombopag by investigators. No deaths occurred during the initiation phase of ENABLE-1. Two patients died as a result of events (hepatorenal syndrome and hepatocellular carcinoma [HCC]), originally recorded during the initiation phase of ENABLE-2, neither of which was considered related to eltrombopag by investigators.

The follow-up results from patients who discontinued from the open-label phase are presented in the Supplementary Appendix.

Antiviral Phase: Efficacy

Compared with placebo, a significantly higher proportion of eltrombopag-treated patients achieved SVR (ENABLE-1, 23% vs 14%, $P = .0064$; ENABLE-2, 19% vs 13%, $P = .0202$; Figure 2*A* and *B*[15]). The ability of eltrombopag to improve SVR was unaffected by stratification factors and was consistent across subgroups (Supplementary Appendix). Eltrombopag was superior to placebo for all virologic response measures except RVR (Figure 2*A* and *B*).

In univariate analyses, the treatment effect observed in the overall population was similar in patients infected with genotype 2/3 (percentage difference in ENABLE-1, 9.2 [CI, -3.0 to 21.5]; ENABLE-2, 10.4 [CI, -2.4 to 23.3]) compared with patients infected with nongenotype 2/3 (percentage difference in ENABLE-1, 7.6 [CI, 1.4–13.7]; ENABLE-2, 5.3 [CI, 0.1–10.6]).

Substantial differences in median platelet counts were apparent by week 2 of the antiviral phase between the eltrombopag and placebo arms (ENABLE-1, 111,000/μL vs 79,000/μL; ENABLE-2, 124,000/μL vs 89,500/μL), and persisted throughout treatment (Figure 2*C* and *D*). In contrast to patients receiving placebo, the median platelet counts for eltrombopag patients remained higher than thresholds for antiviral dose reductions throughout treatment. In ENABLE-1 and ENABLE-2, 69% and 81% of eltrombopag patients vs 15% and 23% of placebo patients maintained platelet counts of 50,000/μL or greater throughout the antiviral phase.

During the antiviral phase, patients in the eltrombopag group, who had higher median platelet counts than patients in the placebo group, experienced significantly longer time to first PEG dose reduction (Kaplan–Meier estimates: ENABLE-1: median, undefined vs 6.1 wk; hazard ratio, 0.41; 95% CI, 0.33–0.52; $P < .0001$; ENABLE-2: median, 43.1 vs 6.1 wk; hazard ratio, 0.39; 95% CI, 0.30–0.49; $P < .0001$; Figure 2*E* and *F*).

Eltrombopag-treated patients required fewer PEG dose reductions; 57% and 59% of eltrombopag patients in ENABLE-1 and ENABLE-2, respectively, avoided PEG dose reductions compared with 30% and 32% of placebo patients, respectively. Consequently, the overall median cumulative exposure to PEG in the eltrombopag groups was 60% and 69% higher than in the placebo groups for ENABLE-1 and ENABLE-2, respectively (Supplementary Appendix).

The results of the sensitivity analyses were consistent with those observed in results of the primary analysis (intent-to-treat population).

Antiviral Phase: Safety

Adverse events. The incidence and type of AEs during this phase was similar between the treatment groups in both studies (Table 2).

SAEs were more common in the eltrombopag arm (eltrombopag 20% vs placebo 15% for both studies), although incidence rates were similar when normalized to actual exposure to antiviral treatment (ENABLE-1: eltrombopag, 31.71/100 patient-years [PYs], 95% CI, 25.16–38.26; placebo, 28.45/100 PYs; 95% CI, 19.02–37.88; ENABLE-2: eltrombopag, 31.25/100 PYs; 95% CI, 25.09–37.41; placebo, 29.06/100 PYs; 95% CI, 19.70–38.42). A greater proportion of placebo patients (eltrombopag, 19%; placebo, 27%) permanently discontinued antiviral treatment because of AEs (ENABLE-1, 17% and 28%; ENABLE-2, 21% and 26%, respectively).

Cataracts (incident or worsening) were more common in eltrombopag patients for ENABLE-1 (eltrombopag, 8%; placebo, 3%) but similar between treatment arms for ENABLE-2 (eltrombopag, 7%; placebo, 6%).

