Common Drug Review
Clinical Review Report

August 2015

Drug	eltrombopag olamine (Revolade) 25 mg and 50 mg tablets
Indication	To increase platelet counts in thrombocytopenic patients with chronic hepatitis C virus (HCV) infection to allow the initiation and maintenance of interferon-based therapy.
Listing request	To increase platelet counts in thrombocytopenic patients with chronic HCV infection due to genotype 2 or 3 to allow the initiation and maintenance of interferon-based therapy.
Manufacturer	GlaxoSmithKline Inc.

This review report was prepared by the Canadian Agency for Drugs and Technologies in Health (CADTH). In addition to CADTH staff, the review team included a clinical expert in hepatology who provided input on the conduct of the review and the interpretation of findings.

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ABBREVIATIONS

AE	adverse event
ALT	alanine aminotransferase
AVT	antiviral therapy
CDR	CADTH Common Drug Review
CASL	Canadian Association for the Study of the Liver
CLDQ	Chronic Liver Disease Questionnaire
CLDQ-HCV	Chronic Liver Disease Questionnaire–Hepatitis C Virus
cEVR	complete early virologic response
CI	confidence interval
DB	double-blind
ELT	eltrombopag
ETR	end of treatment response
EVR	early virologic response
HBV	hepatitis B virus
HCV	hepatitis C virus
HRQoL	health-related quality of life
IFN	interferon
ITT	intention-to-treat
IVRS	interactive voice response system
LOCF	last observation carried forward
NA	not applicable
NR	not reported
OR	odds ratio
PEG-IFN	pegylated interferon
PL	placebo
PP	per-protocol
RBV	ribavirin
RCT	randomized controlled trial
RNA	ribonucleic acid
RVR	rapid virologic response
SAE	serious adverse event
SD	standard deviation
SF-36	Short-Form (36) Health Survey
SVR	sustained virologic response
SVR12	sustained virologic response at 12 weeks
TCP	thrombocytopenia

EXECUTIVE SUMMARY

Introduction

Hepatitis C virus (HCV) infection is estimated to affect nearly 245,000 individuals in Canada. The prevalence of thrombocytopenia (TCP) in patients with chronic HCV infection is reported to range between 0.16% and 45.4%,[1] although it may be as high as 80% in patients with cirrhosis.[2] While TCP itself is rarely life-threatening, it complicates the medical management of patients with HCV infection as it may preclude patients from being initiated or maintained on antiviral therapy (AVT). Further reductions in platelet counts are anticipated during pegylated interferon- (PEG-IFN) and ribavirin- (RBV) based AVT due to the myelosuppressive effects of PEG-IFN. Currently, the only treatment option is to reduce the dose of PEG-IFN in response to platelet levels.[3] While this is a common approach in clinical practice, it is burdened by decreased likelihood of obtaining a sustained virologic response (SVR) due to reduced treatment effectiveness,[4] and patients who discontinue AVT are less likely to achieve SVR compared with patients who complete a full course of treatment (Appendix 6).

Eltrombopag is an oral, small molecule thrombopoietin receptor (TPO-R) agonist that stimulates thrombopoiesis, thus inducing proliferation and differentiation of megakaryocytes from bone marrow progenitor cells to platelets.[5] It is available as 25 mg and 50 mg oral tablets and the recommended dose is 25 mg to 100 mg once daily, adjusted as necessary, to achieve the target platelet count to initiate or maintain AVT.[5] There is currently no other approved intervention in Canada specifically indicated for treatment of TCP associated with HCV infection.

Indication under review
To increase platelet counts in thrombocytopenic patients with chronic HCV infection to allow the initiation and maintenance of IFN-based therapy.
Listing criteria requested by manufacturer
To increase platelet counts in thrombocytopenic patients with chronic HCV infection due to genotype 2 or 3 to allow the initiation and maintenance of IFN-based therapy.

The objective of this review was to perform a systematic review was undertaken to evaluate the beneficial and harmful effects of eltrombopag 25 mg and 50 mg tablets used in combination with PEG-IFN and RBV to increase platelet counts in patients with TCP and chronic HCV infection to allow the initiation and maintenance of IFN-based therapy.

Results and Interpretation

Included Studies

Three prospective, multi-centre, double-blind (DB), randomized trials were included in the review, all of which were placebo-controlled, superiority trials (ENABLE 1 [n = 682], ENABLE 2 [n = 759], and TPL102357 [n = 74]). The objective of all three trials was to assess the efficacy and safety of eltrombopag to increase platelets to sufficient levels for the initiation and maintenance of PEG-IFN and RBV therapy in patients with TCP associated with chronic HCV infection. All three trials incorporated an initiation, pre-AVT phase (Part 1) of two weeks to nine weeks (ENABLE 1 and ENABLE 2) and four weeks (TPL102357) and a DB AVT phase (Part 2) of 24 weeks to 48 weeks (ENABLE trials) and 8 weeks to 16 weeks (TPL102357). In Part 2 of the ENABLE trials, patients were randomized 2:1 to eltrombopag 25 mg to 100 mg daily or matched placebo, whereas in TPL102357 patients were randomized 1:1:1:1 to

eltrombopag 30 mg, 50 mg, or 75 mg daily, or matched placebo at study entry. The trials differed in the primary outcome, as the ENABLE trials evaluated achievement of SVR and the TPL102357 study assessed platelet response. The trials included patients who were primarily Caucasian males in their early 50s. Most patients were infected with HCV genotype 1, followed by genotype 2 or 3, and had TCP associated with chronic HCV infection and mainly compensated liver disease.

A key limitation of the trials was the requirement for PEG-IFN and RBV dose adjustments and discontinuations to be done in accordance with the product's approved labelling. It is acknowledged that this was unavoidable due to the requirement to ensure patients were not exposed to unnecessary risk and to comply with regulatory requirements. Nonetheless, the clinical expert consulted for this review advised that this is not consistent with clinical practice in Canada, as experienced physicians will initiate and maintain AVT at much lower platelet counts than recommended in the labelling. This may have overestimated efficacy results in favour of eltrombopag, as in practice, patients would have been initiated and maintained on AVT at lower platelet levels than in the trials. The efficacy of eltrombopag could also have been overestimated due to the fact that only responders in Part 1 were eligible for AVT in Part 2, as those who did not respond in accordance with the pre-specified platelet threshold did not continue on to the DB portion of the studies. In addition, safety outcomes may have been underestimated in favour of placebo, because AVT in the placebo groups was stopped sooner than is normally done in clinical practice, resulting in less patient exposure to IFN and RBV in those placebo groups. Furthermore, the safety assessment was seriously compromised by the high dropout rate in the placebo groups, especially in TPL102357, where 78% of placebo patients dropped out of Part 1.

Efficacy

The primary outcome in the ENABLE trials was achievement of SVR, which is stated to be the primary objective of HCV therapy.[6] The proportion of patients achieving SVR was statistically significantly greater with eltrombopag compared with placebo in the ENABLE 1 (23% versus 14%; $P = 0.0064$) and ENABLE 2 (19% versus 13%; $P = 0.0202$) trials. These findings are supported by statistically significantly greater proportions of eltrombopag-treated patients also achieving early virologic response (EVR), complete early virologic response (cEVR), end of treatment response (ETR), and SVR at 12 weeks (SVR12) compared with placebo. The TPL102357 trial did not include SVR as an outcome.

The manufacturer has requested listing eltrombopag only for patients with HCV genotype 2 or 3; however, the SVR results support similar efficacy of eltrombopag across all genotypes. The proportions of patients with HCV genotype 2 or 3 who achieved SVR with eltrombopag were numerically greater than with placebo in both ENABLE 1 (35% versus 24%) and ENABLE 2 (18% versus 10%), as were patients with non-genotype 2 or 3 (i.e., 18% versus 10% and 13% versus 7%, respectively). Statistical testing showed no difference in attainment of SVR due to HCV genotype 2 or 3 or non-genotype 2 or 3 compared with the overall study population. Similar findings of no difference were reported for the other strata pertaining to baseline platelet count and HCV ribonucleic acid (RNA) levels. The trials were not powered to make comparisons between strata.

Bleeding events were infrequent across the three trials. In the ENABLE trials, ≤ 2% of patients had variceal bleeding in any of the treatment groups. There were no reports of variceal bleeding in the TPL102357 trial. Non-variceal bleeding occurred more frequently than variceal bleeding in all three trials, and although it was reported by 10.7% to 16.5% of patients treated with eltrombopag, non-variceal bleeding was reported more frequently in placebo-treated patients (16.7% to 24.6%). The low rate of bleeding events may reflect the fact that despite being thrombocytopenic, platelets in these patients generally remain healthy and functional, which may be the reason that serious bleeding is rare.

Eltrombopag was associated with a rapid and pronounced platelet response in all three trials, with almost all patients achieving threshold platelet levels for AVT initiation within two weeks to four weeks. In Part 1, 97% (ENABLE 1) and 96% (ENABLE 2) of patients achieved threshold platelet levels within a median of 2.1 weeks. In the DB AVT phase (Part 2) of the ENABLE trials, mean platelet counts at antiviral baseline were similar across all groups, ranging from 144.0 Gi/L to 151.9 Gi/L. At end of treatment (or withdrawal), mean platelet counts in the eltrombopag groups were 96.6 Gi/L (ENABLE 1) and 113.1 Gi/L (ENABLE 2), compared with 51.6 Gi/L and 57.6 Gi/L in the corresponding placebo groups. The maximum continuous durations of platelet counts ≥ 50 Gi/L in ENABLE 1 and ENABLE 2 were longer with eltrombopag (25.6 weeks and 26.3 weeks) compared with placebo (7.5 weeks and 9.7 weeks), respectively. In the TPL102357 trial, there were more responders (defined as a shift from baseline [day 1] platelet count between 20 Gi/L and < 70 Gi/L to ≥ 100 Gi/L at day 28) in the eltrombopag groups when compared with placebo (i.e., 75% to 95% versus 0%). The odds ratio for response was statistically significantly greater in all three eltrombopag dose groups (30 mg, 50 mg, or 75 mg daily) compared with placebo; $P < 0.0001$; however, this may, in part, be due to the large dropout rate of placebo-treated patients. Across trials, patients in the eltrombopag groups received a higher cumulative dose of PEG-IFN and RBV and for a longer duration than patients in the placebo groups. For example, in the ENABLE 1 and ENABLE 2 trials, eltrombopag-treated patients received PEG-IFN for a mean of 281 days and 212 days, compared with 173 days and 162 days in placebo-treated patients, respectively. The high platelet response also appeared to be achieved with doses of 25 mg to 50 mg eltrombopag daily, which implies that small doses of eltrombopag can be used for a relatively short time to recover platelets.

In the ENABLE trials, health-related quality of life (HRQoL) did not appear to be impacted by eltrombopag as there were no statistically significant differences between treatment groups measured by the Short-Form (36) Health Survey (SF-36) or Chronic Liver Disease Questionnaire–Hepatitis C Virus (CLDQ-HCV) instruments (i.e., with the exception of the worry subscale in the CLDQ-HCV instrument in ENABLE 2, where a treatment difference of 2.6 [95% confidence interval (CI), 1.1 to 4.1]; $P = 0.001$ was demonstrated). The TPL102357 trial did not measure HRQoL.

In the ENABLE 1 and ENABLE 2 trials, there were 10 (2%) and 19 (4%) deaths in the eltrombopag groups and six (3%) and four (2%) deaths in the placebo groups, respectively. There was one death in the TPL102357 trial. None of the deaths was attributed specifically to eltrombopag, although five deaths across the three trials were attributed to all three study drugs (i.e., eltrombopag, IFN, and RBV). Due to the small numbers, no conclusions can be drawn from these data.

The proportions of patients with events suggestive of hepatic decompensation (e.g., ascites, hepatic encephalopathy, variceal bleeding) during AVT plus 30 days were available in the ENABLE trials. In both trials, 13% of eltrombopag-treated patients compared with 8% (ENABLE 1) and 6% (ENABLE 2) of placebo-treated patients experienced such an event. There were no similar results reported in TPL102357. The clinical expert expressed concern regarding this finding; however, it was noted that no underlying cause could be identified other than given the baseline characteristics of the patients in the trials, many were at the brink of decompensation.

Adherence (defined as receipt of 80% of the prescribed dose of both PEG-IFN and RBV for 80% of the planned duration) was measured only in the ENABLE trials and was statistically significantly higher in eltrombopag-treated patients compared with placebo patients in both ENABLE 1 (55% versus 44%; $P = 0.0066$) and ENABLE 2 (52% versus 33%; $P < 0.0001$). The association between adherence and SVR was also shown to be statistically significant ($P < 0.0001$). These findings lend further support for the ability of eltrombopag to maintain AVT in patients who might otherwise be unable to undergo the

required dosing regimen to attain SVR. Adherence was not measured in the TPL102357 trial. Health care resource utilization was also not measured in any of the three included trials.

Harms

During Part 1 (initiation phase), the frequency of adverse events (AEs) in the eltrombopag groups in the three trials ranged from 34% to 61%. The most common AE in both treatment groups during Part 1 in all trials was headache. During Part 2, almost all patients experienced at least one AE regardless of treatment (e.g., 96% and 94% of eltrombopag and 97% and 93% of placebo-treated patients in ENABLE 1 and ENABLE 2, respectively). The most common AEs experienced by patients during Part 2 were hematology-related (e.g., anemia, neutropenia, TCP). Thrombocytopenia was reported in 15% (ENABLE 1) and 12% (ENABLE 2) of eltrombopag-treated patients, compared with 37% and 33% of placebo-treated patients. In the TPL102357 trial, 70% of eltrombopag-treated patients and 17% of placebo-treated patients experienced at least one AE. The most commonly reported AE in TPL102357 was influenza-like illness, a frequent AE associated with use of IFN, reported by 30% (eltrombopag) and 6% (placebo) of patients.

The proportion of patients in the eltrombopag-treated groups who experienced at least one serious adverse event (SAE) during Part 1 of the ENABLE trials was 1%. During Part 2, 20% of eltrombopag-treated patients and 15% of placebo-treated patients in each ENABLE trial experienced at least one SAE. There was no clear pattern with regard to the type of SAEs reported; however, SAEs related to gastrointestinal and hepatobiliary disorders occurred more frequently in the eltrombopag group. In the TPL102357 trial, 11% of patients treated with eltrombopag and 6% of patients treated with placebo experienced at least one SAE. The proportion of patients with withdrawal due to adverse event (WDAE) was ≤ 1% during Part 1 of the ENABLE trials. In Part 2, the number of WDAEs ranged from 19% to 23% in eltrombopag-treated patients and 28% to 29% of placebo-treated patients. There also did not appear to be a clear pattern for WDAEs in eltrombopag-treated patients; however, in placebo-treated patients the main reason for withdrawal was TCP (i.e., 13% and 12% of patients in ENABLE 1 and ENABLE 2, respectively). In TPL102357, over the entire study, 9% of patients in the eltrombopag group compared with none (0%) of the patients in the placebo group had a WDAE.

Notable harms data in Part 2 (DB AVT phase) of the trials included thromboembolic events, hepatobiliary AEs, malignancies, TCP AEs, bone marrow fibrosis, and ocular AEs. In the ENABLE studies, the proportion of patients who experienced at least one thromboembolic event ranged from 3% to 4% in the eltrombopag groups and < 1% to 2% in the placebo groups. Of these, portal vein thromboses occurred in five (1%) and seven (1%) of eltrombopag-treated patients in ENABLE 1 and ENABLE 2, compared with two (1%) and none (0%) of the placebo-treated patients, respectively. No thromboembolic events occurred in any treatment group in the TPL102357 trial. Patients who received eltrombopag also had a higher incidence of events suggestive of hepatic decompensation, and although the cause remains unknown, it is possible it may be related to thrombosis. Hepatobiliary AEs were reported in 31% to 35% of eltrombopag-treated patients compared with 15% to 17% of placebo-treated patients. In both ENABLE trials, hyperbilirubinemia accounted for the majority of the imbalance in hepatobiliary AEs. In the TPL102357 trial, 4% of eltrombopag-treated patients and none (0%) of the placebo-treated patients experienced at least one hepatobiliary AE. During Part 2 of ENABLE 1, there were 15 (3%) eltrombopag-treated patients and 8 (3%) placebo-treated patients with a confirmed malignancy. In ENABLE 2, the corresponding results were 31 (6%) and 12 (5%). In both trials, the majority of confirmed malignancies were due to hepatic neoplasm in both treatment groups, which is not unexpected in this patient population. No malignancies were reported in TPL102357. In both ENABLE trials, TCP AEs occurred more frequently in placebo-treated patients (41% in ENABLE 1 and 38% in ENABLE 2), compared with eltrombopag-treated patients (17% in both trials). No TCP AEs were reported in the TPL102357 trial.

Bone marrow fibrosis was not reported as an AE in any of the three trials. In ENABLE 1, ocular AEs occurred with similar frequency (13%) in both treatment groups, but in ENABLE 2, ocular AEs occurred in more eltrombopag-treated patients (15%) compared with placebo (12%). Of these, 26 (5%) patients treated with eltrombopag and 6 (2%) patients treated with placebo experienced cataract or worsening cataract. Ocular-related AEs were reported in nine (16%) eltrombopag-treated and one (6%) placebo-treated patients in the TPL102357 trial. Two (4%) patients in the eltrombopag group only had cataracts.

Other Considerations

Two patient groups provided input, as summarized in Appendix 1. The expectation of the patient groups is that eltrombopag will enable patients with HCV who cannot receive optimal treatment due to TCP to initiate and maintain treatment at optimal doses and for the required duration to achieve cure. The ENABLE trials appear to have met this expectation as a statistically significantly higher proportion of eltrombopag-treated patients achieved SVR compared with placebo-treated patients. The serious AE profile of eltrombopag was also acknowledged by the patient groups, as was the need for careful preparation and monitoring of patients during treatment; however, it was noted that patients are willing to endure fairly severe AEs if they can potentially be cured.

A DB, randomized, placebo-controlled trial (ELEVATE) that evaluated the efficacy of eltrombopag for increasing platelet counts and reducing the need for platelet transfusions in 292 patients with TCP and chronic liver disease who were undergoing an invasive elective procedure was terminated early due to an imbalance of thromboembolic events in the eltrombopag group.[7] Thrombotic events of the portal venous system were observed in six patients (seven events) who received eltrombopag and two patients (three events) who received placebo (odds ratio 3.04 [95% CI, 0.62 to 14.82]), which resulted in the early termination of the study. The incidence and severity of other AEs were similar between the eltrombopag and placebo groups. A post-hoc analysis identified an association between patients who had a platelet count of 200 Gi/L or higher and risk of thrombotic events. It was concluded that further investigation of eltrombopag is required, including better identification of risk factors for the development of thrombosis, dose optimization, and careful patient selection.

Conclusions

Three prospective, multi-centre, DB, placebo-controlled trials (ENABLE 1, ENABLE 2, and TPL102357) were included in this review. The trials enrolled patients primarily infected with HCV genotype 1 or genotype 2 or 3 with associated TCP and mainly compensated liver disease. In all three trials, eltrombopag 25 mg to 100 mg once daily facilitated the introduction of PEG-IFN and RBV therapy by increasing platelet counts to a threshold that allowed for the initiation of AVT in ≥ 94% (ENABLE 1 and ENABLE 2) and ≥ 66% (TPL102357) of patients within two to four weeks. Patients treated with eltrombopag had a higher cumulative dose and duration of PEG-IFN and RBV therapy versus placebo-treated patients. In the ENABLE trials, a statistically significantly greater proportion of eltrombopag-treated patients achieved SVR compared with placebo-treated patients. Bleeding events were infrequent across treatment groups in all trials and eltrombopag did not appear to negatively affect patients' HRQoL in the ENABLE trials. Eltrombopag in combination with PEG-IFN and RBV was associated with a higher frequency of thromboembolic events, hepatobiliary AEs, and events suggestive of hepatic decompensation compared with placebo in combination with PEG-IFN and RBV.

