Supplemental Appendix

1. Protocol Definition of Sustained Virologic Response

A patient has a sustained virologic response if:

1. The patient is a responder at the end of treatment and all subsequent planned visits through 24 weeks after completing treatment. Twenty-four weeks after completing treatment corresponds to Week 48 for genotype 2/3, and Week 72 for nongenotype 2/3.

2. If a patient has a positive HCV RNA (“blip”) between 2 visits with undetectable HCV RNA, then the patient will be considered a sustained virological responder provided that the detectable HCV RNA is of the same order of magnitude as the limit of detection.

Otherwise, a patient will be considered a nonresponder with respect to SVR.

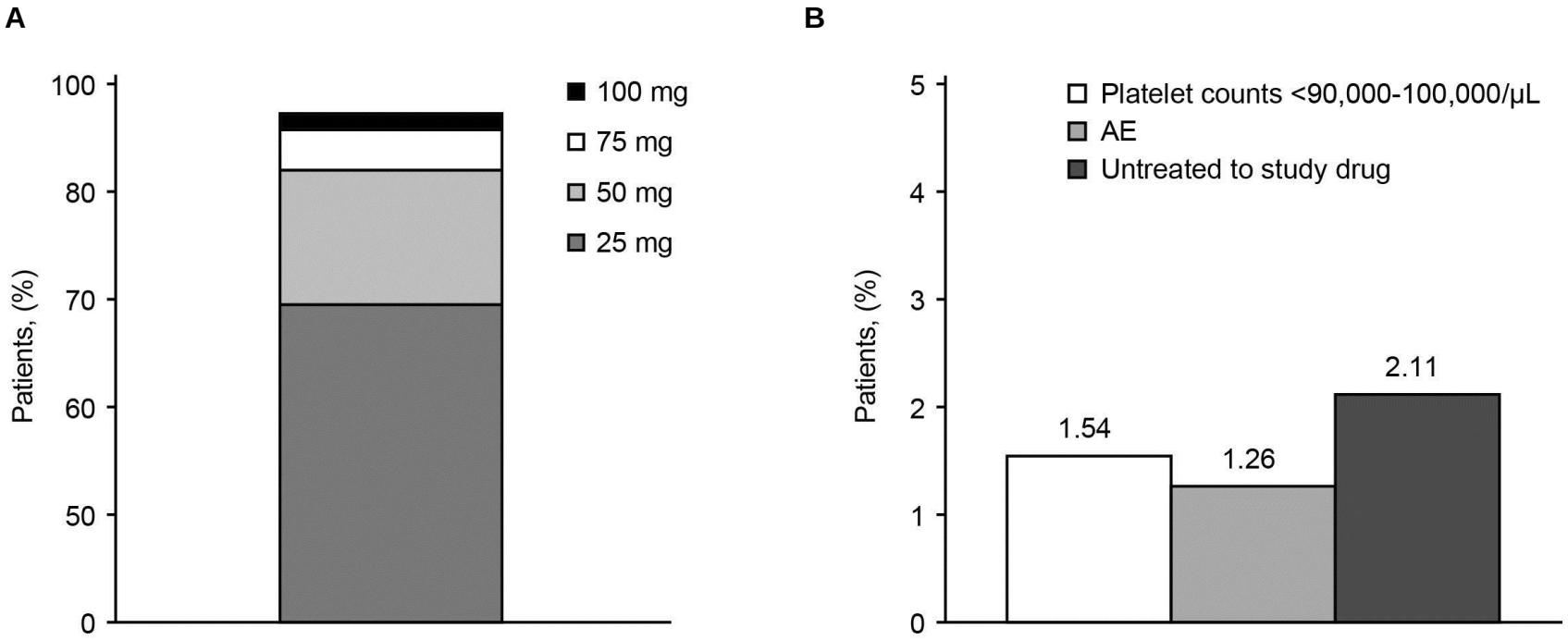
2. Exclusion Criteria

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 *and* any additional 2 risk factors; hepatitis B virus or human immunodeficiency virus infection; any condition involving active bleeding or need for anticoagulation; and history of clinically significant bleeding from esophageal or gastric varices.

3. Adverse Events of Particular Interest

Adverse events (AEs) of particular interest included thromboembolic events, hepatobiliary laboratory abnormalities, malignancies, and cataracts (incident or worsening). These events were identified through clinical review of all reported AEs.