HCC and death were similar between arms in each study. Malignancies were diagnosed in a similar proportion of patients in each arm (eltrombopag, 5%; placebo, 4%). Thirty-nine patients (3%) died during the course of the studies, 29 (3%) in the eltrombopag group and 10 (2%) in the placebo group, mostly from complications of chronic liver disease (Supplementary Appendix). Deaths that were attributed to investigational products including eltrombopag during the double-blind phase included 5 patients on treatment for 30 days or fewer post-treatment (treatment days during the double-blind phase: hepatic failure on day 72, death on day 38, esophageal varices hemorrhage on day 117, sudden death on day 104, and hematemesis on day 182); and 1 death at more than 30 days post-treatment (thrombocytopenia on day 383). Deaths that were attributed to TEEs are listed in Table 3, and all deaths occurring during the study are listed in the Supplementary Appendix.

Thromboembolic events. During the antiviral phase, there were 34 TEEs in 31 eltrombopag patients (3%) and 5 TEEs in 5 placebo patients (1%) (Table 3). Portal vein thrombosis (PVT) was the most common TEE in both treatment groups (n = 12, 1% eltrombopag; n = 2, <1% placebo). Summary characteristics and outcomes of

Table 2. Most Common Adverse Events During ENABLE-1 and ENABLE-2

	Open-label initiation phase[a]	
	ENABLE-1 (N = 715)	ENABLE-2 (N = 805)
Total adverse events, n (%)[b]		
Any	268 (37)	277 (34)
Headache	49 (7)	35 (4)
Fatigue	31 (4)	18 (2)
Nausea	21 (3)	21 (3)
Diarrhea	18 (3)	22 (3)
Grade ≥3 adverse events, n (%)[c]		
Any	16 (2)	27 (3)
Blood bilirubin level increased	2 (<1)	1 (<1)
Hepatic neoplasm malignant	2 (<1)	1 (<1)
Serious adverse events, n (%)[c]		
Any	8 (1)	9 (1)
Hepatic neoplasm malignant	2 (<1)	1 (<1)

	Antiviral phase[d]			
	Placebo (n = 232)	Eltrombopag (n = 449)	Placebo (n = 252)	Eltrombopag (n = 506)
Total adverse events, n (%)[e]				
Any	226 (97)	430 (96)	235 (93)	475 (94)
Anemia	78 (34)	184 (41)	90 (36)	200 (40)
Neutropenia	96 (41)	172 (38)	83 (33)	139 (27)
Fatigue	60 (26)	139 (31)	53 (21)	124 (25)
Pyrexia	53 (23)	141 (31)	61 (24)	143 (28)
Headache	47 (20)	107 (24)	50 (20)	95 (19)
Nausea	30 (13)	87 (19)	39 (15)	92 (18)
Diarrhea	27 (12)	84 (19)	24 (10)	94 (19)
Insomnia	44 (19)	79 (18)	28 (11)	72 (14)
Decreased appetite	30 (13)	78 (17)	37 (15)	94 (19)
Cough	34 (15)	77 (17)	26 (10)	64 (13)
Leukopenia	39 (17)	71 (16)	32 (13)	57 (11)
Influenza-like illness	40 (17)	70 (16)	36 (14)	100 (20)
Pruritus	27 (12)	68 (15)	34 (13)	71 (14)
Asthenia	34 (15)	66 (15)	29 (12)	87 (17)
Thrombocytopenia	86 (37)	69 (15)	84 (33)	62 (12)
Grade ≥3 adverse events, n (%)[f]				
Any	131 (56)	229 (51)	129 (51)	243 (48)
Neutropenia	49 (21)	75 (17)	40 (16)	66 (13)
Anemia	9 (4)	35 (8)	23 (9)	44 (9)
Thrombocytopenia	72 (31)	25 (6)	59 (23)	25 (5)
Hepatic neoplasm malignant	2 (<1)	5 (1)	5 (2)	12 (2)
Hyperbilirubinemia	2 (<1)	21 (5)	4 (2)	30 (6)
Leukopenia	12 (5)	22 (5)	8 (3)	23 (5)
Lymphopenia	2 (<1)	4 (<1)	5 (2)	13 (3)
Blood bilirubin level increased	5 (2)	19 (4)	1 (<1)	14 (3)
Hemoglobin level decreased	1 (<1)	4 (<1)	3 (1)	11 (2)
Weight decreased	0	6 (1)	4 (2)	8 (2)
WBC count decreased	4 (2)	9 (2)	3 (1)	10 (2)
Pyrexia	3 (1)	8 (2)	5 (2)	14 (3)
Asthenia	0	6 (1)	3 (1)	10 (2)
Neutrophil count decreased	5 (2)	7 (2)	7 (3)	3 (<1)
Platelet count decreased	6 (3)	2 (<1)	4 (2)	5 (<1)
AST level increased	4 (2)	1 (<1)	2 (<1)	1 (<1)
Ascites	3 (1)	5 (1)	0	8 (2)
Serious adverse events, n (%)[g]				
Any	35 (15)	90 (20)	37 (15)	99 (20)
Esophageal varices hemorrhage	2 (<1)	7 (2)	2 (<1)	3 (<1)
Hepatic failure	1 (<1)	7 (2)	0	3 (<1)
Hepatic neoplasm malignant	2 (<1)	6 (1)	4 (2)	14 (3)
Ascites	3 (1)	4 (<1)	1 (<1)	6 (1)