TABLE 1: SUMMARY OF RESULTS

Outcome	ENABLE 1		ENABLE 2		TPL102357	
	ELT	PL	ELT	PL	ELT	PL
Patients entering Part 1[a], N	716		805		56	18
Patients entering Part 2[a], N	450	232	506	253	45	4
Sustained virologic response[b]						
Overall, n (%)	104 (23)	33 (14)	97 (10)	32 (13)	NR	NR
Per cent diff. (95% CI)	7.9 (2.4 to 13.4)[c]		6.0 (1.2 to 10.9)[c]		NR	
Genotype 2 or 3, n/N (%)	50/142 (35)	18/76 (24)	52/153 (34)	19/76 (25)	NR	NR
Per cent diff. (95% CI)	9.2 (–3.0 to 21.5)		10.4 (–2.4 to 23.3)		NR	
Non-genotype 2 or 3, n/N (%)	54/307 (18)	15/156 (10)	45/346 (13)	13/186 (7)	NR	NR
Per cent diff. (95% CI)	7.6 (1.4 to 13.7)		5.3 (0.1 to 10.6)		NR	
Bleeding events[b]						
Variceal bleeding, n (%)	10 (2)	2 (< 1)	3 (< 1)	2 (< 1)	0	0
Non-variceal bleeding, n (%)	74 (16.5)	57 (24.6)	80 (16)	45 (18)	6 (10.7)	3 (16.7)
Platelet counts[b]						
Achieved platelet threshold in Part 1 for AVT initiation in Part 2, n (%)	691 (97)		773 (96)		45 (80)	4 (18)
Max. duration of platelet count ≥ 50 Gi/L in Part 2:						
Max. continuous duration, weeks, mean (SD) For 5 visits, n (%)	25.6 (15.6) NR	7.5 (11.7) NR	26.3 (15.0) NR	9.7 (12.6) NR	NR 19 (42)	NR 0
Withdrawals						
Part 1 total, n (%)	33 (4.6)		46 (5.7)		11 (19.6)	14 (78)
Part 2 total, n (%)	53 (11.8)	35 (15.1)	102 (20.2)	47 (20.4)	15 (33.3)	3 (75)
Deaths (all-cause)[d]						
Part 1 total, n (%)	0		2 (< 1)		0	1 (6)
Part 2 total, n (%)	10 (2)	6 (3)	19 (4)	4 (2)	0	1 (6)
SAEs[d]						
Part 1, n (%)	8 (1)	NA	9 (1)	NA	6 (11)	1 (6)
Part 2, n (%)	90 (20)	35 (15)	99 (20)	37 (15)	6 (11)	1 (6)
WDAEs[d]						
Part 1, n (%)	9 (1.3)	NA	2 (< 1)	NA	5 (9)	0
Part 2, n (%)	85 (19)	68 (29)	115 (23)	70 (28)	5 (9)	0
Notable harms						
Thromboembolic events, n (%)	11 (3)	4 (2)	20 (4)	1 (< 1)	0	0
Hepatobiliary AEs, n (%)	155 (35)	35 (15)	157 (31)	43 (17)	2 (4)	0
Confirmed malignancies, n (%)	15 (3)	8 (3)	31 (6)	12 (5)	-	-
Thrombocytopenia AEs, n (%)	77 (17)	95 (41)	87 (17)	97 (38)	6 (11)	3 (17)
Bone marrow fibrosis, n (%)	NR	NR	NR	NR	NR	NR
Ocular AEs, n (%)	60 (13)	30 (13)	30 (12)	74 (15)	9 (16)	1 (6)

AE = adverse event; AVT = antiviral therapy; CI = confidence interval; diff = difference; ELT = eltrombopag; Gi/L = giga per litre; Max. = maximum; n = number of patients with event; N = number of patients; NA = not applicable; NR = not reported; PL = placebo; SAE = serious adverse event; SD = standard deviation; WDAE = withdrawal due to adverse event.

[a] Patients entering Part 1 of the ENABLE trials were not randomized to treatment until they entered Part 2, whereas patients in the TPL102357 trial were randomized to treatment upon entry into Part 1.

[b] Results are from Part 2 of all studies.

[c] $P < 0.05$.

[d] In the TPL102357 trial, SAEs, WDAEs, and deaths were not reported separately for Part 1 and Part 2; thus, results are for the entire study.

1. INTRODUCTION

1.1 Disease Prevalence/Incidence

The prevalence of hepatitis C virus (HCV) infection in Canada is estimated to be 0.8%, affecting nearly 245,000 individuals, although it is estimated that 21% of them may be unaware of their infection.[8] Thrombocytopenia (TCP) is a frequent complication of chronic liver disease with varying prevalence in HCV-infected patients.[3] The prevalence of TCP is reported to range between 0.16% and 45.4% in patients with chronic HCV infection,[1] and may be as high as 80% in patients with cirrhosis.[2] A conservative prevalence estimate that is independent of the clinical characteristics of patients is reported to be 24%.[1,9]

Several pathophysiological mechanisms are responsible for the development of TCP in chronic liver disease and more than one mechanism may be active at a given time in a patient.[10] Suggested etiological factors include hypersplenism secondary to portal hypertension and splenic sequestration of platelets, myelosuppression (either disease-related or induced by antiviral therapy [AVT]), and decreased hepatic production of thrombopoietin (TPO).[10,11] While TCP itself is rarely life-threatening, it complicates the medical management of patients as it may increase the risk of bleeding from surgical or medically invasive procedures or preclude patients with HCV infection from being initiated or maintained on AVT.[11] Prior to initiating AVT [i.e., generally pegylated interferon and ribavirin (PEG-IFN and RBV)], it is recommended that baseline platelet counts be ≥ 100 x 10^9/L (100 Gi/L) for peginterferon alfa-2b (PEG-Intron/Pegetron)[12] and ≥ 90 x 10^9/L (90 Gi/L) for peginterferon alfa-2a (Pegasys).[13] Further reductions in platelet counts are anticipated during interferon (IFN)-based AVT due to the myelosuppressive effects of IFN. It has been reported that TCP is responsible for IFN dose reductions in up to 12.8% of patients with low pre-treatment platelet counts, which in turn results in lower likelihood of attaining sustained virologic response (SVR) due to reduced effectiveness of HCV treatment.[14]

1.2 Standards of Therapy

There is currently no licensed intervention in Canada that is specifically indicated for the treatment of TCP associated with HCV infection. To date, platelet transfusion has been the only therapeutic option available to manage TCP in patients with liver disease; however, the short duration and small effect on increasing platelet counts, coupled with the risk and costs associated with platelet transfusion, make this an unlikely approach for patients with TCP and HCV infection requiring AVT.[3,15,16] An indirect practice to improve platelet counts when patients develop TCP during IFN-based AVT is to reduce the dose of IFN.[3] While this is a common approach in clinical practice, it is burdened by decreased likelihood of obtaining a SVR.[4] Radiological and surgical approaches such as partial splenic embolization and laparoscopic splenectomy have been proposed to increase platelet counts and to allow initiation of AVT in patients with TCP associated with HCV; however, they have not been taken up in clinical practice as they are high-risk procedures associated with significant morbidity and lack consistent data on efficacy.[17,18]

1.3 Drug

Eltrombopag is an oral, small molecule thrombopoietin receptor (TPO-R) agonist that stimulates thrombopoiesis. It interacts with the transmembrane domain of human TPO-R and initiates signalling cascades similar, but not identical, to that of endogenous TPO, thus inducing proliferation and differentiation of megakaryocytes from bone marrow progenitor cells to platelets.[5] This activation cascade leads to changes in gene expression, which in turn result in an increase in platelet production. Eltrombopag is available as 25 mg and 50 mg oral tablets and the recommended dose is 25 mg to 100 mg once daily, adjusted as necessary, to achieve the target platelet count to initiate or maintain

AVT.[5] Eltrombopag is also indicated for the treatment of adult chronic immune thrombocytopenia purpura (ITP) to increase platelet counts in splenectomized patients who are refractory to first-line treatments (e.g., corticosteroids, immunoglobulins).[5] The indication for ITP for Revolade was previously reviewed by the Canadian Drug Expert Committee in September 2011 and the recommendation was that it should not be listed.[19]

Indication Under Review
To increase platelet counts in thrombocytopenic patients with chronic HCV infection to allow the initiation and maintenance of IFN-based therapy.
Listing Criteria Requested by Manufacturer
To increase platelet counts in thrombocytopenic patients with chronic HCV infection due to genotype 2 or 3 to allow the initiation and maintenance of IFN-based therapy.

TABLE 2: KEY CHARACTERISTICS OF ELTROMBOPAG

	Eltrombopag Olamine
Mechanism of Action	TPO-R agonist that induces proliferation and differentiation of megakaryocytes to platelets, resulting in an increase of platelet production.
Indication[a]	To increase platelet counts in thrombocytopenic patients with chronic HCV infection to allow the initiation and maintenance of IFN-based therapy.
Route of Administration	Oral
Recommended Dose	Initiate treatment at a dose of 25 mg once daily and adjust dosage in 25 mg increments every two weeks as necessary to achieve the target platelet count required to initiate AVT. During AVT, the dose may be adjusted as necessary to avoid PEG-IFN dose reduction. The maximum dose is 100 mg once daily.
Serious Side Effects and Safety Issues	Contraindicated in patients with severe hepatic impairment or hypersensitivity to the drug or excipients. Patients with chronic HCV with cirrhosis receiving AVT may be at risk of hepatic decompensation and death. Serious risks include thrombotic or thromboembolic complications, recurrence of TCP upon discontinuation, bone marrow reticulin formation and fibrosis, hematologic malignancies, hepatic impairment and toxicity, and cataract formation.
Other	The ELEVATE study that investigated the efficacy of eltrombopag for increasing platelet counts and reducing need for platelet transfusion in patients with TCP and chronic liver disease who were undergoing an elective invasive procedure was terminated early due to an increased frequency of thrombotic events in patients treated with eltrombopag.[7]

AVT = antiviral therapy; HCV = hepatitis C virus; IFN = interferon; mg = milligram; PEG-IFN = pegylated interferon; TCP = thrombocytopenia; TPO-R = thrombopoietin receptor.
[a] Health Canada indication.

2. OBJECTIVES AND METHODS

2.1 Objectives

To perform a systematic review of the beneficial and harmful effects of eltrombopag 25 mg and 50 mg tablets in combination with PEG-IFN and RBV for use to increase platelet counts in patients with TCP and chronic HCV infection to allow the initiation and maintenance of IFN-based therapy.

2.2 Methods

Studies were selected for inclusion in the systematic review based on the selection criteria presented in Table 3.

TABLE 3: INCLUSION CRITERIA FOR THE SYSTEMATIC REVIEW

Patient Population	Adult (≥ 18 years of age) patients with TCP and chronic HCV infection who are being initiated or maintained on PEG-IFN and RBV therapy **Potential subgroups** • baseline platelet counta • screening HCV RNAa • HCV genotypea • fibrosis score • Child-Pugh score • prior IFN use
Intervention	Eltrombopag 25 mg to 100 mg daily through oral administration in combination with PEG-IFN and RBV
Comparators	Placebo in combination with PEG-IFN and RBV
Outcomes	**Key efficacy outcomes** • SVR • bleeding events • platelet counts • HRQoL measured with a validated scale • mortality (all-cause and liver-related) **Other efficacy outcomes** • initiation of AVT • other antiviral end points (e.g., EVR, RVR, ETR) • antiviral dose (i.e., adjustment, discontinuation, exposure) • hepatic-related morbidity outcomes (e.g., histologic changes, cirrhosis, hepatocellular carcinoma, liver decompensation, liver transplant) • adherence • health care resource utilization **Harms outcomes** • AEs, SAEs, WDAEs • Harms of Special Interest (i.e., thromboembolic events, TCP, cataract formation, bone marrow fibrosis)
Study Design	Published and unpublished RCTs

AE = adverse event; AVT = antiviral therapy; ETR = end of treatment response; EVR = early virologic response; HCV = hepatitis C virus; HRQoL = health-related quality of life; IFN = interferon; PEG-IFN = pegylated interferon; RBV = ribavirin; RCT = randomized controlled trial; RNA = ribonucleic acid; RVR = rapid virologic response; SAE = serious adverse event; SVR = sustained virologic response; TCP = thrombocytopenia; WDAE = withdrawal due to adverse event.

[a] In the phase 3 trials, patients were stratified at randomization according to baseline platelet count (< 50 x 10^9/L versus ≥ 50 x 10^9/L to < 75 x 10^9/L), screening HCV RNA (< 800,000 IU/mL versus ≥ 800,000 IU/mL), and HCV genotype (genotype 2 or 3 versus non-genotype 2 or 3).

The literature search was performed by an information specialist using a peer-reviewed search strategy.

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946–) with in-process records and daily updates through Ovid; Embase (1974–) through Ovid; and PubMed. The search strategy consisted of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concept was Revolade (eltrombopag).

Where possible, retrieval was limited to the human population. Retrieval was not limited by publication year or by language. Conference abstracts were excluded from the search results. The initial search was completed on October 6, 2014. Regular alerts were established to update the search until the meeting of the Canadian Drug Expert Committee (CDEC) on February 18, 2015. Regular search updates were performed on databases that do not provide alert services.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the following sections of the Grey Matters checklist (http://www.cadth.ca/en/resources/finding-evidence-is/grey-matters):

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Clinical Trials.

Google and other Internet search engines were used to search for additional Web-based materials. These searches were supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts. In addition, the manufacturer of the drug was contacted for information regarding unpublished studies.

Two CADTH Common Drug Review (CDR) clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least one reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion. Included studies are presented in Table 4: Details of Included Studies; excluded studies (with reasons) are presented in Appendix 4: Excluded Studies.

3. RESULTS

3.1 Findings From the Literature

A total of three studies were identified from the literature for inclusion in the systematic review (Figure 1). The included studies are summarized in Table 4 and described in Section 3.2. A list of excluded studies is presented in Appendix 4.

FIGURE 1: QUOROM FLOW DIAGRAM FOR INCLUSION AND EXCLUSION OF STUDIES

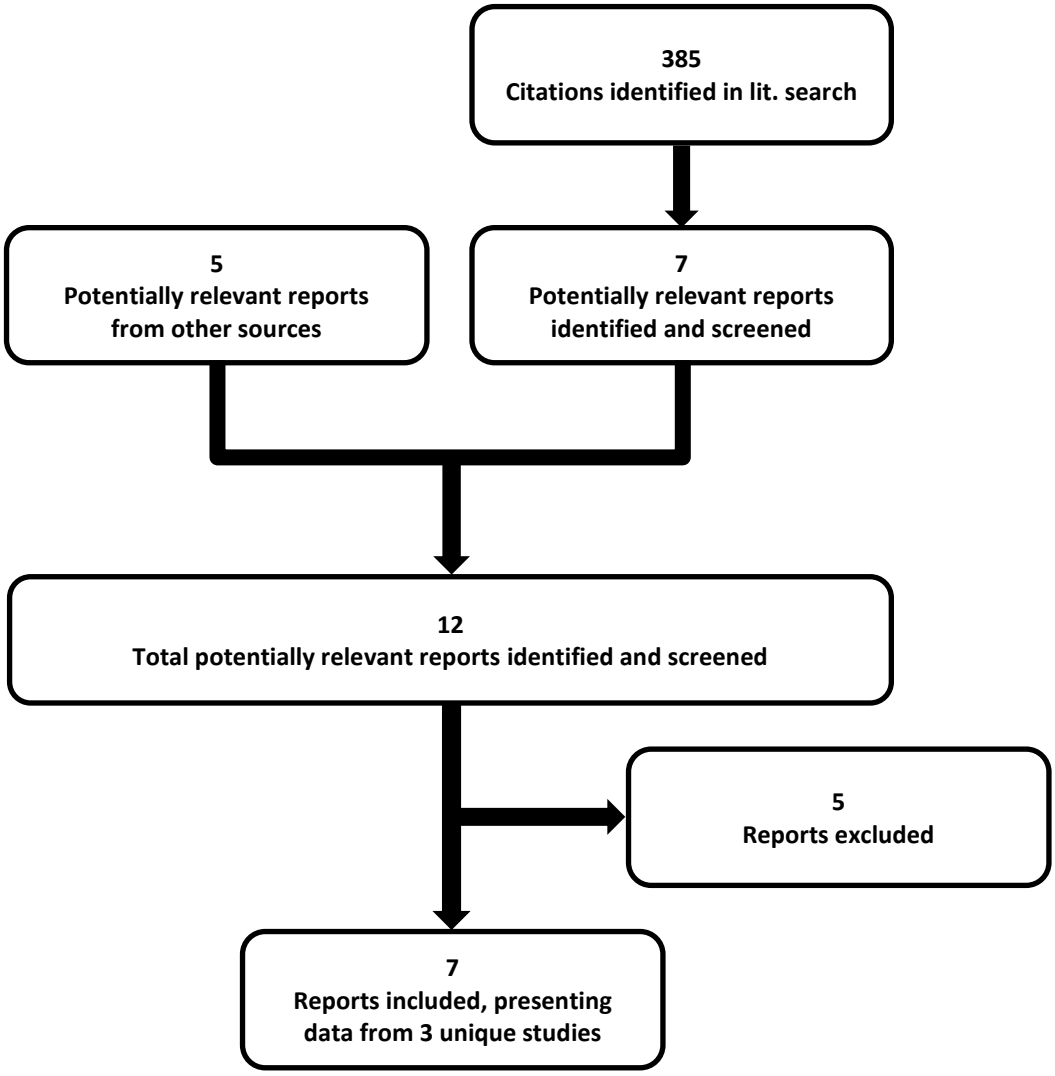


TABLE 4: DETAILS OF INCLUDED STUDIES

		ENABLE 1	ENABLE 2	TPL102357
DESIGNS AND POPULATIONS	**Study design**	Phase 3, DB, RCT, PG, MC x 24/48 weeks	Phase 3, DB, RCT, PG, MC x 24/48 weeks	Phase 2, DB, RCT, PG, MC x 8/16 weeks
	Locations	150 centres in 23 countries (US, Germany, Spain, Italy)	172 centres in 22 countries (US, Europe, India, Israel)	22 centres in 5 countries (US, France, Germany, UK, Greece)
	Enrolled Part 1, N	716	805	74
	Randomized Part 2[b], N (%)	682 (95%)	759 (94%)	49 (66%)
	Inclusion criteria	Adult (≥ 18 years) patients with confirmed chronic HCV infection and platelet count < 75 Gi/L who were candidates for PEG-IFN and RBV. Patients achieving platelet counts ≥ 90 Gi/L (ENABLE 1) or ≥ 100 Gi/L (ENABLE 2) in the initiation phase (Part 1) were eligible for entry into the DB AVT phase (Part 2).		Adult (≥ 18 years) patients with chronic HCV infection, cirrhosis, compensated liver disease and TCP (defined as platelet count of 20 to < 70 Gi/L)
	Exclusion criteria	Prior non-responders to PEG-IFN and RBV (due to reasons other than TCP), history of TEEs, HBV, HIV infection or any condition associated with active bleeding or history of clinically significant bleeding from esophageal or gastric varices.		History of thrombosis or coinfected with HBV or HIV
DRUGS	**Intervention**	**Initiation Phase (Part 1)**: Eltrombopag 25 mg to 100 mg daily PO **DB AVT Phase (Part 2)**: Eltrombopag 25 mg to 100 mg daily PO plus PEG-IFN and RBV		**Initiation Phase (Part 1)**: Eltrombopag 30 mg to 75 mg daily PO **DB AVT Phase (Part 2)**: Eltrombopag 30 mg to 75 mg daily PO plus PEG-IFN and RBV
	Comparator(s)	**Initiation Phase (Part 1)**: NA **DB AVT Phase (Part 2)**: PL daily PO plus PEG-IFN and RBV		**Initiation Phase (Part 1)**: PL daily PO **DB AVT Phase (Part 2)**: PL daily PO plus PEG-IFN and RBV
DURATION	**Phase:**			
	Run-in/initiation phase (Part 1)	2 to 9 weeks		4 weeks
	DB/AVT phase (Part 2)	24 to 48 weeks		8 to 16 weeks
	Follow-up	24 weeks		4 weeks
OUTCOMES	**Primary end point**	SVR (defined as undetectable serum HCV RNA 24 weeks after completion of AVT)		Platelet count response (defined as ≥ 100,000 mm^3 [100 Gi/L] at 4 weeks)
	Other end points	Platelet counts, PEG-IFN and/or RBV dose reductions or DC, rates of RVR, EVR, cEVR, ETR, SVR12, HRQoL, and safety end points.		Continuation of AVT, EVR, and safety end points.