4. Doses Enabling Patients to Reach Platelet Count Thresholds (A) and Reasons for Discontinuation (B).*



AE, adverse event.
*Few patients experienced and serious adverse events, and there were 2 fatal adverse events; hepatorenal syndrome and hepatic neoplasm malignant. Headache was the only adverse event that occurred in >5% of patients (n=84, 6%).

5. Forest Plots

Subgroup analyses of differences in sustained virologic response rates. The magnitude and direction of SVR rate differences in eltrombopag- versus placebo-treated patients were similar across all subgroups except age, which likely reflects the very small sample size of the ≥65-year age group.

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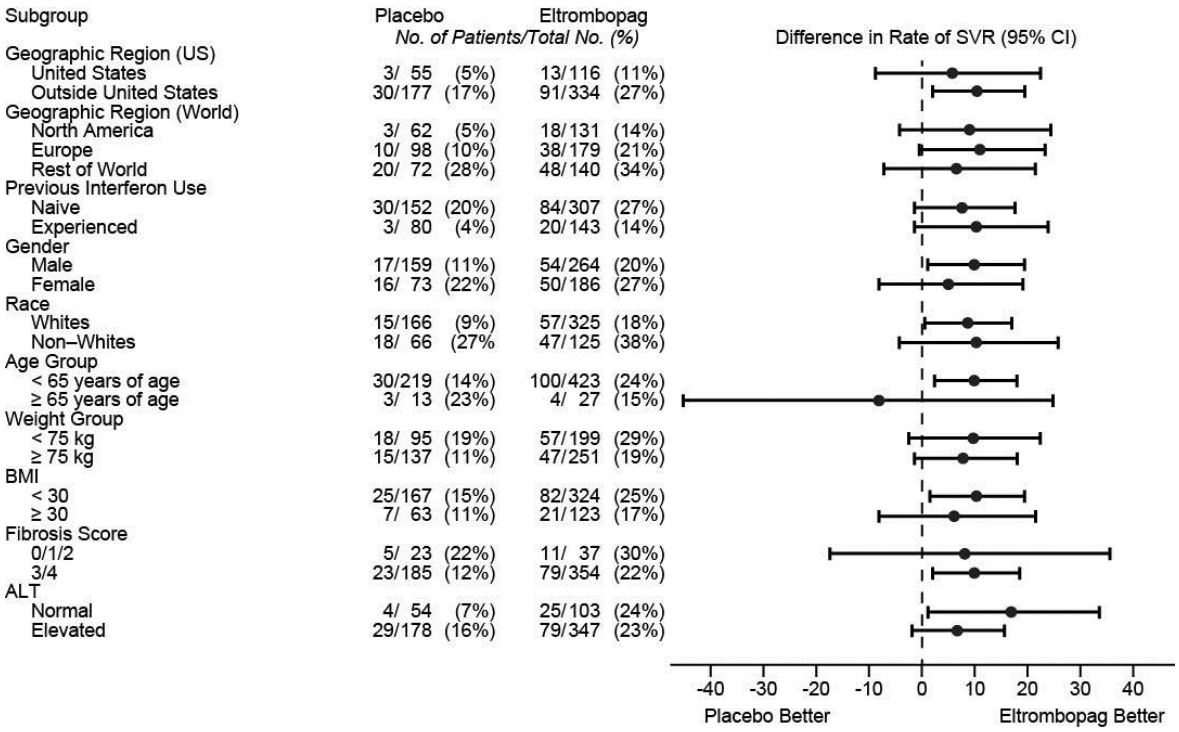