Table 2. Continued

	Antiviral phase[d]			
	Placebo (n = 232)	Eltrombopag (n = 449)	Placebo (n = 252)	Eltrombopag (n = 506)
Pneumonia	2 (<1)	4 (<1)	4 (2)	6 (1)
Gastroenteritis	1 (<1)	4 (<1)	0	0
Upper gastrointestinal hemorrhage	0	4 (<1)	0	2 (<1)
Hepatic encephalopathy	0	4 (<1)	0	8 (2)
Anemia	1 (<1)	3 (<1)	2 (<1)	3 (<1)
Neutropenia	1 (<1)	3 (<1)	0	1 (<1)
Pancytopenia	1 (<1)	3 (<1)	0	1 (<1)
Urinary tract infection	0	3 (<1)	2 (<1)	1 (<1)
Pyrexia	0	3 (<1)	1 (<1)	2 (<1)
Peritonitis bacterial	2 (<1)	3 (<1)	0	2 (<1)
Cataract	2 (<1)	2 (<1)	0	8 (2)
Gastrointestinal hemorrhage	0	2 (<1)	0	5 (<1)
Sepsis	1 (<1)	1 (<1)	0	3 (<1)

AST, aspartate aminotransferase; WBC, white blood count.
[a]Safety population.
[b]Adverse events seen in ≥3% of patients in any group are shown.
[c]Events seen in ≥2 patients in any group are shown.
[d]Double-blind safety population.
[e]Adverse events in ≥15% of patients in any group are shown.
[f]Events seen in ≥2% of patients in any group are shown.
[g]Events seen in ≥3 patients in any group are shown.

these TEEs are presented in the Supplementary Appendix. Thirty-eight percent of TEEs were detected by scheduled regular surveillance (Doppler of portal vein, ocular surveillance) and were asymptomatic.

We observed a higher incidence of TEEs during the antiviral phase of ENABLE-2; 20 patients (4%) in the eltrombopag group experienced 22 TEEs, and 1 patient (0.4%) in the placebo group experienced 1 TEE (2.5% and 1.7%, respectively, in ENABLE-1). Observation time-adjusted incidence rates were higher for the eltrombopag group than for the placebo group in ENABLE-2 (eltrombopag, 5.95/100 PYs; 95% CI, 3.34–8.56; placebo, 0.73/100 PYs; 95% CI, 0–2.17) but similar in ENABLE-1 (eltrombopag, 3.58/100 PYs; 95% CI, 1.46–5.70; placebo, 3.03/100 PYs; 95% CI, 0.06–6.00). PVT was observed in 7 (1%) eltrombopag patients but no placebo patients. No correlation with high proximal platelet counts or dose was observed, but in multivariable analyses pretreatment albumin level less than 3.5 g/dL was a risk factor (data not shown).