		ENABLE 1	ENABLE 2	TPL102357
NOTES	**Publications**	Afdhal et al., 2014[20]		McHutchison et al., 2007[21]

AVT = antiviral therapy; cEVR = complete early virologic response; DB = double-blind; DC = discontinuation; ETR = end of treatment response; EVR = early virologic response; Gi/L = giga per litre; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; HRQoL = health-related quality of life; MC = multi-centre; N = number of patients; NA = not applicable; PEG-IFN = pegylated interferon; PG = parallel group; PL = placebo; PO = orally; RBV = ribavirin; RCT = randomized controlled trial; RNA = ribonucleic acid; RVR = rapid virologic response; SVR = sustained virologic response; SVR12 = sustained virologic response at 12 weeks; TCP = thrombocytopenia; TEEs = thromboembolic events.
[a] Represents the number of patients who achieved threshold platelet levels for entry into and actually entered Part 2.
Source: ENABLE 1 CSR,[22] ENABLE 2 CSR,[23] and TPL102357 CSR.[24]
Note: Five additional reports were included: ENABLE 1 Clinical Study Report (CSR),[22] ENABLE 2 CSR,[23] and TPL102357 CSR,[24] manufacturer's submission,[25] and Health Canada Reviewer's Report.[26]

3.2 Included Studies

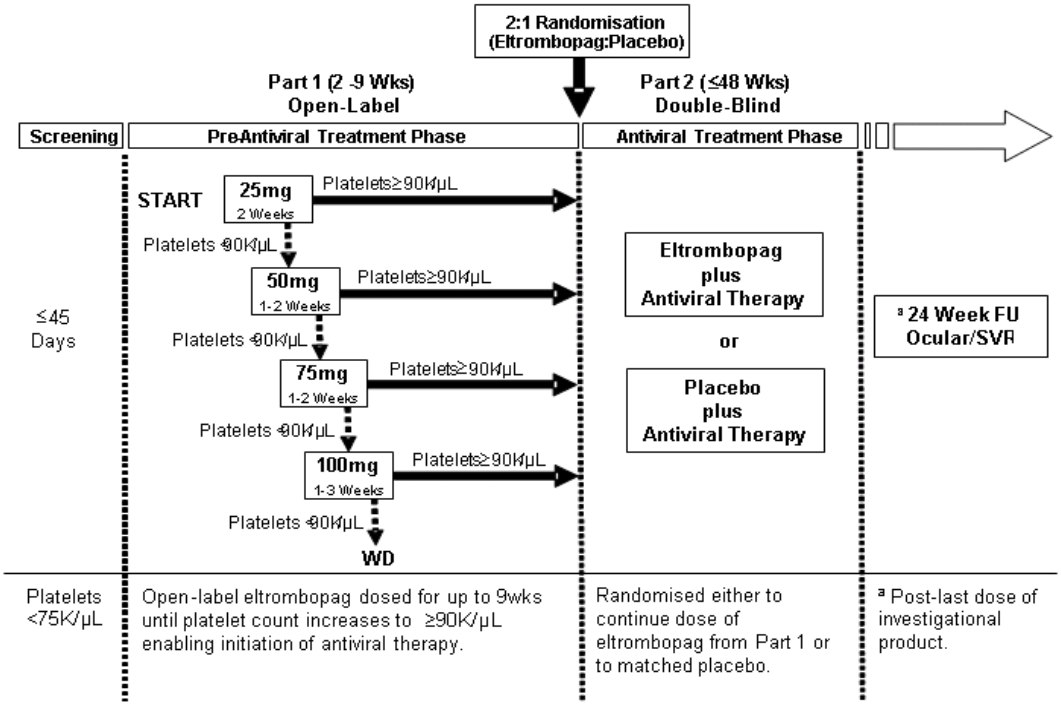
3.2.1 Description of Studies

Three prospective double-blind (DB), randomized controlled trials (RCTs) met the selection criteria for inclusion in the systematic review. All were DB, randomized, and placebo-controlled during the AVT phases (Part 2) of each trial [ENABLE 1 (TPL103922; n = 682),[20,22] ENABLE 2 (TPL108390, n = 759),[20,23] and TPL102357 (n = 74)].[21,24]

The phase III ENABLE 1 and ENABLE 2 trials were of identical design with the exception of the type of PEG-IFN used and the corresponding platelet threshold for initiating AVT. The ENABLE 1 trial utilized peginterferon alfa-2a (Pegasys), which requires a platelet threshold of ≥ 90 Gi/L for initiating AVT as illustrated in Figure 2. The ENABLE 2 trial was of identical design, but used peginterferon alfa-2b (Peg-Intron), which requires a platelet threshold of ≥ 100 Gi/L for initiation. Both trials were phase 3, multi-centre trials with the same objective: to assess the efficacy and safety of eltrombopag as supportive therapy to increase platelets to sufficient levels to facilitate the initiation and maintenance of PEG-IFN and RBV therapy in patients with TCP associated with chronic HCV infection.

Both ENABLE 1 and ENABLE 2 comprised two parts. Part 1 was an initiation pre-AVT phase and Part 2 was a randomized, DB, placebo-controlled AVT phase (Figure 2). During Part 1, patients received eltrombopag in a dose-escalating fashion (i.e., eltrombopag 25 mg to 100 mg once daily for two weeks to nine weeks) depending upon platelet response. Patients who achieved the minimum platelet threshold for initiating AVT were randomized 2:1 to eltrombopag or placebo in Part 2, where they were treated for 24 weeks to 48 weeks (HCV genotype 2 or 3) or 48 weeks (genotype non-2 or 3). Study centres registered and randomized patients by telephone using an interactive voice response system (IVRS). Randomization was stratified by HCV genotype (2 or 3 versus non-2 or 3), platelet counts (< 50 Gi/L versus ≥ 50 Gi/L), and HCV RNA level (< 800,000 versus ≥ 800,000 IU/mL) at baseline. In Part 1, patients who received eltrombopag 100 mg daily for three weeks and failed to meet the platelet threshold were deemed non-responders and entered into the follow-up phase to monitor adverse events (AEs).

FIGURE 2: STUDY DESIGN FOR ENABLE 1



FU = follow-up; K/µL = thousand per microlitre; SVR = sustained virologic response; wks = weeks.
Source: ENABLE 1.[22]

Study TPL102357 was a phase 2, multi-centre, DB RCT that assessed whether eltrombopag could increase platelet counts in patients with TCP associated with cirrhosis due to chronic HCV infection. After study entry, eligible patients were randomized 1:1:1:1 to eltrombopag 30 mg, 50 mg, or 75 mg once daily or placebo with the use of permuted-block randomization and a block size of four. Registration and randomization of patients was also done using an IVRS. Randomization was stratified by baseline platelet count (20 Gi/L to < 50 Gi/L versus ≥ 50 Gi/L to < 70 Gi/L). In the initial treatment phase (Part 1), patients received eltrombopag or placebo according to their randomized treatment for four weeks. Patients who completed the initial phase were eligible for AVT if they achieved the minimal platelet threshold count of ≥ 70 Gi/L for peginterferon alfa-2a or ≥ 100 Gi/L for peginterferon alfa-2b. The choice of either interferon was at the investigator's discretion and was not dictated by the protocol. In the AVT phase (Part 2), patients received PEG-IFN and RBV for 8 weeks to 16 weeks. A follow-up visit was scheduled for four weeks after the last dose of study drug had been received.

Study TPL102357 was originally planned to have a sample size of 160 patients, with 40 patients randomly assigned to each of four study groups. The study was also to be performed without any interim analyses with the exception of a blinded review by the independent data monitoring committee of the safety and AE profiles after 40 patients had completed the initial treatment phase. A subsequent protocol amendment stipulated the performance of a formal interim analysis from all patients enrolled as of December 22, 2005 (n = 74). The criterion for stopping the study early was a two-sided *P* value no greater than 0.0001, based on the O'Brien-Flemming adjustment for a group-sequential design from an interim analysis of the efficacy data. The criterion was not met in the first interim analysis, but it was met in the second interim analysis (i.e., overall comparison for the four study groups, $P < 0.0001$; 30 mg of eltrombopag versus placebo, $P = 0.00067$; 50 mg of eltrombopag versus placebo, $P = 0.00015$; and

75 mg of eltrombopag versus placebo, $P < 0.0001$). As a result, the predetermined stopping rules were met on this analysis and enrolment for the study was terminated early after enrolment of 74 patients.

3.2.2 Populations

a) Inclusion and Exclusion Criteria

In the ENABLE 1 and ENABLE 2 studies, eligible patients were 18 years or older, with confirmed HCV infection, baseline platelet count < 75 Gi/L, and otherwise adequate hepatic, renal, and hematologic function to receive AVT. Patients were eligible if, in the investigator's opinion, they were appropriate candidates for PEG-IFN and RBV therapy. Patients could have received prior treatment with PEG-IFN and RBV if the reason for stopping treatment was documented TCP. Key study exclusion criteria included non-responders to previous PEG-IFN and RBV therapy for reasons other than: TCP; decompensated liver disease; serious cardiac, cerebrovascular, or pulmonary disease that would preclude PEG-IFN and RBV therapy; history of thromboembolic events (e.g., evidence of portal vein thrombosis, or arterial or venous thrombosis, and any additional two risk factors); hepatitis B virus (HBV) or human immunodeficiency virus (HIV) infection; any condition involving active bleeding or need for anticoagulation with heparin or warfarin; and a history of clinically significant bleeding from esophageal or gastric varices.

In Study TPL102357, eligible patients were 18 years of age or older and had chronic HCV infection (defined as presence of anti-HCV antibodies and detectable serum HCV RNA levels, as determined with the use of a clinically available assay chosen by the investigator), compensated liver disease, and TCP (defined as a platelet count of 20 Gi/L to < 70 Gi/L). Patients were also required to have a liver-biopsy specimen indicative of cirrhosis, radiographic evidence of cirrhosis, or endoscopic evidence of portal hypertension. Patients were excluded if they were pregnant, had a history of thrombosis, or were co-infected with HIV or HBV.

b) Baseline Characteristics

Across all three trials, the study populations comprised patients in their early 50s who were primarily Caucasian and male (Table 5). Most patients were infected with HCV genotype 1 (50% to 65%) and then genotype 2 or 3 (30% to 39%). Median baseline platelet counts ranged from 55 Gi/L to 60 Gi/L. In the ENABLE trials, patients had mainly compensated liver disease (i.e., Child-Pugh A: score 5–6 in 94% to 97% of patients). The treatment groups appeared to be well matched within each trial as well as between trials.

TABLE 5: SUMMARY OF BASELINE CHARACTERISTICS (ITT POPULATION)

Characteristic	ENABLE 1		ENABLE 2		TPL102357	
	ELT (N = 450)	PL (N = 232)	ELT (N = 506)	PL (N = 253)	ELT (N = 56)[a]	PL (N = 18)
Age (yrs)						
Mean (SD)	52.1 (8.4)	51.4 (8.52)	52.4 (8.6)	52.0 (9.2)	NR	NR
Median	52.0	51.0	52.0	53.0	50 to 56	52
(Min–Max)	(19 to 76)	(23 to 72)	(22 to 83)	(26 to 74)	(30 to 74)	(41 to 71)
Male, n (%)	264 (59)	159 (69)	321 (63)	160 (63)	41 (73.2)	11 (61)
Race, n (%)						
Caucasian	326 (72)	166 (72)	388 (77)	188 (74)	48 (85.7)	16 (89)
Asian	107 (24)	57 (25)	107 (21)	61 (24)	1 (1.2)	1 (6)
HCV genotype, n (%)	n = 449	n = 232	n = 504	n = 252	n = 55	n = 17
1	292 (65)	149 (64)	320 (63)	160 (63)	31 (56)	9 (50)
2	27 (6)	22 (9)	40 (8)	28 (11)	5 (9)	0
3	115 (26)	54 (23)	113 (22)	47 (19)	15 (27)	7 (39)
4	11 (2)	5 (2)	30 (6)	17 (7)	4 (7)	1 (6)
6	4 (< 1)	2 (< 1)	1 (< 1)	0	0	0
Child-Pugh score, n (%)	n = 449	n = 232	n = 504	n = 253		
A (score 5–6)	424 (94)	217 (94)	487 (97)	242 (96)	NR	NR
B (score 7–9)	25 (6)	15 (6)	17 (3)	11 (4)	NR	NR
Prior IFN use, n (%)						
Naive	307 (68)	152 (66)	347 (69)	182 (72)	NR	NR
Experienced	143 (32)	80 (34)	159 (31)	71 (28)	NR	NR
FibroSURE score, n (%)	n = 391	n = 208	n = 451	n = 218		
0/1/2	37 (8)	23 (10)	46 (9)	19 (8)	NR	NR
3/4	354 (79)	185 (80)	405 (80)	199 (79)	NR	NR
ALT, n (%)						
Normal	103 (23)	54 (23)	113 (22)	49 (19)	NR	NR
Elevated	347 (77)	178 (77)	393 (78)	204 (81)	NR	NR
HCV RNA (IU/mL)	n = 449	n = 231	n = 504	n = 252		
Mean	1,870,562.1	1,880,278.4	1,702,729.6	1,656,788.0	NR	NR
(SD)	(3,080,918.0)	(3,395,777.0)	(3,066,411.11)	(2,564,763.5)		
Median	696,000.0	825,000.0	737,500	748,500	NR	NR
(Min–Max)	(217 to 32,200,000)	(208 to 33,500,000)	(65 to 28,800,000)	(118 to 27,200,000)		
Platelet count (Gi/L)						
Mean	56.9	57.4	56.9	56.6	51.4 to 56.6	53.9
(SD)	(13.6)	(12.9)	(13.3)	(13.6)	(9.89 to 15.94)	(13.2)
Median	59.5	60.3	59.0	59.0	52 to 59	55
(Min–Max)	(4.0 to 87.5)	(15.5 to 78.0)	(10.5 to 83.0)	(18.0 to 84.0)	(26 to 94)	(27 to 75)
Stratification Variables						
HCV RNA genotype, n (%)					NA	NA
Genotype 2 or 3	142 (32)	76 (33)	153 (30)	75 (30)		
Non-genotype 2 or 3	307 (68)	156 (67)	351 (69)	177 (70)		
Platelet count, n (%)						
< 50 Gi/L	124 (28)	62 (27)	140 (28)	77 (30)	NA	NA
≥ 50 Gi/L	326 (72)	170 (73)	366 (72)	176 (70)	NA	NA
20 Gi/L to < 50 Gi/L	NA	NA	NA	NA	20 (36)	6 (33)
50 Gi/L to < 70 Gi/L	NA	NA	NA	NA	32 (57)	11 (61)
Out of range (> 70 Gi/L)	NA	NA	NA	NA	4 (7)	1 (6)

Characteristic	ENABLE 1		ENABLE 2		TPL102357	
	ELT (N = 450)	PL (N = 232)	ELT (N = 506)	PL (N = 253)	ELT (N = 56)[a]	PL (N = 18)
HCV RNA, n (%)					N/A	N/A
< 800,000 IU	236 (52)	112 (48)	266 (53)	132 (52)		
≥ 800,000 IU	214 (48)	119 (51)	238 (47)	120 (47)		

ALT = alanine aminotransferase; ELT = eltrombopag; Gi/L = giga per litre; HCV = hepatitis C virus; IFN = interferon; ITT = intention-to-treat; IU = international units; IU/mL = international units per millilitre; Min–Max = minimum to maximum; n = number of patients with event; N = number of patients; NA = not applicable; NR = not reported; PL = placebo; RNA = ribonucleic acid; SD = standard deviation; yrs = years.

[a] Results are for the combined ELT groups (30 mg, 50 mg, and 75 mg once daily) for simplicity and this is why a range for the median is reported.

In the ENABLE trials, the majority (66% to 72%) of patients were naive to prior IFN treatment, whereas 28% to 34% were considered to be IFN treatment-experienced. This information was not reported in Study TPL102357. Details of the type of prior IFN therapy received in treatment-experienced patients is provided in Table 6. Of these, 15% to 18% of patients had been previously treated with a combination of PEG-IFN and RBV.

TABLE 6: PRIOR HCV THERAPIES (ITT POPULATION)

Characteristic	ENABLE 1		ENABLE 2		TPL102357	
	ELT (N = 450)	PL (N = 232)	ELT (N = 506)	PL (N = 253)	ELT (N = 56)	PL (N = 18)
No. with prior HCV txt,[a] n (%)	146 (32)	81 (35)	161 (32)	74 (29)	NR	NR
Pegylated IFN	37 (8)	20 (9)	43 (8)	11 (4)		
Pegylated IFN and RBV	72 (16)	37 (16)	89 (18)	37 (15)		
Regular IFN	26 (6)	25 (11)	35 (7)	20 (8)		
Regular IFN and RBV	30 (7)	9 (4)	35 (7)	17 (7)		
> 1 Prior IFN-based txt	24 (5)	11 (5)	43 (8)	16 (6)		
Other non-approved	12 (3)	3 (1)	11 (2)	9 (4)		

ELT = eltrombopag; HCV = hepatitis C virus; IFN = interferon; ITT = intention-to-treat; N = number of patients; NR = not reported; PL = placebo; RBV = ribavirin; txt = treatment.

[a] Patient demographic and disease characteristics entering Part 2 (double-blind, antiviral therapy phases).

3.2.3 Interventions

a) Eltrombopag

In the ENABLE 1 and ENABLE 2 trials, all patients received eltrombopag 25 mg daily for two weeks during Part 1. If platelet counts were < 90 Gi/L (ENABLE 1) or 100 Gi/L (ENABLE 2) after two weeks, the dose of eltrombopag was increased to 50 mg daily for up to two weeks. Further dose escalations to 75 mg daily (up to two weeks) and 100 mg daily (up to three weeks) were allowed if platelets remained below threshold levels. Once patients achieved platelet counts > 90 Gi/L (ENABLE 1) or > 100 Gi/L (ENABLE 2), they were eligible to enter Part 2 of the trials. Patients whose platelet counts failed to reach the threshold after nine weeks were discontinued from eltrombopag but were required to attend post-treatment follow-up visits.

In Part 2, patients were randomized to either: 1) continuation of the same dose of eltrombopag from Part 1 (dose that effectively raised platelets to threshold levels); or 2) withdrawal from active eltrombopag treatment and receipt of matched placebo. Eltrombopag and placebo were given in combination with AVT for the planned treatment duration (i.e., either 24 weeks or 48 weeks for patients

with genotype 2 or 3, or 48 weeks for patients with non-genotype 2 or 3). Dose modifications of eltrombopag or placebo (i.e., up to 100 mg daily) were permitted to maintain platelet counts at a level to enable AVT. The dose of eltrombopag was reduced if platelets exceeded 200 Gi/L, and treatment was interrupted and the dose was reduced if platelets exceeded 400 Gi/L.

In Study TPL102357, patients received either eltrombopag 30 mg, 50 mg, 75 mg, or matching placebo once daily for four weeks during Part 1. Patients who completed Part 1 were eligible for AVT in Part 2 if they attained a platelet count of 70 Gi/L or more for the use of peginterferon alfa-2a (Pegasys) or 100 Gi/L or more for the use of pegylated interferon alfa-2b (Peg-Intron). Treatment with eltrombopag was interrupted if the platelet count reached 200 Gi/L or more and was reinstated on an individual basis, generally when platelet counts returned to 100 Gi/L or less.

b) PEG-IFN and RBV

In ENABLE 1, patients successfully randomized into the AVT phase (Part 2) received peginterferon alfa-2a (Pegasys) 180 mcg/week through self-administered subcutaneous injection and RBV 200 mg oral tablets dosed at 800 mg/day for HCV genotype 2 or 3, or 1,000 mg/day for patients weighing less than 75 kg, or 1,200 mg/day for patients weighing 75 kg or more for HCV genotypes other than 2 or 3. In ENABLE 2, in Part 2 patients received peginterferon alfa-2b (Peg-Intron) 1.5 mcg/kg weekly by self-administered subcutaneous injection and oral RBV 200 mg tablets dosed at 800 mg/day, 1,000 mg/day, 1,200 mg/day, or 1,400 mg/day based on body weights of 65 kg or less, 65 kg to 80 kg, 81 kg to 105 kg, or more than 105 kg, respectively and HCV genotype. Investigators were instructed to follow the current local product labels for peginterferon dose reductions and discontinuations.

In Study TPL102357 the choice of peginterferon was not dictated by the protocol, but rather was at the investigator's discretion. In Part 2, peginterferon alfa-2a (Pegasys) 180 mcg per week or peginterferon alfa-2b (Peg-Intron) 1.5 mcg/kg per week and RBV (1,000 to 1,200 mg per day for patients receiving peginterferon alfa-2a and 800 mg per day for those receiving peginterferon alfa-2b) were administered for eight weeks concomitantly with eltrombopag or placebo. The protocol was later amended to extend this phase to 12 weeks, at which time eltrombopag was stopped and AVT was continued at the investigator's discretion. Throughout the AVT phase, the dose of peginterferon alfa-2a was reduced by half if the platelet count had decreased to 25 Gi/L to 50 Gi/L and was discontinued altogether if the platelet count was below 25 Gi/L, as per the product's label. The dose of peginterferon alfa-2b was reduced by half if the platelet count had decreased to 50 Gi/L to 80 Gi/L and was discontinued altogether if the platelet count was less than 50 Gi/L, also according to the product's label.