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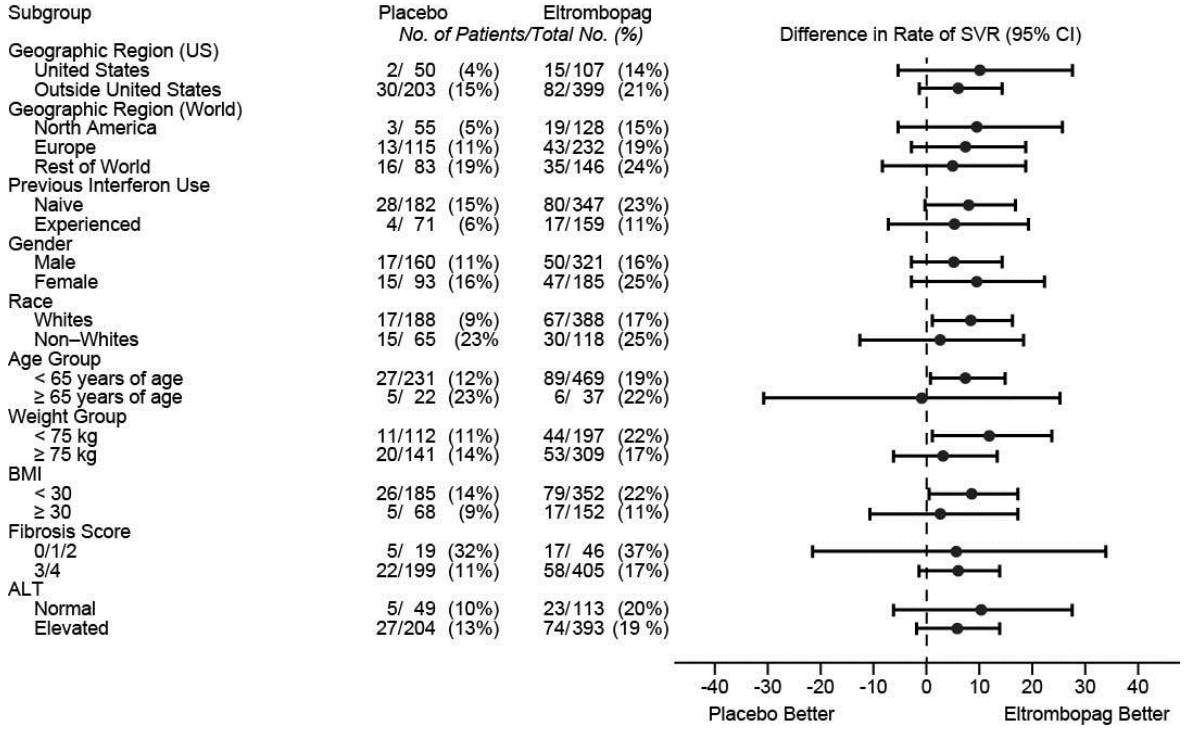


ALT, alanine aminotransferase; BMI, body mass index; SVR, sustained virologic response.

6. PEG Exposure (Safety Population)

Exposure to interferon alfa-2a **ENABLE-1**	Placebo (N=232)	Eltrombopag (N=449)	Percent difference
Mean weekly dose, μg	(n=231)	(n=444)	
Mean (SD)	139.56 (34.631)	161.68 (26.013)	16
Median (min-max)	144.59 (6.9-210)	172.80 (41.0-265.3)	20
Cumulative dose, μg	(n=231)	(n=446)	
Mean (SD)	3320.1 (2383.79)	5029.8 (2558.06)	51
Median (min-max)	2700.0 (130-8820)	4320.0 (180-8820)	60
Exposure to interferon alfa-2b **ENABLE-2**	Placebo (N=252)	Eltrombopag (N=506)	Percent difference
Mean weekly dose, μg	(n=252)	(n=505)	
Mean (SD)	94.27 (28.859)	109.80 (29.372)	16
Median (min-max)	92.62 (32.0-165.3)	109.17 (0-372.0)	18
Cumulative dose, μg	(n=252)	(n=506)	
Mean (SD)	2111.0(1682.50)	3299.4 (1812.73)	56
Median (min-max)	1700.0 (100-7300)	2880.0 (0-7206)	69
Integrated exposure to interferon **ENABLE-1 and ENABLE-2**	Placebo (N=484)	Eltrombopag (N=955)	Percent difference
Cumulative duration,* days	(n=484)	(n=951)	
Mean (SD)	167.2 (113.35)	214.9 (101.51)	28
Median (min-max)	162.5 (7-364)	183.0 (7-371)	13
Days on study drug	(n=484)	(n=951)	
Mean (SD)	170.7 (114.17)	217.5 (101.86)	27
Median (min-max)	168.0 (7-364)	186.0 (7-371)	11

*Cumulative duration includes only the days a patient took treatment (adding 6 days for each dosing stage; Excludes dose interruptions.