Hepatic decompensation. During the antiviral phase, hepatic decompensation (ascites, hepatic encephalopathy, variceal hemorrhage, or spontaneous bacterial peritonitis) was more common in eltrombopag-treated vs placebo-treated patients (both studies: eltrombopag, 10%; placebo, 5%) (Supplementary Appendix). Ascites and hepatic encephalopathy were the primary reasons for the difference (ascites: eltrombopag, 6%; placebo, 3%; encephalopathy: eltrombopag, 3%; placebo, <1%).

Hyperbilirubinemia. In total, 55% and 53% of eltrombopag-treated patients vs 24% and 25% of placebo-treated patients for ENABLE-1 and ENABLE-2, respectively, had a total bilirubin level more than 2× upper limit of normal. Consistent with eltrombopag's inhibition of UGT1A1, the primary enzyme for bilirubin glucuronidation, these increases were predominantly from indirect bilirubin (Supplementary Appendix). The median bilirubin values decreased rapidly after the end of treatment and were similar to baseline values by week 4 of follow-up evaluation. Bilirubin increases were not correlated with prolongation of the prothrombin time.

Discussion

ENABLE-1 and ENABLE-2 clearly showed eltrombopag's ability to increase platelet counts and allow initiation and maintenance of interferon-based therapy. Eltrombopag in combination with interferon-based therapy improved SVR in a difficult-to-treat group of hepatitis C patients with advanced fibrosis/cirrhosis and TCP, who have been excluded from prior studies.

In both studies, eltrombopag increased platelets to concentrations permitting antiviral therapy in more than 95% of patients whose baseline platelet counts would have made them ineligible or marginal candidates for PEG therapy. Eltrombopag treatment delayed and/or prevented PEG dose reductions and discontinuations, leading to significant increases in SVR rates compared with placebo.

The low SVR rate observed in the placebo arm (13%) was similar to that reported in previous studies in patients with portal hypertension.[16,17] Greater adherence to PEG therapy was observed in the eltrombopag group. As observed in other studies, greater adherence to PEG therapy was associated with higher SVR in ENABLE-1 and ENABLE-2