3.2.4 Outcomes

a) Sustained Virologic Response

In the ENABLE 1 and ENABLE 2 trials, the primary end point was the rate of SVR, defined as the proportion of patients with undetectable serum HCV RNA at end of treatment and all subsequent planned visits up to 24 weeks after completing treatment (i.e., corresponding with weeks 48 or 72 for HCV genotype 2 or 3, or week 72 for HCV non-genotype 2 or 3).

If a patient had a positive HCV RNA ("blip") between two visits with undetectable HCV RNA, the patient was considered a SVR responder, provided that the detectable HCV RNA was of the same order of magnitude as the limit of detection. Otherwise, a patient was considered a SVR non-responder. Patients who received AVT during follow-up or after discontinuing PEG-IFN and RBV were also considered to be non-responders. If a patient's HCV RNA at 24-week follow-up was missing for any reason, the patient

was considered a non-responder. A patient with missing data due to premature discontinuation of treatment, or from the study for any reason, was considered a non-responder for all subsequent visits.

b) Other Virologic End Points

In the ENABLE 1 and ENABLE 2 trials, other rates of virologic response were included as secondary end points and were defined as follows:

- rapid virologic response (RVR) was undetectable HCV RNA after four weeks of AVT
- early virologic response (EVR) was a clinically significant reduction in HCV RNA (≥ 2 $\log_{10}$ drop or undetectable) after 12 weeks of AVT
- end of treatment response (ETR) was undetectable HCV RNA at the end of AVT
- sustained virologic response at 12 weeks (SVR12) was undetectable HCV RNA at the end of AVT and at the 12-week follow-up
- complete EVR (cEVR) was undetectable HCV RNA at the week 12 assessment.

In Study TPL102357, the primary end point was the proportion of patients with a shift from baseline platelet count (between 20 Gi/L and ≤ 70 Gi/L) to ≥ 100 Gi/L after four weeks during Part 1.

c) Platelet Counts

Platelet count data were collected as part of the complete blood count performed by local laboratories at each site.

d) Health-Related Quality of Life

Health-related quality of life (HRQoL) was assessed in the ENABLE 1 and ENABLE 2 trials using the Short-Form (36) Health Survey (SF-36) and Chronic Liver Disease Questionnaire–Hepatitis C Virus (CLDQ-HCV).

The SF-36 is a generic, 36-item, nine-question patient self-report survey of health status and HRQoL. It produces an eight-scale profile (i.e., physical function, role limitations due to physical problems [role-physical], bodily pain, general health perceptions [general health], vitality, social function, role limitations due to emotional problems [role-emotional], and mental health) and two summary indexes (component scores) for physical and mental health. The acute recall (past seven days) version of the SF-36 was used in the ENABLE studies. Greater scores in the SF-36 indicate better HRQoL and a clinically important difference in the physical or mental component scores is considered to be 2.5 points to 5.0 points.

The CLDQ-HCV is a 29-item patient self-report questionnaire developed for measurement of HRQoL among patients with chronic liver disease and HCV as reported in Appendix 5: Validity of Outcome Measures. The CLDQ-HCV assesses four domains: activity/energy, emotion, systemic symptoms, and worry. A higher score indicates better HRQoL. A clinically important difference is defined as a change in score of 0.5.

e) Adherence

In the ENABLE 1 and ENABLE 2 studies, adherence was defined according to an 80-80-80 rule. This required receipt of at least 80% of the prescribed (investigator-prescribed) dose of PEG-IFN and at least 80% of the prescribed (investigator-prescribed) dose of RBV, for at least 80% of the planned duration (38 weeks for patients with 48 weeks of planned treatment, and at least 19 weeks for patients with 24 weeks of planned treatment).

f) Harms

Assessment of safety and tolerability of eltrombopag was measured by the nature and frequency of AEs, laboratory abnormalities, ocular examinations, 12-lead electrocardiogram, and clinical monitoring and observation.

Notable harms were derived from AEs of Special Interest that included TCP, bleeding (hemorrhages and potentially bleeding-related AEs), hepatobiliary disorders, thromboembolic events (including myocardial infarction), malignancies, renal-related AEs, and ocular and lens disorders.

3.2.5 Statistical Analysis

a) Efficacy Criteria

The ENABLE 1 and ENABLE 2 studies were powered to demonstrate a 10% clinically meaningful difference between eltrombopag and placebo on the primary end point (SVR) for the intention-to-treat (ITT) population. The sample sizes were determined based on the assumptions that SVR with placebo would be 10%, randomization would be 2:1 eltrombopag to placebo, and the study would have 92.5% power to detect a statistically significant treatment effect of 10% at two-sided alpha level of 5%. A total of 675 patients (450 eltrombopag and 225 placebo) were required; however, assuming 10% would not complete Part 1, it was planned that 750 patients were to be enrolled in each study.

For both the ENABLE 1 and ENABLE 2 studies, the primary statistical comparison was the proportion of patients with SVR for eltrombopag versus placebo for the ITT population. All statistical comparisons and confidence intervals (CIs) were two-sided: continuous variables were summarized using descriptive statistics, and categorical 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. Both studies used last observation carried forward (LOCF) imputation to account for missing values. If a patient had a missing value between visits, then the previous non-missing assessment and associated classification was carried forward to fill in the missing value.

In the ENABLE trials, the primary end point (SVR) was examined separately for pre-specified subgroups of geographic region and various demographic and baseline characteristics.

Study TPL102357 was powered to compare the odds of being a responder (i.e., having a shift from baseline platelet count of between 20 Gi/L to < 70 Gi/L to ≥ 100 Gi/L after week 4 [prior to AVT]) for eltrombopag relative to placebo, which was the primary end point. Assuming a placebo response rate of 20% and an active rate of 60%, then 34 completed patients per group would provide more than 90% power at the 5% (two-sided) overall level of significance. In order to allow for missing data and premature discontinuation, 40 patients per treatment group were to be randomized.

The primary end point was analyzed with the use of multiple logistic-regression analysis adjusting for randomization strata. Each of the three eltrombopag groups was compared with the placebo group by means of a closed testing procedure. The global null hypothesis of no significant difference was tested among the four study groups and, if rejected, the null hypothesis of no significant difference was tested between the placebo group and each eltrombopag group, with testing performed in the predetermined order of the highest dose (75 mg) to the lowest dose (30 mg). The sequential testing was continued until the null hypothesis could not be rejected. Mean change from baseline in platelet count during Part 2, after the start of AVT, was also summarized by treatment group. Platelet counts were summarized using descriptive statistics by treatment group and visit, for all visits collected.

b) Analysis Populations

In the ENABLE 1 and ENABLE 2 trials, efficacy was analyzed using the ITT population and safety analyses were based on the safety population. The analyses populations were defined as follows:

- **ITT population:** consisted of all randomized patients. Patients were analyzed according to the stratum and treatment they were assigned at randomization, regardless of whether it was assigned correctly. The ITT population was the primary population for the analysis of efficacy during the DB AVT phase (Part 2).
- **Safety population:** consisted of all patients who had received open-label study drug during Part 1. The safety population was used for the following objectives:
  - to evaluate the ability of eltrombopag to enable initiation of AVT
  - to evaluate the safety and tolerability of eltrombopag.
- **Safety DB population**: consisted of all randomized patients who received DB study drug. Patients were analyzed according to the treatment received. The safety DB population was used to compare the safety of eltrombopag (plus AVT) with placebo (plus AVT).
- **Per-protocol (PP) population:** Consisted of all randomized patients who did not violate any important inclusion and exclusion criteria that pertained to the assessment of treatment efficacy and who incurred no protocol deviations that pertained to the assessment of treatment efficacy. The PP population, identified prior to unblinding of the study, was used to provide supporting analyses for the primary end point.

In Study TPL102357, the primary population for analysis was the **ITT exposed population**, which was defined as all patients who were randomly assigned to a study group and who received at least one dose of the study medication. The **PP population** was defined as patients who were not major protocol violators or deviators and was used for supportive analysis of the primary end point. The **safety population** was defined as all patients who received at least one dose of study medication, and was identical to the ITT population.

3.3 Patient Disposition

Overall, 4.6% (ENABLE 1) and 5.6% (ENABLE 2) discontinued Part 1 of the trials, mainly due to lack of efficacy (Table 7). In Part 2, 11.8% and 20.2% of eltrombopag-treated patients and 15.1% to 20.4% of placebo-treated patients discontinued treatment. The main reasons were lost to follow-up, withdrawal of consent, and AEs. Overall, the retention in the ENABLE trials ranged from 80% to 88% across all treatment groups. In Study TPL102357, a high proportion of patients withdrew from the placebo group in Part 1 (78%) compared with the eltrombopag group (19.6%), primarily due to lack of efficacy, patient decision, and unspecified reasons (Table 7). Of those patients who entered Part 2, 75% of placebo-treated patients and 33.3% of eltrombopag-treated patients prematurely discontinued the trial. Given the high dropout rate, it is difficult to draw any conclusions based on these data, as very few patients in the placebo group remained in the trial (i.e., only four patients entered Part 2).

TABLE 7: PATIENT DISPOSITION

	ENABLE 1		ENABLE 2		TPL102357	
	ELT	PL	ELT	PL	ELT	PL
Screened, N	NR		NR	NR	NR	NR
Part 1 (open-label/pre-AVT)						
Patients entering Part 1, N	**716**[a]		**805**		**56**	**18**
Discontinued, N (%)	33 (4.6)		46 (5.7)		11 (19.6)[b]	14 (78)[b]
Lack of efficacy	11 (1.5)		13 (1.6)		5 (8.9)	7 (39)
AE	9 (1.3)		5 (0.6)		1 (1.8)	0
Investigator discretion	7 (0.8)		8 (1.0)		0	0
Subject decision	3 (0.4)		3 (0.4)		2 (3.6)	2 (11)
Lost to follow-up	2 (0.3)		12 (1.5)		0	0
Protocol deviation	1 (0.1)		5 (0.6)		0	0
Unspecified reasons	0		0		3 (5.4)	5 (28)
Safety, N	715		805		74	
Part 2 (double-blind/AVT)						
Patients entering Part 2, N	**450**	**232**	**506**	**253**[c]	**45**	**4**
Discontinued, N (%)	53 (11.8)	35 (15.1)	102 (20.2)	47 (20.4)	15 (33.3)	3 (75)
Lost to follow-up	22 (4.9)	12 (5.2)	48 (9.5)	15 (5.9)	2 (4.4)	0
Withdrew consent	17 (3.8)	13 (5.6)	19 (3.8)	16 (6.3)	2 (4.4)	0
AE	13 (2.9)	8 (3.5)	27 (5.3)	10 (4.0)	4 (8.8)	0
Protocol deviation	1 (0.2)	2 (0.9)	0	1 (0.4)	0	0
Investigator decision	0	0	8 (1.6)	5 (2.0)	0	0
Lack of efficacy	0	0	0	0	1 (2.2)	1 (25)
Other	0	0	0	0	6 (13.3)	2 (50)
Completed, N (%)[d]	396 (88)	197 (85)	404 (80)	205 (81.0)	30 (66.7)	1 (25)
ITT, N	450	232	506	253	56	18
PP, N	216	424	482	236	44	16
Safety, N	449[a]	232	506	252[a]	56	18

AE = adverse event; AVT = antiviral therapy; ELT = eltrombopag; ITT = intention-to-treat; N = number of patients; NR = not reported; PL = placebo; PP = per protocol.

Note: In the ENABLE trials, patients were not randomized into treatment groups until Part 2, whereas in TPL102357 they were randomized into groups at the time of entry into Part 1 (and into three ELT treatment groups, which have been combined in the above table for simplicity).

[a] One patient withdrew consent in each treatment group.

[b] Patients were randomized in Part 1 to placebo (n = 18) or eltrombopag (n = 56), so percentages are based on these denominators.

[c] One patient was randomized to DB treatment but was withdrawn due to a protocol deviation and did not receive DB treatment.

[d] Patients who received DB treatment, AVT, and completed all follow-up visits.

3.4 Exposure to Study Treatments

In the ENABLE trials, patients in the eltrombopag groups received numerically higher cumulative doses of eltrombopag and were treated for a longer mean cumulative duration (i.e., approximately 217 days and 210 days for eltrombopag compared with 176 days and 163 days for matched placebo) in ENABLE 1 and 2, respectively (Table 8). In Study TPL102357, the cumulative dose of eltrombopag increased as the dose increased in each eltrombopag treatment group (i.e., 1,799 mg to 5,243 mg), as did the mean cumulative duration of treatment in days (i.e., 67 days to 84 days compared with 37 days for matched placebo) (Table 8).

In the ENABLE trials, patients treated with eltrombopag experienced greater exposure to PEG-IFN than patients who received placebo (Table 9). The mean cumulative dose of PEG-IFN received by patients in the eltrombopag groups (5,029 mcg and 3,299 mcg) was higher than that received by patients in the placebo groups (3,320 mcg and 2,111 mcg) and the mean cumulative duration of PEG-IFN treatment was longer (i.e., 218 days and 212 days in eltrombopag-treated patients and 173 days and 162 days in placebo-treated patients), in ENABLE 1 and 2, respectively. Exposure to PEG-IFN dose was not reported in Study TPL102357.

TABLE 8: EXPOSURE TO ELTROMBOPAG (SAFETY POPULATION)

	ENABLE 1[a]		ENABLE 2[a]		TPL102357			
	ELT (N = 449)	PL (N = 232)	ELT (N = 506)	PL (N = 252)	ELT 30 (N = 14)	ELT 50 (N = 19)	ELT 75 (N = 23)	PL (N = 18)
Cumulative dose, mg								
N	446	231	503	252	14	17	22	18
Mean (SD)	14,505.5 (9,541.8)	14,231.8 (10,782.28)	13,800.3 (9,349.2)	13,692.4 (10,824.2)	1,799 (1,211)	3,209 (1,695)	5,243 (2,103)	0
Median (Min–Max)	13,337.5 (175 to 34,400)	12,550.0 (150 to 35,500)	12,250.0 (0 to 34,300)	11,087.5 (0 to 41,000)	1,905 (150 to 3,600)	3,250 (150 to 5,650)	5,925 (975 to 8,550)	0
Cumulative duration, days								
N	447	231	506	252	14	19	23	18
Mean (SD)	217.3 (101.8)	176.1 (112.5)	209.8 (101.7)	163.2 (111.5)	67 (40)	72 (41)	84 (30)	37 (24)
Median (Min–Max)	184.0 (6 to 357)	167.0 (5 to 352)	181.0 (1 to 365)	151.5 (1 to 357)	85 (7 to 120)	85 (4 to 122)	87 (13 to 114)	29 (22 to 112)

ELT = eltrombopag; N = number of patients; PL = placebo; SD = standard deviation.
[a] For the ENABLE trials, the population is the safety double-blind population; for Study TPL102357, the population is the safety population; N indicates the number of patients with complete data.

TABLE 9: ENABLE 1 AND ENABLE 2: EXPOSURE TO PEGYLATED INTERFERON (SAFETY DB POPULATION)

	ENABLE 1		ENABLE 2	
	ELT (N = 449)	PL (N = 232)	ELT (N = 506)	PL (N = 252)
Cumulative dose, mcg				
N	446	231	506	252
Mean (SD)	5,029.8 (2,558.1)	3,320.1 (2,383.8)	3,299.4 (1,812.7)	2,111.0 (1,682.5)
Median (Min–Max)	4,320.0 (180 to 8,820)	2,700.0 (180 to 8,820)	2,880.0 (0 to 7,206)	1,700.0 (100 to 7,300)
Cumulative duration, days				
N	446	232	505	252
Mean (SD)	218.4 (100.95)	172.6 (113.98)	211.9 (102.0)	162.1 (112.8)
Median (Min–Max)	185.5 (7 to 359)	167.5 (7 to 364)	182.0 (7 to 371)	153.5 (7 to 358)

DB = double-blind; ELT = eltrombopag; mcg = microgram; N = number of patients; PL = placebo; SD = standard deviation.
Note: N indicates the number of patients with complete data.

3.5 Critical Appraisal

3.5.1 Internal Validity

In all three included trials, the methods used for randomization (IVRS) and allocation concealment (matched placebo eltrombopag tablets) were appropriate. It does not appear that any treatment-emergent AEs related to eltrombopag compromised the DB conditions of the trials. Although it is well known that the AE profile of IFN can compromise DB conditions, AVT was used by all treatment groups in the included trials and was given in an open-label manner. The rapid platelet response in eltrombopag-treated patients could have compromised DB conditions, as it may have been readily apparent to which treatment group a patient was randomized. This is likely only a potential issue in Study TPL102357 due to the randomization to eltrombopag or placebo being done at study entry, as the magnitude of the platelet response was greatest in Part 1.

Approximately 30% of patients in the ENABLE trials had received prior IFN therapy. The inclusion and exclusion criteria permitted patients who received previous IFN therapy to be included in the trials provided that the reason for discontinuation of IFN therapy was due to TCP and not another reason. It is not appropriate to re-treat with IFN therapy if a patient previously demonstrated poor virologic response or failure with IFN and discontinued therapy as a result. According to the clinical expert, the only appropriate reason to re-treat with IFN is if there was a prior tolerance issue with IFN that has been resolved (e.g., depression or suicidal ideation). While the type of prior IFN therapy was reported in the ENABLE trials (Table 6), the reason(s) for discontinuation of IFN were not provided.

The use of two different formulations of pegylated IFN with different recommendations for threshold platelet levels for initiation of AVT (i.e., peginterferon alfa-2a at ≥ 90 Gi/L and peginterferon alfa-2b at ≥ 100 Gi/L) in ENABLE 1 and ENABLE 2, respectively (and both in Study TPL102357) adds a confounding factor that complicates comparisons of results between trials and precludes the ability to pool data from the ENABLE trials. Nonetheless, the clinical expert advised that it is not expected that the two forms of PEG-IFN would have clinically significant differences in efficacy or safety that could affect treatment outcomes. The clinical expert also advised that at present, the best course of treatment for the patients in the study population would be the new IFN-free therapies (e.g., sofosbuvir, simeprevir) as cure rates, especially in a very sick, cirrhotic population as was included in the trials, are superior to those of PEG-IFN and RBV. It is anticipated that IFN-free therapies will become the standard of care in the future. Given the poor cure rates expected with PEG-IFN in this patient population, coupled with the AE profile and complications associated with PEG-IFN therapy, the clinical expert advised that a physician may opt to not treat these patients at all, but rather wait for a liver transplant.

It could not be confirmed if any patients infected with HCV genotype 2 or 3 in the ENABLE trials received more than 24 weeks of treatment, as the duration of therapy was not reported in this way. Rather, the cumulative dose and duration of therapy was reported. The length of treatment in an individual patient may have important consequences for achievement of SVR and notably for the cost of treatment, especially if 48 weeks of treatment is required. The 2012 Canadian Association for the Study of the Liver (CASL) guidelines for treatment of chronic HCV infection recommend that in patients with HCV genotype 3 who do not achieve RVR but have an EVR, consideration should be given to extending treatment for 36 weeks to 48 weeks, particularly in the setting of predictors of poor response (e.g., fibrosis) such as the patients in the included trials.[6]

Rates of patient discontinuations in the ENABLE trials were modest, especially given the very sick patient population (e.g., 12% to 20% of patients across treatment groups discontinued the trials). In contrast, in Study TPL102357, a high proportion of patients withdrew (e.g., 75% of placebo-treated patients and

33.3% of eltrombopag-treated patients prematurely discontinued the trial). This large differential in dropout rates not only compromises randomization but could also have affected efficacy results, as almost all the patients in the placebo group were considered to have had no response. In all trials, the LOCF method was used for imputation of missing values, which could have introduced bias in the assessment of treatment effect, as it underestimates the variability of the estimated result (i.e., it is assumed that no change occurred over the duration of time that the result is carried forward). As well, use of LOCF could have overestimated the true efficacy in all trials due to only responders being eligible for Part 2 (i.e., due to use of LOCF, patients who were lost to follow-up could still have been considered to be responders, even if their platelets fell below the threshold for continuation of AVT).