7. Deaths

Time of Death Study Day (Days Post-treatment)[a]	Fatal Adverse Event(s)	Relation to Investigational Product
Placebo Group: ≤30 days post-treatment		
118 (6)	Acinetobacter bacteremia	No
50 (9)	Lung neoplasm malignant Multi-organ failure Sepsis	No No No
220 (25)	Death	No
244 (-1)	Esophageal varices hemorrhage	No
Placebo Group: >30 days post-treatment		
318 (42)	Hepatic failure Hypoglycemic coma Renal failure	No No No
635 (434)	Hepatic neoplasm malignant	No
144 (43)	Hepatic neoplasm malignant Portal vein thrombosis	No No
98 (35)	Peritonitis bacterial	No
210 (174)	Multi-organ disorder	No
102 (31)	Cardio-respiratory arrest Hepatic neoplasm malignant	No No
Eltrombopag Group: ≤30 days post-treatment		
128 (11)	Respiratory failure	No
100 (16)	Ascites Hepatorenal syndrome	No No
164 (9)	Esophageal varices hemorrhage	No
72 (12)	Hepatic failure	All 3 IPs
38 (-6)	Death	All 3 IPs
186 (19)	Hepatic failure Renal failure Sepsis	No No No
368 (11)	Myocardial infarction	No
171 (-19)[b]	Gastrointestinal hemorrhage	No
196 (21)	Pneumonia	Peginterferon
117 (-2)	Esophageal varices hemorrhage	All 3 IPs
104 (-6)	Sudden death	DB medication
127 (-2)	Death	No
216 (14)	Cardiac arrest Cerebrovascular accident	No No
206 (-6)	Hepatic encephalopathy Sepsis	PEG PEG
161 (-5)	Abdominal sepsis	PEG
333 (12)	Gastrointestinal hemorrhage Generalized edema Hepatic failure Multi-organ failure	No No No No

	Peritonitis bacterial Renal failure	No No
133 (-5)	Upper gastrointestinal hemorrhage	PEG+RBV
94 (24)	Upper gastrointestinal hemorrhage	No
182 (21)	Hematemesis	All 3 IPs
Eltrombopag Group: >30 days post-treatment		
470 (316)	Hepatic neoplasm malignant	No
255 (36)	Meningitis cryptococcal	No
492 (128)	Ascites Encephalopathy	No No
149 (44)	Cerebellar hemorrhage	No
358 (58)	Hepatorenal syndrome	No
144 (64)	Hepatic encephalopathy Pneumonia	No No
357 (136)	Hepatic cirrhosis	No
399 (160)	Mechanical ileus	No
222 (61)	Respiratory failure	PEG
383 (163)	Thrombocytopenia	All 3 IPs

IP, investigational products; PEG, pegylated interferon; RBV, ribavirin;
[a]Interferon treatment was dosed weekly. Therefore, 6 days was added to interferon treatment stop date.
[b]The investigator reported that Patient512 died on Study Day 171 and reported Study Day 184 as the stop date of interferon treatment.
NOTE: Five patients died following completion of the study; their deaths were not captured in the electronic clinical report form and so are not included in this table. These patients were Patient 311: NSCLC, and Patient 4217 and Patient 2557, HCC, in ENABLE-1; and Patient 3300, HCC and Patient 3500, hepatorenal syndrome with septic shock, both in ENABLE-2.