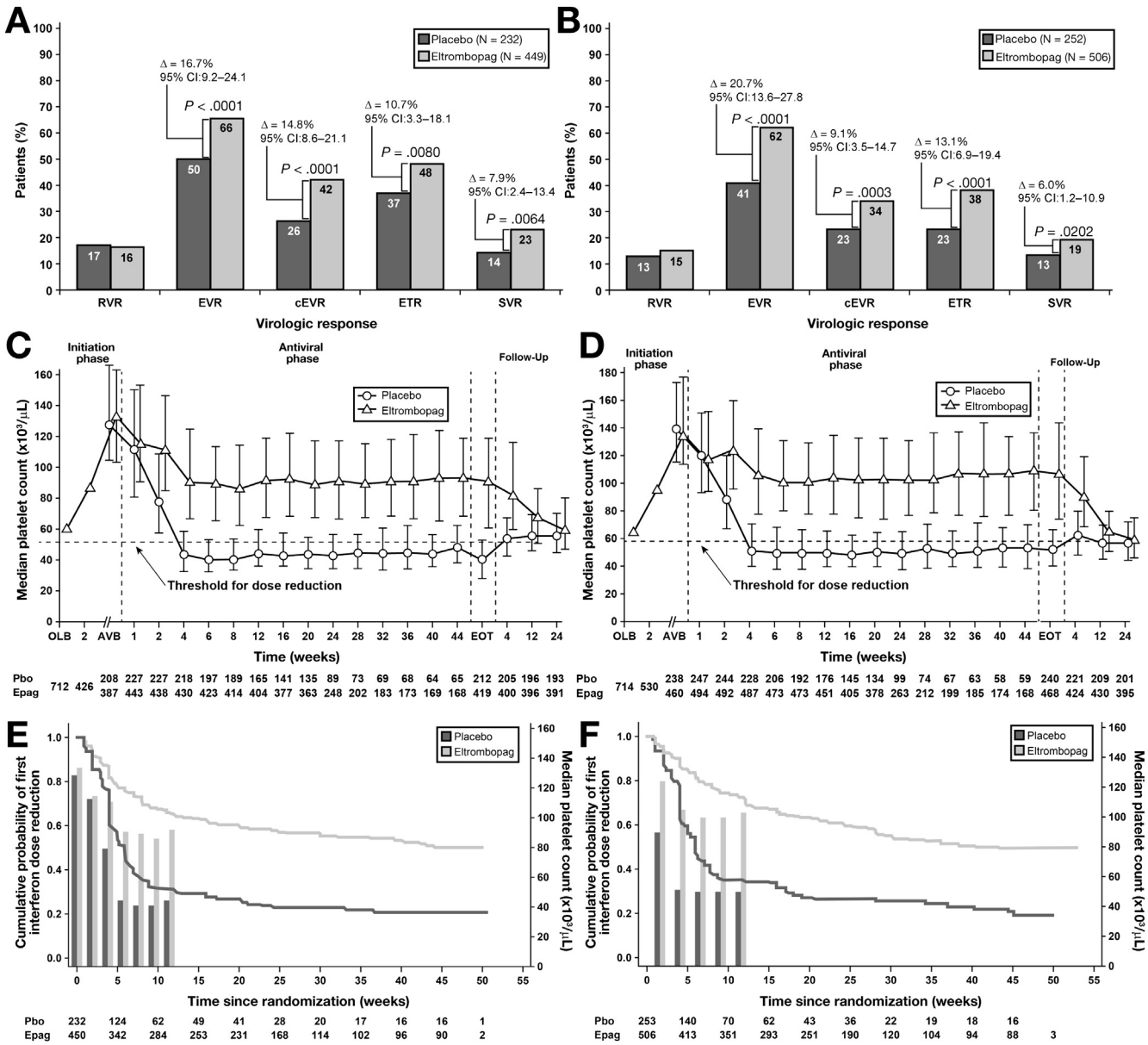

Figure 2. Efficacy during ENABLE-1 and ENABLE-2. (*A*) Virologic responses during ENABLE-1.[15] (*B*) Virologic responses during ENABLE-2.[15] (*C*) Median platelet counts during ENABLE-1; 95% of patients from the open-label initiation phase entered the antiviral phase and were randomized to receive placebo or eltrombopag (1:2) in addition to PEG-2a+RBV. (*D*) Median platelet counts during ENABLE-2; 94% of patients from the initiation phase entered the antiviral phase and were randomized to receive placebo or eltrombopag (1:2) in addition to PEG-2b+RBV. (*C* and *D*) *Bars* represent the interquartile ranges. (*E*) Correlation of platelet counts (*bars*) with time to first PEG-2a dose reduction (*lines*) in ENABLE-1. (*F*) Correlation of platelet counts (*bars*) with time to first PEG-2b dose reduction (*lines*) in ENABLE-2. Δ, percentage change; AVB, antiviral baseline; cEVR, complete EVR; Epag, eltrombopag; OLB, open-label baseline; Pbo, placebo. Some of the data in panels *A* and *B* was published previously in a recent review based on meeting abstracts.

(data not shown). Eltrombopag-treated patients showed higher EVR and ETR. In particular, the high relapse rate (50%) is consistent with previous findings and reflects the known shortcomings of PEG therapy and the insensitivity to PEG therapy in patients with cirrhosis.

The prognosis for patients with chronic HCV and platelet counts less than 100,000/μL is poor. Annualized incidence rates for HCC or clinical decompensation, death or liver transplantation, or death alone are as high as 7.9%, 7.3%, and 5.3%, respectively.[18] These incidence rates mean that 2 of 5 patients with chronic HCV and platelet counts less than 100,000/μL will have a life-threatening complication in the next 5 years, and at least 1 of 4 will die during the same period. Although not evaluated in this study, the importance of SVR on reducing morbidity in patients with hepatitis C is reflected by a reported 4- to 10-fold decrease in mortality and a 2- to 4-fold decrease in the incidences of decompensated liver disease and HCC in patients achieving SVR compared with those with persistent HCV infection who did not achieve SVR in a previous study.[19] Moreover, achieving