The early termination of enrolment in Study TPL102357 compromises interpretation of the results as the study was powered on the basis of enrolling 160 patients, with 40 patients randomized to each treatment group. Only 74 patients entered into Part 1 before enrolment was terminated and of these, 49 patients continued into Part 2. At the completion of the trial, only 30 patients remained across the three eltrombopag groups and only one patient in the placebo group, which compromises randomization and meaningful interpretation of the results.

3.5.2 External Validity

Due to only responders (i.e., those meeting the platelet threshold levels for AVT) being eligible to continue on to the DB AVT phase (Part 2) of the trials, it is possible that the overall efficacy could have been overestimated as those who did not respond, or had only a partial response in Part 1, were not able to go on to DB treatment. Of note, in the ENABLE trials this may not be a significant issue as almost all patients treated with eltrombopag in Part 1 (≥ 94%) were eligible to participate in Part 2.

All three included trials were limited by the requirement for PEG-IFN and RBV dose adjustments or discontinuations to be done in accordance with the product's approved labelling. It is acknowledged that this was unavoidable due to the requirement to ensure patients were not exposed to unnecessary risk and to comply with regulatory requirements. Nonetheless, according to the clinical expert, the PEG-IFN dose adjustments and discontinuations in the trials are not reflective of clinical practice in Canada, as many experienced physicians would treat more aggressively and initiate and maintain treatment at much lower platelet counts than was done in the clinical trials. As a result, this may have overestimated the efficacy results compared with a Canadian population of patients with similar baseline characteristics, because PEG-IFN treatment may have been stopped sooner than what is currently done in clinical practice in Canada. If patients with lower platelet counts had been maintained on PEG-IFN and RBV longer, it is possible that treatment outcomes in these patients would have improved. On the other hand, by discontinuing PEG-IFN and RBV earlier, safety outcomes (which reflect the cumulative effects of PEG-IFN and RBV treatment in addition to eltrombopag or placebo) may have been underestimated. Compared with placebo-treated patients, patients treated with eltrombopag not only were exposed to eltrombopag longer, but also received a greater cumulative dose and duration of therapy with PEG-IFN and RBV (and their associated AEs and complications).

Various baseline patient and disease characteristics may further affect generalizability of the results of the included trials to a broad population of patients with chronic HCV infection. Although in general, the clinical expert advised that the study populations are representative of Canadian patients, they comprise a very sick patient population that makes up only a small subset of all chronically infected HCV patients in Canada. These patients would most likely be treated by a physician or group of physicians specializing in viral hepatitis in a specialized care setting, as opposed to practising in the community.

The distribution of HCV genotypes may also differ somewhat from that seen in Canada, and there did not appear to be any Canadian sites in any of the trials. In Canada, individuals of East Indian or Asian descent are most frequently infected with HCV genotype 2 or 3, whereas in the US, primarily Caucasian patients are infected with genotype 2 or 3. In addition, all three trials excluded patients who were co-infected with HIV or HBV. This also limits the generalizability of the results, as many patients with HCV infection also have HIV and/or HBV co-infection. The clinical expert advised that it is unlikely that eltrombopag would behave differently in patients with HIV and/or HBV co-infection; however, the presence of these viruses could affect disease progression and liver outcomes. There is also the possibility of drug-to-drug interactions with concomitant HIV treatment, as the combination of lopinavir/ritonavir co-administered with eltrombopag is known to cause a decrease in plasma concentrations of eltrombopag.[5] Furthermore, the clinical expert advised that HIV-infected patients generally do not respond well to IFN-based therapies, usually due to tolerance issues, so it may be possible that patients co-infected with HIV would not have comparable virologic response, although there are no data presently available to confirm this.

Overall, the treatment outcomes measured in the included trials were appropriate, although the objective of the primary end point differed between the ENABLE trials (i.e., virologic response) and Study TPL102357 (platelet response). According to the manufacturer, the HCV clinical program for Revolade was developed with input from both the European Medicines Agency (EMEA) and the US Food and Drug Administration (FDA). The originally proposed end point for the ENABLE trials was platelet count response. Both regulators stated that improvement in platelet counts alone may not be of clinical benefit since TCP is indicative of advanced liver disease and may be a marker of refractoriness to IFN therapy. Therefore, the clinical program was designed to demonstrate that treatment of TCP facilitates AVT (i.e., minimizes or prevents IFN dose modifications and premature discontinuations) and this is best measured as the achievement of SVR. The CASL guidelines state that the primary objective of anti-HCV therapy is complete elimination of the virus, otherwise termed SVR.[6]

3.6 Efficacy

Only those efficacy outcomes identified in the review protocol are reported below (see Section 2.2, Table 3). See Appendix 3 for detailed efficacy data.

3.6.1 Sustained Virologic Response

The proportion of patients achieving SVR with eltrombopag was statistically significantly higher than with placebo in both the ENABLE 1 (23% versus 14%; *P* = 0.0064) and ENABLE 2 (19% versus 13%; *P* = 0.0202) trials (Table 12). The results of the PP analysis support the primary analysis. In both the ENABLE trials, patients were stratified at baseline according to genotype 2 or 3 versus non-genotype 2 or 3, platelet count < 50 Gi/L versus ≥ 50 Gi/L, or HCV RNA < 800,000 IU/mL or ≥ 800,000 IU/mL. The manufacturer has requested listing only for patients with HCV genotype 2 or 3 and due to the pre-specified stratification by genotype, the effect of eltrombopag in these patients can be specifically examined. The proportions of patients with genotype 2 or 3 who achieved SVR with eltrombopag were numerically greater than placebo in both ENABLE 1 (35% versus 24%) and ENABLE 2 (18% versus 10%); however, this was also observed in patients with non-genotype 2 or 3 (i.e., 18% versus 10% and 13% versus 7% of eltrombopag- versus placebo-treated patients achieved SVR in ENABLE 1 and ENABLE 2, respectfully). These results support that while eltrombopag appears to work to facilitate attainment of SVR in patients with HCV genotype 2 or 3, it also works similarly in patients with non-genotype 2 or 3. The same was observed between other baseline strata (i.e., platelet count and HCV RNA.) Study TPL102357 did not include SVR as an outcome.

3.6.2 Bleeding Events

In the ENABLE trials, few patients (≤ 2%) experienced variceal bleeding (i.e., esophageal and/or gastric bleeding) in any of the treatment groups (Table 13). There were no reports of variceal bleeding in Study TPL102357. Non-variceal bleeding (e.g., epistaxis, gingival bleeding, retinal hemorrhage) occurred more frequently than variceal bleeding in all three trials. Although non-variceal bleeding was reported by 10.7% to 16.5% of patients treated with eltrombopag, it was consistently reported more frequently in placebo-treated patients (16.7% to 24.6%) across all three trials.

3.6.3 Platelet Counts

During the open-label initiation phase (Part 1), almost all patients in the ENABLE trials achieved the threshold level for initiation of PEG-IFN (i.e., 97% of patients achieved levels ≥ 90 Gi/L in ENABLE 1 and 96% of patients achieved levels of ≥ 100 Gi/L in ENABLE 2), as detailed in Table 14. In ENABLE 1 and ENABLE 2, 39% and 25% of patients, respectively, achieved the threshold level within two weeks, whereas 84% and 77% of patients achieved the threshold level in less than four weeks. In the DB AVT phase (Part 2), mean platelet counts at antiviral baseline were similar across all treatment groups, ranging from 144.0 Gi/L to 151.9 Gi/L (Table 15). At end of treatment (or withdrawal), mean platelet counts were 96.6 Gi/L and 113.1 Gi/L in the eltrombopag groups of ENABLE 1 and ENABLE 2, respectively, compared with 51.6 Gi/L and 57.6 Gi/L in the corresponding placebo groups. More patients had minimum platelet counts < 50 Gi/L in the placebo groups of the ENABLE 1 (85%) and ENABLE 2 (76%) trials compared with patients treated with eltrombopag (32% and 19%, respectively), as per Table 16. The maximum continuous durations of platelet counts ≥ 50 Gi/L in ENABLE 1 and ENABLE 2 were longer in eltrombopag-treated patients (25.6 weeks and 26.3 weeks) compared with placebo-treated patients (7.5 weeks and 9.7 weeks), respectively (Table 17). Median platelet counts over the duration of the ENABLE studies are illustrated in Figures 3 and 4.

In Study TPL102357, there were more responders (defined as a patient with a shift from baseline (day 1) platelet count between 20 Gi/L to < 70 Gi/L to ≥ 100 Gi/L at day 28) in the eltrombopag groups as compared with placebo (i.e., 75% to 95% versus 0%). The odds ratio for response was statistically significantly greater in all three eltrombopag dose groups compared with placebo; $P < 0.0001$ (Table 18). During Part 1 of Study TPL102357, the mean change in platelet counts from baseline was statistically significantly greater in all three eltrombopag dose groups when compared with placebo; $P \leq 0.003$ (Table 19). Median platelet counts over the duration of the trial are illustrated in Figure 5.

3.6.4 Health-Related Quality of Life

In the ENABLE trials, there were no statistically significant differences between treatment groups in the change from baseline of any individual component score or physical or mental health summary scores of the SF-36 instrument (Table 21). Similarly, there were no statistically significant treatment differences in the change from baseline in any subscale of the CLDQ-HCV instrument, with the exception of worry in the ENABLE 2 study (i.e., treatment difference 2.6 [95% CI, 1.1 to 4.1]; $P = 0.001$ (Table 22). Study TPL102357 did not include HRQoL as an outcome.

3.6.5 Mortality (All-Cause and Liver-Related)

In ENABLE 1 and ENABLE 2, there were 10 (2%) and 19 (4%) deaths in the eltrombopag groups and 6 (3%) and 4 (2%) deaths in the placebo groups (Table 23). In ENABLE 1, there was no relationship to the study drugs except for two deaths in the eltrombopag group where the deaths were related to all three study drugs (eltrombopag, PEG-IFN, and RBV). In ENABLE 2, 10 deaths in the eltrombopag group and none of the deaths in the placebo group were considered to be related to study drugs. The most common causes of deaths were gastrointestinal (GI) bleeding, infections, and hepatic decompensation.

Five deaths were considered related to PEG-IFN with or without RBV, three deaths to all three study drugs, and one death to "DB medication." There was only one death in Study TPL102357 due to abdominal pain/renal failure in the placebo group.

Deaths due to hepatobiliary disorders were reported only in the ENABLE trials and the number of deaths across treatment groups was small (i.e., three deaths each in the eltrombopag groups of both ENABLE trials and two deaths in the placebo group of ENABLE 1). In all instances, the proportion of patients with death due to a hepatobiliary disorder was < 1% in individual treatment groups.

3.6.6 Other Efficacy Outcomes

a) Initiation of Antiviral Therapy

In the ENABLE 1 and ENABLE 2 trials, 95% and 94% of patients, respectively, initiated AVT in Part 2. In the majority of cases (> 80%), the dose of eltrombopag that enabled initiation of AVT was 25 mg or 50 mg once daily (Table 24).

In Study TPL102357, 71%, 74%, and 91% of patients in the eltrombopag 30 mg, 50 mg, and 75 mg once-daily treatment groups initiated AVT compared with 22% of patients in the placebo group (Table 25).

b) Other Antiviral End Points

In the ENABLE trials, there were no statistically significant differences between treatment groups in the proportion of patients who achieved a RVR or eRVR. In contrast, in both trials, the proportions of patients who achieved an EVR, cEVR, ETR, and SVR12 were all statistically significantly higher with eltrombopag than with placebo (Table 26). In Study TPL102357, the number of patients who achieved an EVR, modified viral response or any viral response was larger in the eltrombopag treatment groups compared with placebo, but the trial was underpowered to conduct any statistical comparisons between groups (Table 27).

c) Antiviral Dose

The proportions of patients without any AVT dose adjustments were statistically significantly higher in the eltrombopag groups compared with placebo groups of both ENABLE 1 (43% versus 28%; $P = 0.0029$) and ENABLE 2 (46% versus 27%; $P < 0.0001$) (Table 28). The mean time to the first PEG-IFN dose adjustment was 9.0 weeks versus 5.8 weeks in ENABLE 1 and 10.6 weeks versus 6.6 weeks in ENABLE 2 for the eltrombopag and placebo groups, respectively. Kaplan–Meier estimates of time to the first PEG-IFN dose reduction are illustrated in Figure 6 (ENABLE 1) and Figure 7 (ENABLE 2). There were also statistically significantly fewer premature discontinuations from AVT in the eltrombopag groups compared with the placebo groups (41% versus 56% in ENABLE 1 and 48% versus 65% in ENABLE 2; $P \leq 0.0001$ for both), as detailed in Table 29. Kaplan–Meier estimates of time to permanent discontinuation of PEG-IFN are illustrated in Figure 8 (ENABLE 1) and Figure 9 (ENABLE 2).

In Study TPL102357, the number of patients with either PEG-IFN or RBV dose reductions comprised at most one patient per treatment group. Two patients in the eltrombopag 30 mg daily and one patient in the eltrombopag 50 mg daily group discontinued PEG-IFN compared with no patients in either the eltrombopag 75 mg daily or placebo groups (Table 30).

d) Hepatic-Related Morbidity Outcomes

Events suggestive of hepatic decompensation during AVT plus 30 days were reported in the ENABLE trials (Table 31). Overall, 13% of eltrombopag-treated patients in both trials compared with 8%

(ENABLE 1) and 6% (ENABLE 2) of placebo-treated patients experienced such an event. There were no similar results reported in Study TPL102357.

e) Adherence

Adherence according to the 80-80-80 rule (i.e., receipt of at least 80% of the investigator-prescribed doses of both PEG-IFN and RBV for at least 80% of the planned duration) was statistically significantly higher in patients treated with eltrombopag compared with placebo in both ENABLE 1 (55% versus 44%; P = 0.0066) and ENABLE 2 (52% versus 33%; P < 0.0001), as per Table 32. The association between adherence and SVR was statistically significant (P<0.0001) in both ENABLE trials (Table 33). Adherence was not reported in Study TPL102357.

f) Health Care Resource Utilization

No data were reported for this outcome in any of the three included trials.

g) Subgroup Analyses

In the ENABLE trials, the proportion of patients achieving SVR was examined by various pre-specified subgroup analyses (Figures 10 and 11). In all analyses, SVR was higher in the eltrombopag treatment groups compared with the placebo groups, with the exception of patients ≥ 65 years in both ENABLE trials and non-Caucasian patients in ENABLE 2. Caution is warranted in interpreting these data as the number of patients in each subgroup was small.

3.7 Harms

Only those harms identified in the review protocol are reported below (see 2.2.1, Protocol). See Appendix 3**Error! Reference source not found.** for detailed harms data. Since mortality (all-cause and liver-related) was a key efficacy outcome, a summary of deaths that occurred during the trials is reported in Table 23 and discussed in Section 3.6.5.

In Study TPL1023567, the proportions of patients with SAEs and WDAEs were not reported separately for Parts 1 and 2 of the trial, thus, the results reported in Tables 10 and 11 are for the entire study.

3.7.1 AEs

During Part 1 (initiation phase) of the three included trials, the proportion of patients that experienced at least one AE in the eltrombopag group ranged from 34% to 61% (Table 10). The most common AE in both treatment groups across all three trials in Part 1 was headache. During Part 2, almost all patients, regardless of treatment group, experienced at least one AE (i.e., 96% and 94% of eltrombopag- and 97% and 93% of placebo-treated patients in ENABLE 1 and 2, respectively) (Table 11). Overall, the most common AEs experienced by patients during Part 2 were hematology-related (e.g., anemia, neutropenia, TCP). Thrombocytopenia was reported in 15% (ENABLE 1) and 12% (ENABLE 2) of eltrombopag-treated patients, as compared with 37% and 33% of placebo-treated patients.

In Study TPL102357, 70% of eltrombopag-treated patients and 17% of placebo-treated patients experienced at least one AE (Table 10 and Table 11). The most common reported AE was influenza-like illness, reported by 30% (eltrombopag) and 6% (placebo) of patients.

3.7.2 SAEs

The proportion of patients in the eltrombopag-treated groups who experienced at least one SAE during Part 1 of the ENABLE trials was 1% (Table 10). During Part 2, 20% of eltrombopag-treated patients and 15% of placebo-treated patients in each ENABLE trial experienced at least one SAE (Table 11). There was

no clear pattern with regard to the type of SAEs reported; however, SAEs related to GI and hepatobiliary disorders occurred more frequently in the eltrombopag group. The SAE reported with the highest frequency in eltrombopag-treated patients was hepatic neoplasm malignant in 14 (3%) patients in ENABLE 1 and 6 (1%) of patients in ENABLE 2 (Table 11). In Study TPL102357, 11% of patients treated with eltrombopag and 6% of patients treated with placebo experienced at least one SAE over the entire study. No one SAE occurred in more than one patient throughout the trial.

3.7.3 WDAEs

The proportion of patients who withdrew due to an AE was ≤ 1% during Part 1 of the ENABLE trials. In Part 2, the number of patients with WDAEs ranged from 19% to 23% in eltrombopag-treated patients and 28% to 29% of placebo-treated patients. There also did not appear to be a clear pattern for WDAEs in eltrombopag-treated patients; however, in placebo-treated patients the main reason for withdrawal was TCP (i.e., cited as the reason for WDAE in 13% and 12% of patients in ENABLE 1 and ENABLE 2, respectively). In Study TPL102357, over the entire study, 9% of patients in the eltrombopag group compared with none (0%) of the patients in the placebo group had a WDAE.

3.7.4 Notable Harms

Results for notable harms are all derived from Part 2 (DB AVT phase) of the included trials (Table 11). In the ENABLE studies, the proportion of patients who experienced at least one thromboembolic event ranged from 3% to 4% in the eltrombopag groups and < 1% to 2% in the placebo groups (Table 11). Of these, portal vein thromboses occurred in five (1%) and seven (1%) of eltrombopag-treated patients in ENABLE 1 and 2, compared with two (1%) and none (0%) of the placebo-treated patients, respectively. No thromboembolic events were reported in either treatment group in Study TPL102357.

In the ENABLE trials, hepatobiliary AEs were reported in 31% to 35% of eltrombopag-treated patients compared with 15% to 17% of placebo-treated patients. In both ENABLE trials, hyperbilirubinemia accounted for the majority of the imbalance in hepatobiliary AEs between eltrombopag and placebo (i.e., 12% and 8% difference between treatment groups in ENABLE 1 and ENABLE 2, respectively). In Study TPL102357, 4% of eltrombopag-treated patients and none (0%) of the placebo-treated patients experienced at least one hepatobiliary AE.

During Part 2 of ENABLE 1, there were 15 (3%) eltrombopag-treated patients and 8 (3%) placebo-treated patients with a confirmed malignancy (Table 10). In ENABLE 2, the corresponding results were 31 (6%) and 12 (5%). In both trials, the majority of confirmed malignancies were due to hepatic neoplasm in both treatment groups. No malignancies were reported in Study TPL102357.

In both ENABLE trials, TCP AEs occurred more frequently in placebo-treated patients (41% in ENABLE 1 and 38% in ENABLE 2), compared with eltrombopag-treated patients (17% in both trials). No TCP AEs were reported in Study TPL102357.

Bone marrow fibrosis was not reported as an AE in any of the three trials.

In ENABLE 1, ocular AEs occurred with similar frequency (13%) in both treatment groups; however, based on adjudication of blinded data, there was a numerically higher incidence of both progressions of pre-existing baseline cataracts and of patients with incident cataracts with eltrombopag. Similarly, in ENABLE 2, ocular AEs occurred in 15% of patients treated with eltrombopag and 12% of patients treated with placebo. Of these, 26 (5%) patients treated with eltrombopag and 6 (2%) patients treated with placebo experienced cataract or worsening cataract. Ocular-related AEs were reported in nine (16%)

eltrombopag-treated patients and one (6%) placebo-treated patient in Study TPL102357. Two (4%) patients in the eltrombopag group only had cataracts.