8. Patients with Adjudicated Thromboembolic Adverse Events During the Antiviral Phase

TEE (Preferred term)	DAIDS Grade/ SAE	Platelet Count ($\times 10^3/\mu L$)/ Study Day	Time to Onset (Study Day)[a]	Action Taken	Outcome
Placebo					
Retinal vascular disorder (Retinal vein occlusion)	Grade 1/No	26/200	163	Dose not changed	Recovered/resolved
Transient ischemic attack[d]	Grade 2/Yes	55/239	301	NA	Recovered/resolved
Angina unstable	Grade 3/Yes	44/120	108	IP withdrawn	Recovered/resolved
PVT	Grade 1/No	32/353	334	NA	Not recovered/not resolved
Retinal ischemia	Grade 1/No	65/82	82	IP withdrawn	Recovered/resolved
PVT[b]	Grade 4/Yes	76/92	69	IP withdrawn	Fatal
Eltrombopag					
PVT[b]	Grade 2/No	46/87	99	Dose not changed	Recovered/resolved
Cerebrovascular accident[d]	Grade 3/Yes	54/373	418	NA	Recovered/resolved
PVT[d]	Grade 2/No	52/369	369	NA	Not recovered/not resolved
DVT	Grade 4/Yes	148/87	91	IP withdrawn	Recovered/resolved
Femoral artery occlusion	Grade 3/Yes	92/212	212	Dose interrupted	Recovered/resolved
Myocardial infarction	Grade 4/Yes	59/358	368	NA	Fatal
Retinal infarction	Grade 1/No	77/116	116	Dose not changed	Recovered/resolved
Retinal infarction	Grade 1/No	81/68	76	Dose not changed	Recovered/resolved
PVT[d]	Grade 1/No	30/407	407	NA	Not recovered/not resolved
Ischemic stroke (CVA) Thrombosis	Grade 4/No Grade 4/No	70/113 70/113	118 126	NA NA	Not recovered/not resolved Not recovered/not resolved
DVT DVT	Grade 3/No Grade 3/No	136/72 136/72	85 103	NA NA	Recovered/resolved Not recovered/not resolved
PVT[c,d]	Grade 1/No	69/582	580	NA	Not recovered/not resolved

TEE (Preferred term)	DAIDS Grade/ SAE	Platelet Count ($\times 10^3/\mu L$)/ Study Day	Time to Onset (Study Day)[a]	Action Taken	Outcome
PVT[b]	Grade 2/No	118/148	148	IP withdrawn	Recovered/resolved with sequelae
PVT[c,d]	Grade 4/Yes	43/200	203	NA	Recovering/resolving
PVT	Grade 2/No	74/155	179	IP withdrawn	Not recovered/not resolved
Retinal vein thrombosis	Grade 3/Yes	129/71	78	IP withdrawn	Recovered/resolved with sequelae
PVT	Grade 2/No	36/91	91	Dose not changed	Recovered/resolved
Pulmonary embolism	Grade 2/No	76/261	269	NA	Not recovered/not resolved
Retinal vascular disorder (Retinal vein occlusion)	Grade 1/Yes	64/29	29	Dose not changed	Recovered/resolved
Pulmonary embolism[d]	Grade 3/Yes	50/476	507	NA	Recovered/resolved
Venous thrombosis	Grade 3/No	181/30	32	IP withdrawn	Recovered/resolved
PVT[c]	Grade 2/No	128/190	199	Dose not changed	Recovered/resolved
DVT	Grade 4/No	179/148	162	Dose not changed	Recovered/resolved with sequelae
Mesenteric vein thrombosis[d]	Grade 3/No	55/296	301	NA	Recovered/resolved
PVT[d]	Grade 3/No	55/296	309	NA	Recovered/resolved
Mesenteric vein thrombosis[b,c]	Grade 3/Yes	104/50	71	NA	Recovered/resolved
PVT[b,c]	Grade 3/Yes	104/50	71	NA	Recovered/resolved
Transient ischemic attack[d]	Grade 1/No	95/414	435	NA	Recovered/resolved
PVT[c]	Grade 3/No	94/128	128	Dose not changed	Recovered/resolved
PVT[c]	Grade 4/No	138/225	247	NA	Recovered/resolved with sequelae
PVT[b,c]	Grade 3/No	155/127	127	IP withdrawn	Recovered/resolved with sequelae
PVT[c,d]	Grade 2/No	64/358	358	NA	Not recovered/not resolved
Cerebrovascular accident	Grade 4/Yes	108/189	213	NA	Fatal
Retinal vein occlusion	Grade 1/No	198/71	82	Dose not changed	Not recovered/not resolved
Thrombosis	Grade 1/No	129/281	283	Dose not changed	Not recovered/not resolved

TEE (Preferred term)	DAIDS Grade/ SAE	Platelet Count ($\times 10^3/\mu L$)/ Study Day	Time to Onset (Study Day)[a]	Action Taken	Outcome
Acute myocardial infarction	Grade 4/Yes	123/127	148	Dose interrupted	Recovered/resolved
PVT[b]	Grade 1/No	89/246	260	NA	Not recovered/not resolved
Venous thrombosis (limb)	Grade 2/Yes	126/35	35	IP withdrawn	Recovered/resolved
Angina unstable	Grade 3/Yes	127/95	115	IP withdrawn	Recovered/resolved
DVT	Grade 3/Yes	97/197	211	IP withdrawn	Recovered/resolved
Retinal vascular occlusion	Grade 1/No	130/77	85	Dose interrupted	Recovered/resolved
PVT	Grade 3/No	105/162	179	NA	Not recovered/not resolved