Table 3. Thromboembolic Events During the Antiviral Phase

	ENABLE-1		ENABLE-2	
	Eltrombopag (n = 449)	Placebo (n = 232)	Eltrombopag (n = 506)	Placebo (n = 252)
Number of events, n (%)	12	4	22	1
Serious	3 (1)	2 (1)	9 (2)	0
Leading to withdrawal from study	0	1 (<1)	7 (1)	0
DAIDS grade 3/grade 4	6 (1)	2 (1)	14 (3)	0
Number of patients with event, n (%)	11 (2)	4 (2)	20 (4)	1 (<1)
Portal venous thromboses	5 (1)	2 (1)	7 (1)	0
Deep venous thromboses	1 (<1)	0	5 (1)	0
Thrombosis	2 (<1)	0	1 (<1)	0
Acute myocardial infarction	1 (<1)	0	1 (<1)	0
Angina unstable	0	1 (<1)	1 (<1)	0
Ischemic stroke	1 (<1)	0	1 (<1)	0
Retinal vascular disorder	2 (<1)	1 (<1)	4 (1)	1 (<1)
Pulmonary embolism	-	-	1 (<1)	0
Femoral artery occlusion	-	-	1 (<1)	0
Outcome of events, n (%)[a]				
Recovered/resolved	6 (55)	2 (50)	12 (60)	1 (100)
Fatal	0	1 (25)	2 (10)	0

DAIDS, Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events.
[a]The denominator for percentages in the categories for outcomes of events are the number of patients with events for each treatment group in ENABLE-1 or ENABLE-2.

an undetectable HCV-RNA level or SVR before liver transplantation can improve outcomes after transplantation by avoiding HCV recurrence.[19]

Since the initiation of the ENABLE studies, the standard of care for treatment of chronic HCV genotype 1 has progressed to a combination of a protease inhibitor (telaprevir or boceprevir), PEG, and RBV.[20] This triple therapy improves overall SVR rates, including for patients with cirrhosis, but SVR rates are lower for patients with cirrhosis compared with patients without cirrhosis.

Hepatic decompensation, primarily ascites and hepatic encephalopathy, was observed at a higher rate in patients treated with eltrombopag and PEG+RBV. In both studies, eltrombopag-treated patients had significantly longer median exposure to PEG, which likely explains the observed differences in hepatic function because interferon has been associated with abnormalities in liver chemistry values and with hepatic decompensation in patients with advanced liver disease.

Although there are no studies comparing the 2 treatment regimens, interim results of an ongoing French cohort study (Compassionate Use of Protease Inhibitors in viral C Cirrhosis [CUPIC] trial) with triple therapy using PEG+RBV and a protease inhibitor (292 patients on triple therapy with telaprevir and 205 patients on boceprevir) in genotype 1 cirrhosis patients reported grade 3/4 liver decompensation in 12 (2.4%) patients.[21] The demographic profile of the patients was somewhat similar to those in the ENABLE studies in that they all had cirrhosis, but the majority were compensated. The mean platelet count at baseline was 152,000/μL (range, 18,000–604,000/μL) for telaprevir and 146,000/μL (range, 33,900–346,000/μL) for boceprevir. The investigators reported SAEs in 45.2% and 32.7%, respectively, and discontinuations because of SAEs in 14.7% and 7.3%, respectively. There were 24 grade 3/4 infections. Six deaths occurred during the study, most of which were related to severe infection. Grade 3/4 hepatic decompensation was reported in 6 patients in each treatment group. These results were similar to what we reported in a much larger and more advanced population in the ENABLE trials and confirm the need for careful monitoring and treatment of patients with cirrhosis and thrombocytopenia only by experienced clinicians.

The second major safety finding was that a higher proportion of eltrombopag-treated patients experienced TEEs. In contrast to ENABLE-1, both total TEEs and PVTs (a known complication of cirrhosis) were observed more commonly in ENABLE-2, although in this study placebo-treated patients had lower than expected PVT incidence.[22] Low albumin levels appeared to be a risk factor for TEEs. The vast majority of TEEs resolved either spontaneously or after anticoagulation treatment, without requiring eltrombopag discontinuation and without interfering with the antiviral therapy. It is recommended that patients being considered for eltrombopag treatment be evaluated for TEE risk and be monitored during treatment, as was performed in this study.