TABLE 10: HARMS DURING OPEN-LABEL PHASE (PART 1) (SAFETY POPULATION)

Outcome	ENABLE 1	ENABLE 2	TPL102357	
	ELT (N = 715)	ELT (N = 805)	ELT (N = 56)	PL (N = 18)
AEs				
Patients with > 0 AEs, N (%)	268 (37)	277 (34)	34 (61)	10 (56)
Most common AEs (≥ 2% of patients)				
Headache	49 (7)	35 (4)	12 (21)	3 (17)
Fatigue	31 (4)	18 (2)	3 (5)	0
Nausea	21 (3)	21 (3)	4 (7)	0
Diarrhea	18 (3)	22 (3)	-	-
Dry mouth	13 (2)	6 (< 1)	6 (11)	1 (6)
SAEs				
Patients with > 0 SAEs, N (%)	8 (1)	9 (1)	6 (11)[a]	1 (6)[a]
WDAEs				
WDAEs, N (%)	9 (1)	2 (< 1)	5 (9)[a]	0[a]

AEs = adverse events; ELT = eltrombopag; N = number of patients; PL = placebo; SAE = serious adverse event; WDAE = withdrawal due to adverse event.
[a] In Study TPL102357, SAEs and WDAEs were not reported separately for Part 1 and Part 2; therefore, results are for the entire study.

TABLE 11: HARMS DURING ANTI-VIRAL THERAPY PHASE (PART 2) (SAFETY POPULATION)

Outcome	ENABLE 1		ENABLE 2		TPL102357	
	ELT (N = 449)	PL (N = 232)	ELT (N = 506)	PL (N = 252)	ELT (N = 56)	PL (N = 18)
AEs						
Patients with > 0 AEs, N (%)	430 (96)	226 (97)	475 (94)	235 (93)	39 (70)	3 (17)
Most common AEs (≥ 20% of patients)						
Anemia	184 (41)	78 (34)	200 (40)	90 (36)	6 (11)	0
Neutropenia	172 (38)	96 (41)	139 (27)	83 (33)	3 (5)	0
Pyrexia	141 (31)	53 (23)	143 (28)	61 (24)	6 (11)	0
Fatigue	139 (31)	60 (26)	124 (25)	53 (21)	14 (25)	1 (6)
Headache	107 (24)	47 (20)	95 (19)	50 (20)	9 (16)	0
Thrombocytopenia	69 (15)	86 (37)	62 (12)	84 (33)	1 (2)	0
Influenza-like illness	70 (16)	40 (17)	100 (20)	36 (14)	17 (30)	1 (6)
SAEs						
Patients with > 0 SAEs, N (%)	90 (20)	35 (15)	99 (20)	37 (15)	6 (11)[a]	1 (6)[a]
Most common SAEs (≥ 2% of patients)						
Esophageal varices hemorrhage	7 (2)	2 (< 1)	3 (< 1)	2 (< 1)	-	-
Hepatic failure	7 (2)	1 (< 1)	3 (< 1)	0	-	-
Hepatic neoplasm malignant	6 (1)	2 (< 1)	14 (3)	4 (2)	-	-
Cataract	2 (< 1)	2 (< 1)	8 (2)	0	-	-
Hepatic encephalopathy	4 (< 1)	0	8 (2)	0	-	-
Pneumonia	4 (< 1)	2 (< 1)	6 (1)	4 (2)	-	-
Retinal exudates	-	-	-	-	1 (2)	-

Outcome	ENABLE 1		ENABLE 2		TPL102357	
	ELT (N = 449)	PL (N = 232)	ELT (N = 506)	PL (N = 252)	ELT (N = 56)	PL (N = 18)
Ascites	-	-	-	-	1 (2)	-
Thrombocytopenia	-	-	-	-	1 (2)	-
Abdominal pain	-	-	-	-	-	1 (6)
Renal failure	-	-	-	-	-	1 (6)
WDAEs						
WDAEs, N (%)	85 (19)	68 (29)	115 (23)	70 (28)	5 (9)[a]	0[a]
Most common reasons (≥ 2% of patients)						
Anemia	11 (2)	5 (2)	13 (3)	10 (4)		-
Thrombocytopenia	6 (1)	31 (13)	17 (3)	30 (12)	1 (2)	0
Neutropenia	3 (< 1)	8 (3)	4 (< 1)	8 (3)	1 (2)	0
Hepatic neoplasm malignant	2 (< 1)	1 (< 1)	6 (1)	5 (2)	-	-
Retinal exudates	-	-	-	-	1 (2)	0
Abdominal pain	-	-	-	-	1 (2)	0
Ascites	-	-	-	-	1 (2)	0
Notable harms						
Thromboembolic events, n (%)	11 (3)	4 (2)	20 (4)	1 (< 1)	0	0
Portal vein thromboses	5 (1)	2 (1)	7 (1)	0		
Deep vein thrombosis	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		
Hepatobiliary AEs, n (%)	155 (35)	35 (15)	157 (31)	43 (17)	2 (4)	0
Blood bilirubin increased/hyperbilirubinemia	82 (18)	13 (6)	78 (15)	18 (7)	1 (2)	0
Confirmed malignancies, n (%)	15 (3)	8 (3)	31 (6)	12 (5)	-	-
Hepatic neoplasm malignant	14 (3)	5 (2)	26 (5)	10 (4)		
Hepatic neoplasm	0	1 (< 1)	2 (< 1)	1 (< 1)		
Thrombocytopenia AEs, n (%)	77 (17)	95 (41)	87 (17)	97 (38)	6 (11)	3 (17)
Thrombocytopenia	69 (15)	86 (37)	62 (12)	84 (33)	1 (2)	-
Platelet count decreased	8 (2)	10 (4)	27 (5)	14 (6)	-	-
Bone marrow fibrosis	NR	NR	NR	NR	NR	NR
Ocular-related AEs (≥ 2% of patients), n (%)						
Cataract	60 (13)	30 (13)	30 (12)	74 (15)	9 (16)	1 (6)
Retinal exudates	20 (4)	9 (4)	6 (2)	26 (5)	2 (4)	0
Visual acuity reduced	15 (3)	8 (3)	3 (1)	18 (4)	2 (4)	0
Vision blurred	9 (2)	5 (2)	9 (4)	12 (2)	2 (4)	0
	6 (1)	6 (3)	3 (1)	7 (1)	-	1 (6)

AE = adverse event; AVT = antiviral therapy; ELT = eltrombopag; n = number of patients with event; N = number of patients; NR = not reported; PL = placebo; SAEs = serious adverse events; WDAE = withdrawal due to adverse event.

[a] In Study TPL102357, SAEs and WDAEs were not reported separately for Part 1 and Part 2; therefore, results are for the entire study.

Note: For the ENABLE 1 and ENABLE 2 trials, results are for on-treatment during Part 2 plus 30 days follow-up.

4. DISCUSSION

4.1 Summary of Available Evidence

Three prospective, multi-centre DB RCTs were included in the review, all of which were placebo-controlled superiority trials (ENABLE 1, n = 682;[20,22] ENABLE 2, n = 759;[20,23] and TPL102357, n = 74).[21,24] The objective of all three trials was to assess the efficacy and safety of eltrombopag to increase platelets to sufficient levels for the initiation and maintenance of PEG-IFN and RBV therapy in patients with TCP associated with chronic HCV infection. All three trials incorporated an initiation, pre-AVT phase (Part 1) and a DB AVT phase (Part 2). The trials differed in the primary outcome, as the ENABLE trials assessed virologic response (SVR) whereas Study TPL102357 evaluated platelet response. The trials included patients who were primarily Caucasian males in their early 50s. Most patients were infected with HCV genotype 1 followed by genotype 2 or 3 and had TCP associated with chronic HCV infection and mainly compensated liver disease. A key limitation of the trials was the requirement for PEG-IFN and RBV dose adjustments and discontinuations to be done in accordance with the product's approved labelling, which is not consistent with clinical practice in Canada. Other limitations include inclusion of IFN-experienced patients, use of two different formulations of pegylated interferon (alfa-2a and alfa-2b) with different platelet thresholds for initiation of AVT, uncertainty regarding length of treatment received by patients with genotype 2 or 3 (i.e., 24 weeks versus 48 weeks), and the large patient dropout rate in the placebo group and early termination of enrolment of patients into Study TPL102357.

4.2 Interpretation of Results

4.2.1 Efficacy

There is currently no approved intervention in Canada for the treatment of TCP associated with chronic HCV infection. According to the clinical expert, the only option available to physicians is to adjust the dosage of PEG-IFN and RBV in response to platelet counts. Platelet transfusion is not an option because the spleen rapidly sequesters administered platelets. Therefore, it is acceptable that the three included trials were placebo-controlled due to the fact that there is currently no active comparator treatment available. The patients included in the three trials reflect a very sick patient population (i.e., cirrhotic patients with platelet counts in the range of 50 Gi/L to 70 Gi/L) who comprise only a small subset of all chronically HCV-infected patients in Canada. Therefore, although the baseline patient and disease characteristics of the study population in the included trials limit the generalizability of the results to a broad population of HCV-infected patients, at the same time, they support use of eltrombopag in a small, well defined group of patients. The clinical expert advised that these patients would be treated by a physician or group of physicians specializing in the treatment of viral hepatitis in a centre focused on treating very ill patients, and thus restriction of eltrombopag to such a physician group may be appropriate.

The primary outcome in the ENABLE trials was achievement of SVR, which is stated to be the overall objective of HCV treatment.[6] In both ENABLE trials, eltrombopag resulted in a statistically significantly greater proportion of patients achieving SVR compared with patients in the placebo groups. This finding is also supported by statistically significantly greater proportions of patients achieving EVR, cEVR, ETR, and SVR12 with eltrombopag compared with placebo.

The manufacturer is requesting listing eltrombopag only for patients with HCV genotype 2 or 3; however, the SVR results support similar efficacy of eltrombopag across all genotypes. When the rates of SVR are examined by the baseline strata of patients with HCV genotype 2 or 3 versus non-genotype 2 or 3, the rates of SVR were higher in the eltrombopag-treated patients compared with placebo-treated patients. Statistical testing, however, showed no difference in attainment of SVR due to HCV genotype 2

or 3 or non-genotype 2 or 3 compared with the overall study population. Similar findings were reported for the other baseline strata. The trials were not powered to make comparisons between strata.

It could not be confirmed from the ENABLE trials if any patients with HCV genotype 2 or 3 received more than 24 weeks of AVT. The 2012 CASL guidelines recommend that for patients with HCV genotype 3 who do not achieve RVR but have an EVR, consideration should be given to extending treatment for 36 weeks to 48 weeks, particularly in the setting of predictors of poor response (e.g., fibrosis), which is consistent with the patients in the trials.[6] The length of treatment in patients with HCV genotype 2 or 3 may have important consequences for achievement of SVR and for the cost of treatment, especially if 48 weeks of treatment is required.

A major limitation of the included trials is that dose adjustment and discontinuation of PEG-IFN and RBV therapy is not representative of clinical practice in Canada due to the requirement to follow the approved product labelling in the trials. According to the clinical expert, many experienced Canadian physicians initiate and maintain PEG-IFN and RBV at much lower platelet counts than was done in the trials. As discussed in Section 3.5.2, this may have overestimated the efficacy results in favour of eltrombopag because AVT was likely stopped sooner than is currently done in practice. Nonetheless, the clinical expert advised that the SVR rates attained in this patient population (e.g., 35% in HCV genotype 2 or 3 infected patients in ENABLE 1) are clinically significant, as these rates would not normally be expected with IFN and RBV therapy in these patients.

Bleeding events occurred infrequently across the three trials and may reflect the fact that despite being thrombocytopenic, bleeding risk does not appear to be a serious issue in these patients. According to the clinical expert, although these patients have TCP, the platelets generally remain healthy and functional and this may be why serious bleeding is rare. This is also, in part, why physicians tend to initiate and maintain AVT at much lower platelet counts than is recommended in the approved labelling.

In all three trials, eltrombopag demonstrated a rapid and pronounced platelet response with almost all patients achieving platelet threshold levels for initiation of AVT within two weeks to four weeks. Following the initiation phase (Part 1) of the trials, during which all patients were treated with eltrombopag (no AVT), almost all patients were able to enter Part 2 and initiate AVT. Patients in the eltrombopag treatment groups were able to receive a higher cumulative dose of PEG-IFN and RBV for a longer duration than patients in the placebo groups. The high platelet response also appeared to be attained with doses of eltrombopag in the order of 25 mg to 50 mg daily. The clinical expert advised that these findings are reassuring and support that eltrombopag may have clinical benefit in that small doses can be used for a relatively short time to recover platelets if required.

HRQoL did not appear to be impacted by eltrombopag as there were no statistically significant differences identified between treatment groups as measured by the SF-36 or CLDQ-HCV instruments (i.e., with the exception of the worry subscale in the CLDQ-HCV, where eltrombopag demonstrated a statistically significant improvement over placebo). Although these findings do not support a clinical benefit on HRQoL with eltrombopag, they may support that eltrombopag does not negatively affect HRQoL in these patients, although there could be other explanations for this.

There were few deaths, especially deaths due to hepatobiliary disorders, despite the very ill study populations. None of the deaths was attributed specifically to eltrombopag although five deaths across all the trials were attributed to all three study drugs (i.e., eltrombopag, IFN, and RBV). Due to the small numbers, no conclusions can be drawn from these data. Of note, in the ENABLE trials, the number of

patients with events suggestive of hepatic decompensation was higher in patients treated with eltrombopag compared with placebo-treated patients. The clinical expert expressed concern regarding this finding; however, no underlying cause could be identified other than due to the baseline characteristics of the patients in the trials, many were at the brink of decompensation.

Adherence was measured only in the ENABLE trials and statistically significantly more eltrombopag-treated patients were adherent (i.e., received 80% of the prescribed dose of both PEG-IFN and RBV for 80% of the planned duration) than placebo-treated patients in both trials. It was also shown that adherence was significantly associated with SVR. These findings lend further support for the ability of eltrombopag to maintain AVT in patients who might otherwise be unable to undergo the required dosing regimen of AVT to attain SVR. Adherence was not measured in Study TPL102357. Health care resource utilization was also not measured in any of the three included trials.

In the opinion of the clinical expert, the place in therapy for eltrombopag is in a very small, well defined patient population with extensive cirrhosis associated with chronic HCV infection and TCP (< 50 Gi/L to 70 Gi/L). These patients would most likely be managed in a specialized care setting by physicians experienced in the treatment of viral hepatitis and the use of eltrombopag should be restricted to such a group. Further to this, the clinical expert advised that the best choice of therapy for these patients is the recently introduced IFN-free therapies due to their superior virologic response rates; however, because of their limited availability, eltrombopag could be useful in facilitating IFN therapy in these patients at least during the short term. Given the poor virologic response rates expected with IFN therapy in this patient population, coupled with the AEs and complications associated with IFN therapy, many physicians may opt not to treat these patients with IFN at all, but rather to wait for a liver transplant.

4.2.2 Harms

Due to the design of the included trials, the assessment of AEs attributed solely to eltrombopag can only be derived from Part 1 (initiation phase) where eltrombopag was used without AVT. As well, since Part 1 ranged only from 2 weeks to 9 weeks, no long-term safety data for eltrombopag alone are provided by these trials. The high dropout rate (78%) in the placebo group during Part 1 of Study TPL102357 also means that very limited comparative AE data were captured. Overall, the most common AE in both treatment groups across all three trials in Part 1 was headache.

In Part 2 (DB AVT phase), the AE profile reflects the combined use of eltrombopag, IFN, and RBV. This makes it difficult to isolate AEs that were directly due to eltrombopag as opposed to the increased exposure to AVT. During Part 2, almost all patients, regardless of treatment group, experienced at least one AE. Caution must be exercised in drawing any comparisons based on Study TPL102357, as only four patients in the placebo group entered Part 2. In the ENABLE trials, the most common AEs in Part 2 were hematology-related (e.g., anemia, neutropenia, TCP) whereas in Study TPL102357, the most common AE was influenza-like illness, an AE commonly associated with IFN therapy.

During Part 1, the proportion of patients with SAEs in the ENABLE trials was 1%, but rates in Part 2 were much higher (i.e., 20% with eltrombopag and 15% with placebo). There was no clear pattern with regard to the type of SAEs reported; however, SAEs related to GI and hepatobiliary disorders occurred more frequently in the eltrombopag group. In Study TPL102357, SAEs occurred less frequently, but the proportion of eltrombopag-treated patients with SAEs was almost double that in the placebo group; however, the results in the placebo group are compromised by the high dropout rate and resultant lack of AE data in this group. The proportion of patients with WDAEs was low (≤ 1%) during Part 1 of the ENABLE trials, but increased in both treatment groups in Part 2, with more patients in the placebo group

with WDAEs compared with the eltrombopag group. There also did not appear to be a clear pattern for WDAEs in eltrombopag-treated patients; however, in placebo-treated patients the main reason for withdrawal was TCP. In Study TPL102357, only patients in the eltrombopag group had WDAEs.

Notable harms in Part 2 (DB AVT phase) of the trials included thromboembolic events, hepatobiliary AEs, malignancy, TCP AEs, bone marrow fibrosis, and ocular AEs. Thromboembolic events occurred only in the ENABLE studies, where a higher proportion of eltrombopag-treated patients experienced at least one thromboembolic event compared with placebo-treated patients. Of note, portal vein thromboses occurred more frequently in eltrombopag-treated patients. Patients who received eltrombopag also had a higher incidence of events suggestive of hepatic decompensation (e.g., ascites, hepatic encephalopathy, and variceal bleeding) and the clinical expert speculated that this could be related to thrombosis, but the cause remains unknown. Hepatobiliary AEs were also reported more frequently in eltrombopag-treated patients, primarily due to hyperbilirubinemia. In the ENABLE trials, confirmed malignancies were reported in similar proportions of patients in both treatment groups with the majority due to hepatic neoplasm, which is not unexpected in this patient population. No malignancies were reported in Study TPL102357. In both ENABLE trials, TCP AEs occurred more frequently in placebo-treated patients compared with eltrombopag-treated patients, which is also expected, given the lower platelet counts in placebo-treated patients. No TCP AEs were reported in Study TPL102357. Bone marrow fibrosis was not reported as an AE in any of the three trials. Ocular AEs occurred with similar frequency in both treatment groups in ENABLE 1 and at slightly higher frequency in eltrombopag-treated patients in ENABLE 2 and Study TPL102357.

The requirement to adhere to product labelling for PEG-IFN and RBV dose adjustments and discontinuations may also have underestimated the safety results, because AVT was stopped sooner than is currently done in Canadian clinical practice. This resulted in less patient exposure to IFN and RBV and their associated AEs and complications, especially in the placebo groups. The clinical expert advised that due to concerns regarding the safety profile of eltrombopag in the context of the increased frequency of thromboembolic events and events suggestive of hepatic decompensation, this is another important reason that use of eltrombopag should be limited to specialized physicians with the expertise to identify patients who will benefit the most from this therapy.

4.3 Other Considerations

Two patient groups provided input as summarized in Appendix 1. The expectation of the patient groups is that eltrombopag will enable patients with HCV who cannot receive optimal treatment due to TCP to initiate and maintain treatment at optimal doses and for the required duration to achieve cure. The results of the ENABLE trials appear to have met this expectation as a statistically significantly higher proportion of eltrombopag-treated patients achieved SVR compared with placebo-treated patients. The serious AE profile of eltrombopag was also acknowledged by the patient groups, as was the need for careful preparation and monitoring of patients during treatment; however, it was noted that patients are willing to endure fairly severe AEs if they can potentially be cured.

The ELEVATE study was a placebo-controlled, DB, randomized trial that evaluated the efficacy of eltrombopag for increasing platelet counts and reducing the need for platelet transfusions in patients with TCP and chronic liver disease who were undergoing an invasive elective procedure.[7] This study was terminated early due to an imbalance of thromboembolic events in the eltrombopag group. In the study, patients with platelet counts < 50 Gi/L were randomly assigned to either eltrombopag 75 mg daily or placebo for 14 days prior to the procedure. The study met its primary end point, which was avoidance of a platelet transfusion in 72% of patients who received eltrombopag compared with 19% of placebo-

treated patients; *P* < 0.001. Thrombotic events of the portal venous system were observed in six patients (seven events) who received eltrombopag and two patients (three events) in patients who received placebo (odds ratio 3.04 [95% CI, 0.62 to 14.82]), resulting in the early termination of the study. The incidence and severity of other AEs were similar between the eltrombopag and placebo groups. A post-hoc analysis identified an association between patients who had a platelet count of 200 Gi/L or higher and risk of thrombotic events; however, it was hypothesized that the combination of a sustained increase in platelets and an associated degree of predisposing injury from the procedure could have contributed to the development of thrombosis. It was concluded that further investigation is required, including better identification of risk factors for the development of thrombosis, dose optimization and careful patient selection for eltrombopag.