CVA, cerebrovascular accident; DAIDS, Division of AIDS; DVT, deep vein thrombosis; IP, investigational product; NA, not applicable; PVT, portal vein thrombosis; TEE, thromboembolic event; SAE, serious adverse event.
[a]Placebo: number of days from first dose of DB treatment; eltrombopag: number of days from first dose of OL eltrombopag treatment.
[b]PVT event was symptomatic based on medical review of patient's data.
[c]PVT event was treated based on medical review of patient's data.
[d]Event occurred >30 days post-treatment for any IP.

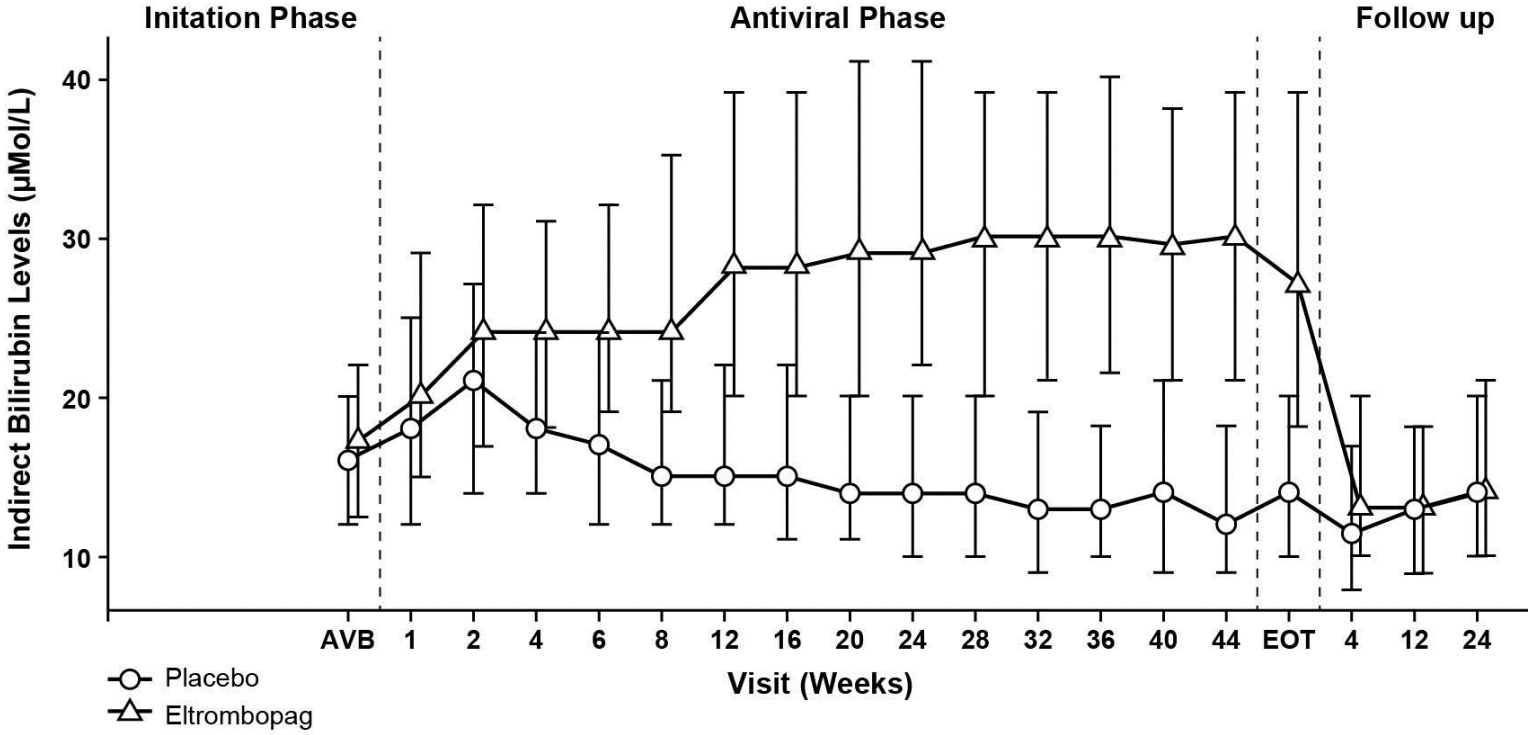
9. Events Suggestive of Hepatic Decompensation During the Antiviral Phase (Double-Blind Safety Population)