This study had several limitations. When dose reductions/discontinuations were required, investigators were instructed to follow the current local prescribing information. However, many experienced clinicians do not reduce the dose of PEG in accordance with product labels, which could significantly bias the results in favor of the eltrombopag arms because treatment may have stopped sooner than what is done in routine practice. Because this was an international trial, we followed the recommendations

in the prescribing information for the PEGs, despite the possibility of lower thresholds being used in practice. However, clinicians should implement PEG dose reductions/discontinuations at platelet thresholds at which they are comfortable.

The results of ENABLE-1 and ENABLE-2 suggest that eltrombopag can be used safely in patients with HCV-related liver disease and TCP. Eltrombopag increased platelets to levels sufficient for initiation and maintenance of interferon-based antiviral therapy for patients who otherwise would be ineligible or marginal candidates, resulting in clinically meaningful and statistically significant increases in SVR. In patients with cirrhosis and TCP, eltrombopag should be evaluated in the setting of newer treatment regimens with triple therapies or quadruple therapies, in which an incremental benefit in SVR may be achieved if thrombocytopenia is avoided or adequately treated.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at http://dx.doi.org/10.1053/j.gastro.2013.10.012.

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Conflicts of interest

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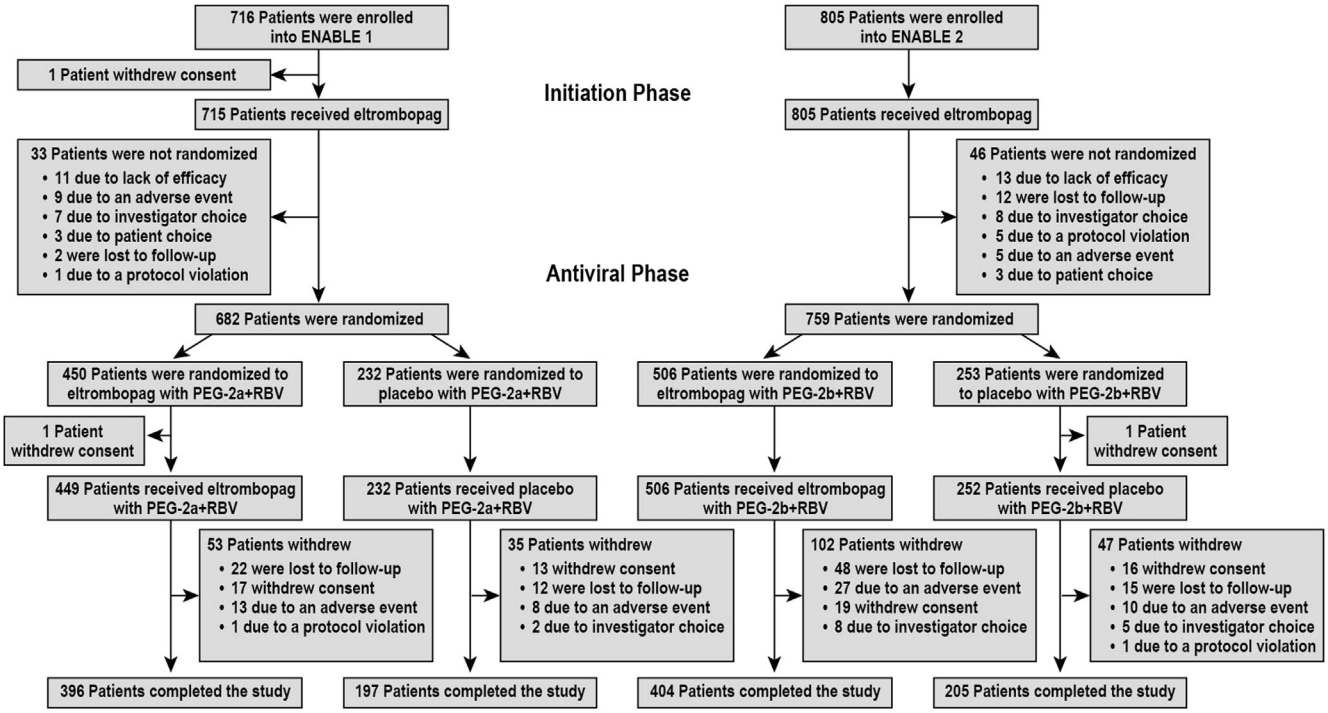

Supplementary Figure 1. Patient flow for ENABLE-1 and ENABLE-2.