5. CONCLUSIONS

Three prospective, multi-centre, DB, placebo-controlled trials (ENABLE 1, ENABLE 2, and TPL102357) were included in this review. The trials enrolled patients primarily infected with HCV genotype 1 or genotype 2 or 3 with associated TCP and mainly compensated liver disease. In all three trials, eltrombopag 25 mg to 100 mg once daily facilitated the introduction of PEG-IFN and RBV therapy by increasing platelet counts to a threshold that allowed for the initiation of AVT in ≥ 94% (ENABLE 1 and ENABLE 2) and ≥ 66% (TPL102357) of patients within 2 weeks to 4 weeks. Patients treated with eltrombopag had a higher cumulative dose and duration of PEG-IFN and RBV therapy versus placebo-treated patients. In the ENABLE trials, a statistically significantly greater proportion of eltrombopag-treated patients achieved SVR compared with placebo-treated patients. Bleeding events were infrequent across treatment groups in all trials and eltrombopag did not appear to negatively affect patients' HRQoL in the ENABLE trials. Eltrombopag in combination with PEG-IFN and RBV was associated with a higher frequency of thromboembolic events, hepatobiliary AEs, and events suggestive of hepatic decompensation compared with placebo in combination with PEG-IFN and RBV.

APPENDIX 1: PATIENT INPUT SUMMARY

This section was summarized by CADTH staff based on the input provided by patient groups. It has not been systematically reviewed.

1. Brief Description of Patient Group(S) Supplying Input

Two patient groups submitted patient input.

The GI (Gastrointestinal) Society is committed to improving the lives of people with GI and liver conditions by supporting research, advocating for patient access in health care, and promoting GI and liver health. In the last two years, the GI Society has received funding from Abbott Laboratories Ltd., AbbVie Corporation, Amgen Canada Inc., Actavis (as Aptalis Pharma, Forest Laboratories, and Warner Chilcott), AstraZeneca Canada Inc., Bristol-Myers Squibb Canada, Canada's Research-Based Pharmaceutical Companies (Rx&D), Ferring Inc., Gilead Sciences Canada Inc., GlaxoSmithKline Inc., Hoffmann-La Roche Ltd., Janssen Canada, Merck Canada Inc., Medical Futures Inc., Novartis Pharma Canada Inc., Cubist Pharmaceuticals (as Optimer Pharma), Pfizer Canada Inc., Sanofi-Aventis Canada Inc., Takeda Canada Inc., and Vertex Pharmaceuticals (Canada) Inc. The GI Society declared no conflict of interest in preparation of this submission.

HepCBC Hepatitis C Education and Prevention Society (HepCBC) provides education, prevention, and support to those living with hepatitis C virus (HCV) in British Columbia. HepCBC received funding over the past three years from Merck Pharmaceuticals, Hoffmann-La Roche, Vertex Pharmaceuticals, Gilead Sciences, Janssen Pharmaceuticals, Bristol-Myers Squibb, Boehringer-Ingelheim, and AbbVie. The author has been funded by the pharmaceutical companies listed above for registration and travel to educational conferences and meetings.

2. Condition and Current Therapy-Related Information

Information was compiled for input by through contact and interviews with patients affected by HCV, HCV nurse specialists, volunteers, and health care professional advisers.

Thrombocytopenia, a condition characterized by low platelet levels, causes bruising and easy bleeding. Patients with HCV may suffer from low platelets due to cirrhosis and are at risk of bleeding to death, particularly if they suffer from bleeding varices. Thrombocytopenia makes it difficult or impossible for an affected patient to receive treatment for their hepatitis C. Without HCV treatment, patients can develop severe liver damage, such as cirrhosis. In addition, patients receiving interferon treatment often develop low platelets, which if not brought under timely control, may require withdrawal from treatment leading to worsening of their condition with a likely development of cirrhosis over time as well as of increased risk of liver cancer and liver failure.

One of the patient groups reported that patients with chronic HCV with low platelets are currently given infusions, injections, and less frequently, transfusions, which are both painful and inconvenient; however, what the infusions and injections are is not specified. The group also noted that patients do not seem to get any treatment at all.

3. Related Information About the Drug Being Reviewed

Neither patient group indicated that they were aware of any patients who had received Revolade. The expectation is that Revolade will enable patients with HCV to initiate and complete treatment — that is, patients who cannot receive optimal treatment due to thrombocytopenia may be able to stay on their

treatment medications at optimal doses and for the required time to achieve cure. Patient groups are aware that Revolade has serious side effects and that patients need to be carefully prepared and monitored during treatment; however, patients are willing to endure fairly severe side effects if they can be cured. Patient groups are also aware that patients with very advanced cirrhosis will likely not be able to take this drug because of its hepato-toxicity and that it should not be used in elderly patients with reduced renal or cardiac function.

Nonetheless, patient groups expect that Revolade would likely result in fewer deaths, higher rates of treatment initiations and completions, fewer hospital visits, and less time off work, which could result in greater financial stability, greater mental stability, and fewer family breakdowns.

APPENDIX 2: LITERATURE SEARCH STRATEGY

OVERVIEW	
Interface:	Ovid
Databases:	Embase 1974 to present MEDLINE Daily and MEDLINE 1946 to present MEDLINE In-Process & Other Non-Indexed Citations **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of search:	October 6, 2014
Alerts:	Bi-weekly search updates until February 18, 2015
Study types:	No search filters were applied
Limits:	No date or language limits were used Human filter was applied Conference abstracts were excluded

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
.sh	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
fs	Floating subheading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
#	Truncation symbol for one character
?	Truncation symbol for one or no characters only
adj	Requires words are adjacent to each other (in any order)
adj#	Adjacency within # number of words (in any order)
.ti	Title
.ab	Abstract
.ot	Original title
.hw	Heading word; usually includes subject headings and controlled vocabulary
.pt	Publication type
.po	Population group [PsycInfo only]
.rn	CAS registry number
.nm	Name of substance word
pmez	Ovid database code; MEDLINE In-Process & Other Non-Indexed Citations, MEDLINE Daily and Ovid MEDLINE 1946 to Present
oemezd	Ovid database code; Embase 1974 to present, updated daily

MULTI-DATABASE STRATEGY			
1	(Revolade or eltrombopag* or Promacta or SB-497115 or SB497115 or SB-497-115 or UNII-S56D65XJ9G or UNIIS56D65XJ9G).ti,ab,ot,sh,hw,rn,nm.	1207	Advanced
2	496775-61-2.rn,nm.	682	Advanced
3	1 or 2	1207	Advanced
4	3 use pmez	315	Advanced
5	(Revolade or eltrombopag* or Promacta or SB-497115 or SB497115 or SB-497-115 or UNII-S56D65XJ9G or UNIIS56D65XJ9G).ti,ab.	742	Advanced
6	*eltrombopag/	324	Advanced

MULTI-DATABASE STRATEGY			
7	5 or 6	779	Advanced
8	7 not conference abstract.pt.	594	Advanced
9	8 use oemezd	329	Advanced
10	4 or 9	644	Advanced
11	remove duplicates from 10	390	Advanced
12	exp animals/	37284525	Advanced
13	exp animal experimentation/ or exp animal experiment/	1812417	Advanced
14	exp models animal/	1219025	Advanced
15	nonhuman/	4380452	Advanced
16	exp vertebrate/ or exp vertebrates/	36332298	Advanced
17	exp humans/	28982931	Advanced
18	exp human experimentation/ or exp human experiment/	341719	Advanced
19	or/17-18	28985020	Advanced
20	or/12-16	38540020	Advanced
21	20 not 19	9556598	Advanced
22	11 not 21	387	Advanced

OTHER DATABASES	
PubMed	Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.
Trial registries (Clinicaltrials.gov and others)	Same keywords, limits used as per MEDLINE search.

Grey Literature

Dates for Search:	September 25, 2014 – October 3, 2014
Keywords:	Revolade (eltrombopag), Chronic hepatitis C-associated thrombocytopenia
Limits:	No date or language limits used

Relevant websites from the following sections of the CADTH grey literature checklist, "Grey matters: a practical tool for evidence-based searching" (http://www.cadth.ca/en/resources/finding-evidence-is/grey-matters) were searched:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Databases (free)
- Internet Search.

APPENDIX 3: DETAILED OUTCOME DATA

TABLE 12: ENABLE 1 AND ENABLE 2: SUSTAINED VIROLOGIC RESPONSE (INTENTION-TO-TREAT POPULATION)

Outcome	ENABLE 1		ENABLE 2	
	ELT (N = 450)	PL (N = 232)	ELT (N = 506)	PL (N = 253)
SVR, n (%)				
Yes	104 (23)	33 (14)	97 (19)	32 (13)
No	346 (77)	199 (86)	409 (81)	221 (87)
Per cent diff.[a] (95% CI)	7.9 (2.4 to 13.4)		6.0 (1.2 to 10.9)	
P value	0.0064		0.0202	
HCV RNA genotype, n/N (%) genotype 2 or 3	50/142 (35)	18/76 (24)	52/153 (34)	19/76 (25)
Per cent diff. (95% CI)	9.2 (–3.0 to 21.5)		10.4 (–2.4 to 23.3)	
Non-genotype 2 or 3	54/307 (18)	15/156 (10)	45/346 (13)	13/186 (7)
Per cent diff. (95% CI)	7.6 (1.4 to 13.7)		5.3 (0.1 to 10.6)	
P value for interaction[b]	0.6393		0.5900	
Platelet Count, n/N (%) < 50 Gi/L	28/124 (23)	10/62 (16)	25/139 (18)	5/83 (6)
Per cent diff. (95% CI)	6.1 (–5.4 to 17.7)		8.1 (–0.1 to 16.3)	
≥ 50 Gi/L	76/326 (23)	23/170 (14)	72/360 (20)	27/180 (15)
Per cent diff. (95% CI)	8.4 (2.1 to 14.7)		4.9 (–1.1 to 11.0)	
P value for interaction[b]	0.5634		0.0741	
HCV RNA, n/N (%) < 800,000 IU/mL	65/236 (28)	22/112 (20)	54/270 (20)	23/135 (17)
Per cent diff. (95% CI)	7.8 (–1.0 to 16.6)		3.7 (–3.4 to 10.8)	
≥ 800,000 IU/mL	39/214 (18)	11/119 (9)	43/239 (18)	9/113 (8)
Per cent diff. (95% CI)	8.0 (0.9 to 15.0)		8.4 (1.6 to 15.1)	
P value for interaction[b]	0.4579		0.0613	

CI = confidence interval; diff. = difference; ELT = eltrombopag; Gi/L = giga per litre; HCV = hepatitis C virus; IU/mL = international units per millilitre; n = number of patients with event; N = number of patients; PL = placebo; RNA = ribonucleic acid; SVR = sustained virologic response.

[a] Adjusted for actual strata: HCV genotype, baseline platelet count, HCV RNA stratum; SVR is defined as the proportion of patients with undetectable HCV RNA at end of treatment and all subsequent planned visits up to 24 weeks after completing treatment (generally week 48 or week 72 for genotype 2 or 3, or week 72 for non-genotype 2 or 3).

[b] *P* value is a test of the null hypothesis of homogeneity (i.e., no treatment by strata subgroup interaction).

TABLE 13: SUMMARY OF VARICEAL AND NON-VARICEAL BLEEDING EVENTS DURING PART 2 PLUS FOLLOW-UP (SAFETY POPULATION)

Outcome	ENABLE 1		ENABLE 2		TPL102357	
	ELT (N = 449)	PL (N = 232)	ELT (N = 506)	PL (N = 253)	ELT (N = 56)	PL (N = 18)
No. with variceal bleeding, n (%)	10 (2)	2 (< 1)	3 (< 1)	2 (< 1)	0	0
No. with non-variceal bleeding, n (%)	74 (16.5)	57 (24.6)	80 (16)	45 (18)	6 (10.7)	3 (16.7)

ELT = eltrombopag; n = number of patients with event; N = number of patients; No. = number; PL = placebo.
Note: Variceal bleeding events included esophageal and/or gastric bleeding events.

TABLE 14: ENABLE 1 AND ENABLE 2: SUMMARY OF PLATELET COUNTS (GI/L) DURING PART 1 (SAFETY POPULATION)

Outcome	ENABLE 1	ENABLE 2
Platelet count increased to threshold	**≥ 90 Gi/L**	**≥ 100 Gi/L**
n (%)	691 (97)	773 (96)
(95% CI)	(85 to 98)	(94 to 97)
Time in weeks to threshold, n, N (%)		
Within 2 weeks	281 (39)	204 (25)
2 to < 4 weeks	324 (45)	421 (52)
4 to < 6 weeks	60 (8)	101 (13)
6 to < 8 weeks	18 (3)	32 (4)
8 to 9 weeks	5 (< 1)	7 (< 1)
> 9 weeks	3 (< 1)	8 (< 1)
Mean number of weeks (SD)	2.41 (1.4)	2.84 (1.7)
Median number of weeks (Min–Max)	2.14 (0.1 to 9.6)	2.1 (0.1 to 14.9)

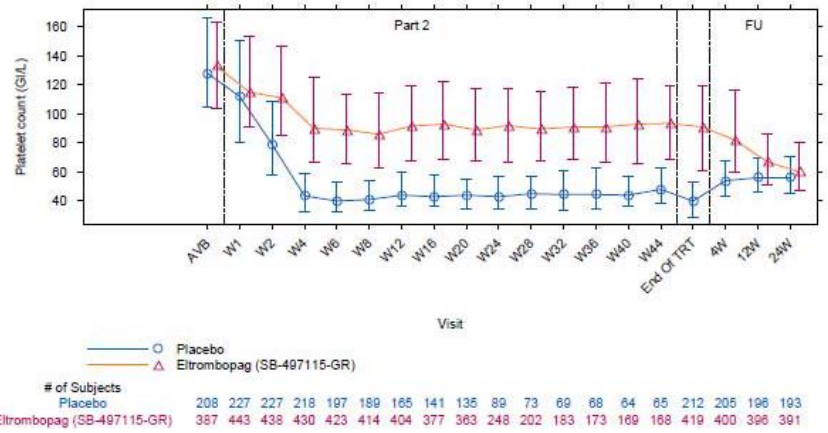
CI = confidence interval; Gi/L = giga per litre; Min–Max = minimum to maximum; n = number of patients with event; N = number of patients; SD = standard deviation.

TABLE 15: ENABLE 1 AND ENABLE 2: SUMMARY OF PLATELET COUNTS (GI/L) DURING PART 2 (INTENTION-TO-TREAT POPULATION)

Outcome	ENABLE 1		ENABLE 2	
	ELT (N = 450)	PL (N = 232)	ELT (N = 506)	PL (N = 253)
Antiviral BL (Part 2)[a]	n = 387	n = 208	N = 460	N = 238
Mean (SD)	146.9 (60.0)	144.0 (57.1)	151.9 (52.1)	151.9 (49.0)
Median (Min–Max)	133 (64 to 509)	128 (84 to 521)	136 (43 to 400)	140 (63 to 365)
Week 4	n = 430	n = 218	N = 487	N = 228
Mean (SD)	103.6 (54.1)	55.2 (38.0)	114.3 (51.2)	59.7 (30.3)
Median (Min–Max)	90 (5 to 430)	43.5 (17 to 275)	105 (19 to 389)	51.0 (20 to 180)
Week 12	n = 404	n = 165	N = 451	N = 176
Mean (SD)	97.9 (43.8)	56.1 (39.96)	110.3 (48.9)	58.2 (32.4)
Median (Min–Max)	91.5 (25 to 298)	44 (16 to 284)	104 (10 to 444)	49.7 (21 to 264)
Week 24	n = 248	n = 89	N = 263	N = 99
Mean (SD)	93.3 (36.9)	56.9 (44.8)	110.6 (52.1)	56.6 (30.5)
Median (Min–Max)	92 (18 to 276)	43 (21 to 333)	102 (18 to 448)	49 (19 to 200)
EOT or withdrawal	n = 419	n = 212	N = 468	N = 240
Mean (SD)	96.6 (48.6)	51.6 (42.3)	113.1 (53.7)	57.6 (30.7)
Median (Min–Max)	91 (17 to 486)	40 (10 to 318)	106.5 (10 to 445)	51 (10 to 275)
4 week follow-up	n = 400	n = 205	N = 424	N = 221
Mean (SD)	91.6 (45.2)	64.2 (44.99)	98.8 (47.8)	66.5 (29.8)
Median (Min–Max)	82 (5 to 304)	54 (5 to 358)	89 (12 to 333)	63 (4 to 225)

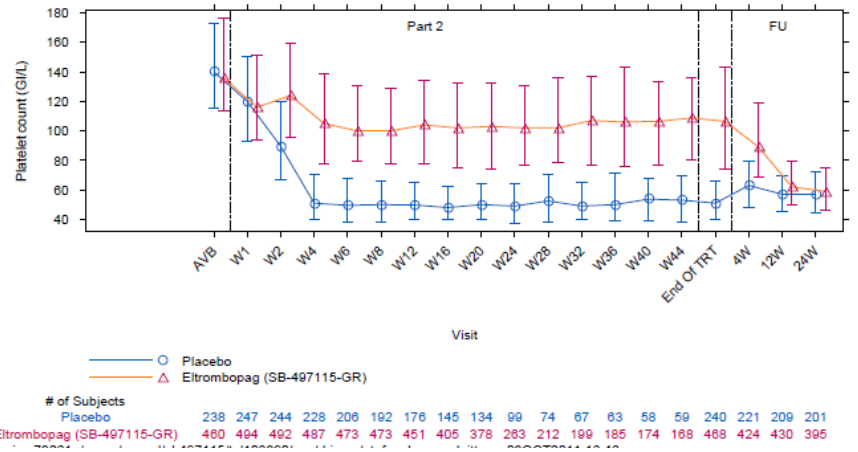
BL = baseline; ELT = eltrombopag; EOT = end of treatment; ITT = intention-to-treat; Gi/L = giga per litre; Min–Max = minimum to maximum; n = number of patients with event; N = number of patients; PL = placebo; SD = standard deviation.
[a] Baseline platelet count at the start of phase 2 DB AVT phase.

FIGURE 3: ENABLE 1: MEDIAN PLATELET COUNTS IN PART 2 (INTENTION-TO-TREAT POPULATION)



FU = follow-up; Gi/L = giga per litre; TRT = treatment; w = week.
Note: Bars represent the interquartile range.
Source: ENABLE 1.[22]

FIGURE 4: ENABLE 2: MEDIAN PLATELET COUNTS IN PART 2 (INTENTION-TO-TREAT POPULATION)



FU = follow-up; Gi/L = giga per litre; TRT = treatment; w = week.
Note: Bars represent the interquartile range.
Source: ENABLE 2.[23]

TABLE 16: ENABLE 1 AND ENABLE 2: SUMMARY OF MINIMUM PLATELET COUNTS (GI/L) DURING PART 2 (INTENTION-TO-TREAT POPULATION)

Outcome	ENABLE 1		ENABLE 2	
	ELT (N = 450)	PL (N = 232)	ELT (N = 506)	PL (N = 253)
Minimum platelet count with AVT (Gi/L), n (%)				
< 25	12 (3)	63 (27)	20 (4)	34 (13)
≥ 25 to < 50	125 (28)	135 (58)	76 (15)	159 (63)
≥ 50 to < 90	245 (54)	19 (8)	263 (52)	49 (19)
≥ 90 to < 150	58 (13)	11 (5)	135 (27)	10 (4)
≥ 150 to < 200	6 (1)	2 (< 1)	8 (2)	0
≥ 200 to < 400	1 (< 1)	2 (< 1)	4 (< 1)	0
≥ 400	0	0	0	0
Missing	3 (< 1)	0	0	1 (< 1)

AVT = antiviral therapy; ELT = eltrombopag; Gi/L = giga per litre; n = number of patients with event; N = number of patients; PL = placebo.