	Placebo (N=484)	Eltrombopag (N=955)
Number (%) of patients with events	**24(5)**	**92(10)**
Serious	12(50)	46 (50)
Drug-related	7 (29)	35(38)
Leading to withdrawal from study	3(13)	9 (10)
Grade 3/4	9(38)	45(49)
Fatal	2(8)	7(8)
Ascites	14 (3)	55 (6)
Hepatic encephalopathy	4 (<1)	24 (3)
Variceal hemorrhage	4 (<1)	13 (1)
Spontaneous bacterial peritonitis	2 (<1)	8 (<1)
Other[a]	1 (<1)	15 (2)
Time to event (days)		
Mean (SD)	160.00 (85.19)	156.78 (84.00)
Median (min-max)	145.50 (42-365)	150.00 (36-378)
Action taken, n (%)		
Investigational product withdrawn	6(25)	29(32)
Dose reduced	0	1 (<1)
Dose increased	0	0
Dose not changed	10 (42)	37(40)
Dose interrupted	2 (8)	7(8)
Not applicable (post-treatment)	8(33)	37(40)
Number of events (%)	**30**	**135**
Recovered/resolved	15(63)	66(72)
Recovering/resolving	0	3(3)
Not recovered/not resolved	5(21)	17(18)
Recovered/resolved with sequelae	3(13)	8(9)
Fatal	2(8)	7 (8)

Min-max, minimum and maximum values; SD, standard deviation.
[a]Other decompensation events included hepatic failure (9 eltrombopag, 1 placebo), hepatic cirrhosis (2 eltrombopag, 1 placebo), hepatorenal syndrome (1 eltrombopag), hepatitis alcoholic (1 eltrombopag), hepatic function abnormal (1 eltrombopag), and liver disorder (1 eltrombopag).

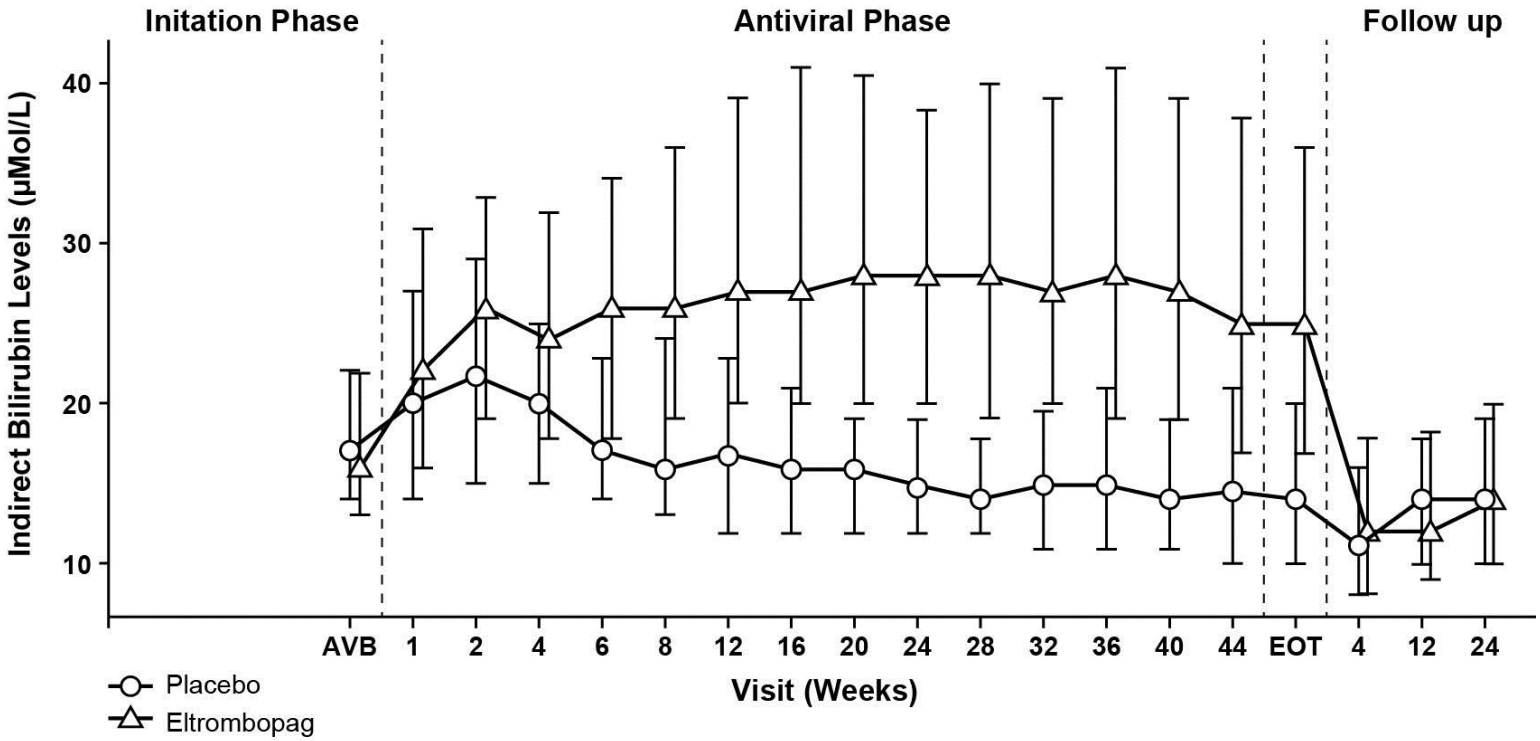
10. Median (Interquartile Range) Indirect Bilirubin Levels During the Antiviral Phase

ENABLE-1



Number of Patients																			
Placebo	210	223	225	219	196	185	162	140	131	87	72	67	66	63	65	209	202	196	194
Eltrombopag	400	431	428	427	414	405	395	367	359	242	199	179	172	168	165	407	400	389	391

ENABLE-2



AVB, antiviral baseline; EOT, end of treatment.

11. Summary of the Results from Patients Who Discontinued from the Open-Label Phase

ENABLE-1
Of the 33 patients who prematurely discontinued open-label (OL) eltrombopag treatment and were not randomized to double-blind (DB) treatment, 18 patients had at least 1 follow-up visit. The median platelet count for these patients post-treatment (Week 12 and 24 follow-up visits) was 38,000/μL, which was similar to the Day 1 median platelet count for these patients (41,000/μL). Overall, 15/33 patients completed their 4-, 12-, and/or 24-week follow-up visits. Of these 15 patients, 7 experienced an AE that started 1 to 30 days after stopping OL eltrombopag. Two events were reported as serious AEs (SAEs) (1 patient had gastric hemorrhage, Grade 4; and 1 patient had malignant hepatic neoplasm, Grade 4). Full clinical narratives are available for these patients.

ENABLE-2
Of the 46 patients who prematurely discontinued OL eltrombopag treatment and were not randomized to DB treatment, 20 patients had at least 1 follow-up visit. The median platelet count for these patients post-treatment (Week 12 and 24 follow-up visits) was 37,000/μL, which was similar to the Day 1 median platelet count for these patients (38,000/μL). Overall, 14/46 patients completed their 4-, 12-, and/or 24-week follow-up visits. Of these 14 patients, 12 patients experienced a total of 21 AEs that started 1 to 30 days after stopping OL eltrombopag. Two events were reported as SAEs (suicidal ideation, Grade 4, onset with resolution on Study Day 10; fatal event of hepatorenal syndrome, Grade 4, onset and patient death on Study Day 46). Full clinical narratives are available for these patients. The remaining events were Grade 1 (12 events), Grade 2 (6 events), or Grade 3 (1 event in 1 patient of prothrombin time prolonged, onset Day 14, resolved Day 49).

12. Clinical Events Committee Adjudicated Cataract Events During the Double-Blind Phase (Safety Population)

Preferred Term	Placebo (N=484)	Eltrombopag (N=955)
Number (%) of patients		
Any event	24 (5)	74 (8)
Patients with progression of pre-existing cataract at baseline	12 (2)	38 (4)
Bilateral incidence	8 (2)	21 (2)
Unilateral incidence	4 (<1)	17 (2)
Patients with an incident cataract	12 (2)	36 (4)
Bilateral progression	5 (1)	23 (2)
Unilateral progression	7 (1)	13 (1)