TABLE 17: ENABLE 1 AND ENABLE 2: SUMMARY OF MAXIMUM DURATIONS OF PLATELET COUNTS ≥ 50 GI/L DURING PART 2 (INTENTION-TO-TREAT POPULATION)

Outcome	ENABLE 1		ENABLE 2	
	ELT (N = 450)	PL (N = 232)	ELT (N = 506)	PL (N = 253)
Maximum continuous duration, weeks				
Overall, n	447	232	504	252
Mean (SD)	25.6 (15.6)	7.5 (11.7)	26.3 (15.0)	9.7 (12.6)
Median (Min–Max)	24.1 (0.1 to 51)	2.4 (0.1 to 51)	24.1 (0.1 to 52.1)	4.1 (0.1 to 49.4)
Genotype 2 or 3, n	141	76	153	75
Mean (SD)	18.9 (10.2)	4.9 (6.2)	23.3 (10.9)	9.1 (10.9)
Median (Min–Max)	23.1 (1 to 48.6)	2.1 (0.1 to 24.4)	23.9 (2.1 to 50)	4.3 (0.1 to 48.6)
Genotype, non 2 or 3, n	306	156	351	177
Mean (SD)	28.7 (16.7)	8.8 (13.4)	27.6 (16.3)	10.0 (13.2)
Median (Min–Max)	28.1 (0.1 to 51)	2.9 (0.1 to 50)	26.1 (0.1 to 52.1)	4.0 (0.1 to 49.4)
Maximum cumulative duration, weeks				
Overall, n	447	232	504	252
Mean (SD)	26.7 (15.3)	8.6 (12.3)	27.1 (14.8)	11.1 (13.3)
Median (Min–Max)	24.1 (0.1 to 51)	3.1 (0.1 to 50)	24.2 (0.1 to 52.1)	4.4 (0.1 to 49.4)
Genotype 2 or 3, n	141	76	153	75
Mean (SD)	19.7 (9.9)	5.5 (6.5)	24.0 (10.4)	10.1 (11.1)
Median (Min–Max)	23.1 (1 to 48.6)	2.4 (0.1 to 24.4)	23.9 (2.1 to 50)	5.3 (0.1 to 48.6)
Genotype, non 2 or 3, n	306	156	351	177
Mean (SD)	29.9 (16.3)	10.1 (14.0)	28.5 (16.2)	11.5 (14.2)
Median (Min–Max)	32.1 (0.1 to 51)	3.3 (0.1 to 50)	27.4 (0.1 to 52.1)	4.1 (0.1 to 49.4)

ELT = eltrombopag; Gi/L = giga per litre; Min–Max = minimum to maximum; n = number of patients with event; N = number of patients; PL = placebo; SD = standard deviation.
Note: Continuous duration is the longest continuous time with platelet count ≥ 50 Gi/L; cumulative duration is the number of cumulative weeks with platelet count ≥ 50 Gi/L.

TABLE 18: TPL102357: RESPONDERS TO TREATMENT IN PART 1 (ITT POPULATION LOCF)

Outcome	ELT 30 mg (N = 14)	ELT 50 mg (N = 19)	ELT 75 mg (N = 23)	PL (N = 18)
	Initiation Phase (Part 1)			
Assessment visit				
Day 8	2 (17)	4 (21)	6 (29)	0
Day 15	8 (67)	12 (63)	18 (86)	0
Day 22	8 (67)	15 (79)	20 (95)	0
Day 28	9 (75)	15 (79)	20 (95)	0
OR (95% CI)	26 (4 to 166)	32 (5 to 190)	86 (12 to 616)	
***P* value vs. PL**	0.00067	0.00015	< 0.0001	
P value for overall treatment effect at day 28 *P* < 0.00010.				

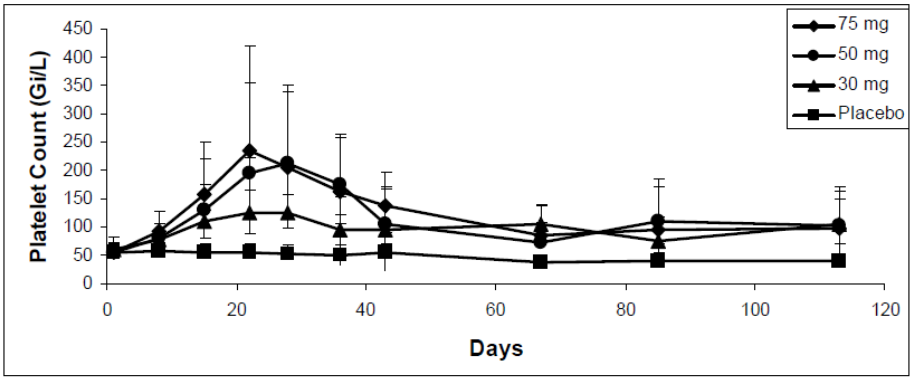
CI = confidence interval; ELT = eltrombopag; ITT = intention-to-treat; LOCF = last observation carried forward; mg = milligram; N = number of patients; OR = odds ratio; PL = placebo; SD = standard deviation; vs. = versus.
Note: Responders were defined as patients with a shift from baseline (day 1) platelet count between 20 Gi/L and < 70 Gi/L to ≥ 100 Gi/L at day 28. The percentage is calculated with the number evaluable as the denominator.

TABLE 19: TPL102357: PLATELET COUNTS (GI/L) IN PART 1 AND PART 2 (ITT POPULATION LOCF)

Outcome	ELT 30 mg (N = 14)	ELT 50 mg (N = 19)	ELT 75 mg (N = 23)	PL (N = 18)
	End of Initiation Phase (Part 1)			
No. patients with BL and post-BL measurements, n	14	19	23	18
Mean platelet count (SD)				
Baseline	56.6 (15.9)	51.4 (9.9)	53.8 (11.6)	53.9 (13.1)
Study end point	176.4 (180.1)	203.2 (135.1)	240.2 (114.8)	50.4 (12.1)
Mean change (SD)	119.9 (176.2)	151.7 (133.7)	186.4 (109.6)	–3.5 (11.0)
Txt. diff vs. PL (95% CI)	138.9 (48.3 to 229.4)	154.5 (74.4 to 234.6)	184.0 (105.7 to 262.3)	NA
P value	0.003	< 0.001	< 0.001	NA
	End of DB AVT Phase (Part 2)			
No. patients entering Part 2	10	14	21	4
Visit 7 (day 36)	N = 10	N = 12	N = 18	N = 3
Median platelet count	95.5	173.5	162.0	51.0
(Min–Max)	(10 to 161)	(62 to 330)	(102 to 304)	(32 to 85)
Visit 11 (day 113)	N = 6	N = 10	N = 15	N = 1
Median platelet count	105.5	100.0	92.0	39.0
(Min–Max)	(43 to 164)	(46 to 156)	(38 to 245)	(39 to 39)

AVT = antiviral therapy; BL = baseline; CI = confidence interval; DB = double-blind; diff = difference; ELT = eltrombopag; Gi/L = giga per litre; ITT = intention-to-treat; LOCF = last observation carried forward; Min–Max = minimum to maximum; mg = milligram; n = number of patients with event; N = number of patients; NA = not applicable; No. = number; PL = placebo; SD = standard deviation; Txt. = treatment; vs. = versus.

FIGURE 5: TPL102357: MEDIAN PLATELET COUNTS IN PARTS 1 AND 2 (ITT POPULATION, OBSERVED DATA)



Gi/L = giga per litre; ITT = intention-to-treat.
Note: Bars represent inclusion of the 25th to 75th percentiles for each treatment group.
Source: TPL102357.[24]

TABLE 20: TPL102357: DURATION OF PLATELET RESPONSE (> 50 GI/L) IN PART 2 (ITT POPULATION)

Outcome	ELT 30 mg (N = 14)	ELT 50 mg (N = 19)	ELT 75 mg (N = 23)	PL (N = 18)
No. patients entering Part 2	10	14	21	4
Completion status, n				
Completed Part 2	5	10	15	1
Prematurely withdrew in Part 2	5	4	6	3
No. patients with platelet count > 50 Gi/L in Part 2, n				
For 5 visits	4	6	9	0
For 4 visits	2	3	6	0
For 3 visits	1	1	3	0
For 2 visits	2	2	3	2
For 1 visit	1	2	0	0
For 0 visits	0	0	0	2

ELT = eltrombopag; Gi/L = giga per litre; ITT = intention-to-treat; n = number of patients with event; N = number of patients; No. = number; PL = placebo.

TABLE 21: ENABLE 1 AND ENABLE 2: SUMMARY OF THE ANALYSIS OF CHANGE FROM BASELINE IN SF-36 SCORES DURING PART 2 (INTENTION-TO-TREAT POPULATION)

Characteristic	ENABLE 1		ENABLE 2	
	ELT (N = 440)	PL (N = 222)	ELT (N = 501)	PL (N = 242)
Physical health summary				
Baseline, mean (SD)	47.3 (8.9)	47.3 (8.3)	46.3 (9.1)	47.9 (8.9)
End of study, mean (SD)	44.5 (10.1)	44.5 (10.1)	44.2 (10.1)	44.3 (9.2)
Mean change (SE)	–2.8 (0.5)	–3.0 (0.6)	–2.3 (0.4)	–2.6 (0.6)
Txt. diff (95% CI)	0.2 (–1.2 to 1.6)		0.4 (–0.97 to 1.7)	
P value	0.787		0.601	
Mental health summary				
Baseline, mean (SD)	47.0 (9.4)	47.7 (8.3)	46.3 (9.7)	47.9 (9.2)
End of study, mean (SD)	44.5 (10.8)	44.6 (10.8)	44.4 (10.5)	45.4 (9.9)
Mean change (SE)	–2.8 (0.5)	–3.5 (0.7)	–1.9 (0.5)	–2.4 (0.6)
Txt. diff (95% CI)	0.7 (–0.8 to 2.2)		0.5 (–0.9 to 1.9)	
P value	0.343		0.456	

CI = confidence interval; ELT = eltrombopag; Diff = difference; N = number of patients; PL = placebo; SD = standard deviation; SE = standard error; SF-36 = Short-Form (36) Health Survey; Txt. = treatment.
Notes: Baseline was defined as the initial assessment in the open-label phase. There were no statistically significant differences between groups for any individual component scores.
Note: Data were analyzed only for patients having baseline and at least one on-AVT-based assessment.

TABLE 22: ENABLE 1 AND ENABLE 2: SUMMARY OF THE ANALYSIS OF CHANGE FROM BASELINE IN CLDQ-HCV SCORES DURING PART 2 (INTENTION-TO-TREAT POPULATION)

Characteristic	ENABLE 1		ENABLE 2	
	ELT (N = 446)	PL (N = 228)	ELT (N = 501)	PL (N = 248)
Activity or energy				
Baseline, mean (SD)	29.6 (8.6)	29.6 (7.6)	29.6 (8.6)	30.4 (8.2)
End of study, mean (SD)	28.2 (8.9)	27.8 (8.7)	27.8 (9.0)	28.3 (8.5)
Mean change (SE)	–1.4 (0.4)	–1.8 (0.6)	–1.8 (0.4)	–2.0 (0.5)
Txt. diff (95% CI)	0.4 (–0.9 to 1.7)		0.2 (–0.98 to 1.4)	
P value	0.520		0.722	
Emotion				
Baseline, mean (SD)	44.4 (9.9)	44.2 (9.5)	44.3 (9.8)	44.9 (9.6)
End of study, mean (SD)	42.9 (10.1)	42.4 (11.0)	43.7 (9.7)	43.2 (9.7)
Mean change (SE)	–1.4 (0.5)	–1.7 (0.7)	–0.5 (0.5)	–1.6 (0.6)
Txt. diff (95% CI)	0.3 (–1.3 to 1.9)		1.1 (–0.3 to 2.5)	
P value	0.713		0.126	
Systemic				
Baseline, mean (SD)	28.7 (7.6)	28.7 (7.0)	29.3 (7.9)	30.1 (7.7)
End of study, mean (SD)	27.7 (7.9)	27.2 (8.1)	27.9 (8.0)	28.2 (7.6)
Mean change (SE)	–0.9 (0.4)	–1.3 (0.5)	–1.4 (0.4)	–2.0 (0.5)
Txt. diff (95% CI)	0.5 (–0.6 to 1.6)		0.5 (–0.5 to 1.6)	
P value	0.385		0.330	
Worry				
Baseline, mean (SD)	38.8 (11.3)	38.5 (10.7)	38.7 (10.9)	39.9 (11.0)
End of study, mean (SD)	39.1 (11.2)	38.4 (12.3)	40.0 (11.1)	38.6 (11.0)
Mean change (SE)	0.4 (0.6)	–0.1 (0.8)	1.3 (0.5)	–1.3 (0.7)

Characteristic	ENABLE 1		ENABLE 2	
	ELT (N = 446)	PL (N = 228)	ELT (N = 501)	PL (N = 248)
Txt. diff (95% CI)	0.5 (–1.2 to 2.1)		2.6 (1.1 to 4.1)	
P value	0.598		0.001	
Overall				
Baseline, mean (SD)	4.9 (1.1)	4.9 (1.0)	4.9 (1.2)	5.0 (1.1)
End of study, mean (SD)	4.7 (1.2)	4.7 (1.2)	4.8 (1.2)	4.8 (1.2)
Mean change (SE)	–0.1 (0.1)	–0.2 (0.1)	–0.1 (0.1)	–0.2 (0.1)
Txt. diff (95% CI)	0.1 (–0.1 to 0.2)		0.1 (–0.01 to 0.3)	
P value	0.483		0.076	

CI = confidence interval; CLDQ-HCV = Chronic Liver Disease Questionnaire–Hepatitis C Virus; diff = difference; ELT = eltrombopag; ITT = intention-to-treat; N = number of patients; PL = placebo; SD = standard deviation; SE = standard error; Txt. = treatment.
Notes: Baseline was defined as the initial assessment in the open-label phase. Data were analyzed only for patients having baseline and at least one on-AV-based assessment.

TABLE 23: SUMMARY OF DEATHS (SAFETY POPULATION)

Characteristic	ENABLE 1		ENABLE 2		TPL102357	
	ELT (N = 450)	PL (N = 232)	ELT (N = 506)	PL (N = 253)	ELT (N = 56)	PL (N = 18)
Deaths due to any cause, n (%)	10 (2)	6 (3)	19 (4)	4 (2)	0	1 (6)
Deaths due to hepatobiliary disorders, n (%)						
Any event	3 (< 1)	2 (< 1)	3 (< 1)	0	0	0
Hepatic cirrhosis	NR	NR	1 (< 1)	0		
Hepatic failure	2 (< 1)	1 (< 1)	1 (< 1)	0		
Hepatic syndrome	0	0	1 (< 1)	0		
Hepatorenal syndrome	1 (< 1)	0	0	0		
Portal vein thrombosis	0	1 (< 1)	0	0		

ELT = eltrombopag; IFN = interferon; n = number of patients with event; N = number of patients; NR = not reported; PEG-IFN = pegylated interferon; PL = placebo; RBV = ribavirin.
Note: In ENABLE 1, there was no relationship to study drugs except for two deaths in the ELT group, where death was attributed to all three drugs. Causes of death were consistent with what would be expected in this study population receiving IFN-based therapy (e.g., hepatic neoplasm malignant, hepatic failure, renal failure, esophageal varices, ascites, sepsis). In ENABLE 2, 10 of 19 deaths in the ELT group and none of the deaths in the PL group were considered to be related to any study drug. The most common causes of death were gastrointestinal bleeding, infections, and hepatic decompensation, and in most, the underlying disease contributed to the fatal outcome. Five deaths were considered related to PEG-IFN with or without RBV, three to all three study drugs and one to double-blind medication. The one death in the PL group of Study TPL102357 was due to abdominal pain/renal failure.

TABLE 24: ENABLE 1 AND ENABLE 2: INITIATION OF ANTIVIRAL THERAPY (SAFETY POPULATION)

Characteristic	ENABLE 1	ENABLE 2
	ELT (N = 715)	ELT (N = 805)
Initiated AVT, n (%)		
Yes	680 (95)	759 (94)
(95% CI)	(93 to 97)	(92 to 96)
No	35 (5)	46 (6)
Dose of ELT that enabled initiation of AVT, n (%)		
25 mg	451 (63)	443 (55)
50 mg	176 (25)	208 (26)
75 mg	39 (5)	77 (10)
100 mg	14 (2)	31 (4)

Characteristic	ENABLE 1	ENABLE 2
	ELT (N = 715)	ELT (N = 805)
Did not initiate AVT, n (%)	35 (5)	46 (6)
Insufficient platelet response	11 (1.5)	13 (1.6)
AE leading to withdrawal	9 (1.3)	5 (0.6)
Investigator discretion	7 (1.0)	8 (1.0)
Withdrew consent	3 (0.4)	3 (0.4)
Lost to follow-up	2 (0.3)	12 (1.5)
Protocol deviation	1 (0.1)	5 (0.6)
Withdrew consent prior to AVT	2 (0.3)	0

AE = adverse event; AVT = antiviral therapy; CI = confidence interval; ELT = eltrombopag; n = number of patients with event; N = number of patients.

TABLE 25: TPL102357: INITIATION OF AVT (SAFETY POPULATION)

Characteristic	ELT 30 mg N = 14	ELT 50 mg N = 19	ELT 75 mg N = 23	PL N = 18
Initiated AVT, n (%)				
Yes	10 (71)	14 (74)	21 (91)	4 (22)
No	4 (29)	5 (26)	2 (9)	14 (78)

AVT = antiviral therapy; ELT = eltrombopag; n = number of patients with event; N = number of patients; PL = placebo.

TABLE 26: ENABLE 1 AND ENABLE 2: OTHER ANTIVIRAL END POINTS (INTENTION-TO-TREAT POPULATION)

Characteristic[a]	ENABLE 1		ENABLE 2	
	ELT (N = 450)	PL (N = 232)	ELT (N = 506)	PL (N = 253)
RVR, n (%)				
Yes	73 (16)	39 (17)	78 (15)	34 (13)
Per cent diff.[b] (95% CI)	1.0 (–2.5 to 4.5)		NA	
P value	0.7495			
eRVR, n (%)				
Yes	68 (15)	28 (12)	69 (14)	27 (11)
Per cent diff.[b] (95% CI)	1.6 (–1.8 to 5.1)		NA	
P value	0.3006			
EVR, n (%)				
Yes	297 (66)	115 (50)	313 (62)	103 (41)
Per cent diff.[b] (95% CI)	16.7 (9.2 to 24.1)		20.7 (13.6 to 27.8)	
P value	< 0.0001		< 0.0001	
cEVR, n (%)				
Yes	187 (42)	60 (26)	174 (34)	57 (23)
Per cent diff.[b] (95% CI)	14.8 (8.6 to 21.1)		9.1 (3.5 to 14.7)	
P value	< 0.0001		0.0003	
ETR, n (%)				
Yes	214 (48)	86 (37)	190 (38)	59 (23)
Per cent diff.[b] (95% CI)	10.7 (3.3 to 18.1)		13.1 (6.9 to 19.4)	
P value	0.0080		< 0.0001	
SVR at 12 week FU, n (%)				
Yes	103 (23)	36 (16)	106 (21)	29 (11)
Per cent diff.[b] (95% CI)	8.3 (2.7 to 13.9)		8.6 (3.7 to 13.5)	
P value	0.0256		0.0009	

cEVR = completed early virologic response; CI = confidence interval; diff. = difference; ELT = eltrombopag; eRVR = extended rapid virologic response; ETR = end of treatment response; EVR = early virologic response; FU = follow-up; ITT = intention-to-treat; n = number of patients with event; N = number of patients; NA = not applicable; PL = placebo; RVR = rapid virologic response; SVR = sustained virologic response.

[a] RVR rate is defined as the absence of detectable HCV RNA at week 4; eRVR rate is defined as the absence of detectable HCV RNA at week 4 that persisted through to week 12; EVR rate is defined as a ≥ 2 $\log_{10}$ reduction from baseline in HCV RNA or undetectable HCV RNA at week 12; cEVR rate is defined as undetectable HCV RNA at week 12; ETR is defined as the absence of detectable HCV RNA at the end of AVT; and SVR12 rate is defined as the absence of detectable HCV RNA at the end of AVT and the 12-week follow-up assessments.

[b] Adjusted for the actual strata: HCV genotype, BL platelet count, HCV RNA stratum.

TABLE 27: TPL102357: NUMBER OF VIRAL RESPONDERS (INTENTION-TO-TREAT POPULATION)

Outcome	ELT 30 mg (N = 14)	ELT 50 mg (N = 19)	ELT 75 mg (N = 23)	PL (N = 18)
EVR (day 28/day 113), n				
Yes	4	3	9	1
No	4	4	3	1
Exclusions	6	12	11	16
Modified viral response (screening or day 28/day 113), n				
Yes	4	3	10	1
No	4	7	3	2
Exclusions	6	9	10	15
Any viral response (screening or day 28/day 113), n				
Yes	4	4	11	1
No	6	7	3	2
Exclusions	4	8	9	15

ELT = eltrombopag; EVR = early virologic response; ITT = intention-to-treat; n = number of patients with event; N = number of patients; PL = placebo.
Note: A viral response was defined as a patient with > 2 $\log_{10}$ reduction from baseline assessment to any end point assessment or HCV RNA undetectable at any end point assessment. Exclusions were patients who did not have hepatitis C virus RNA measurements at baseline or end point.

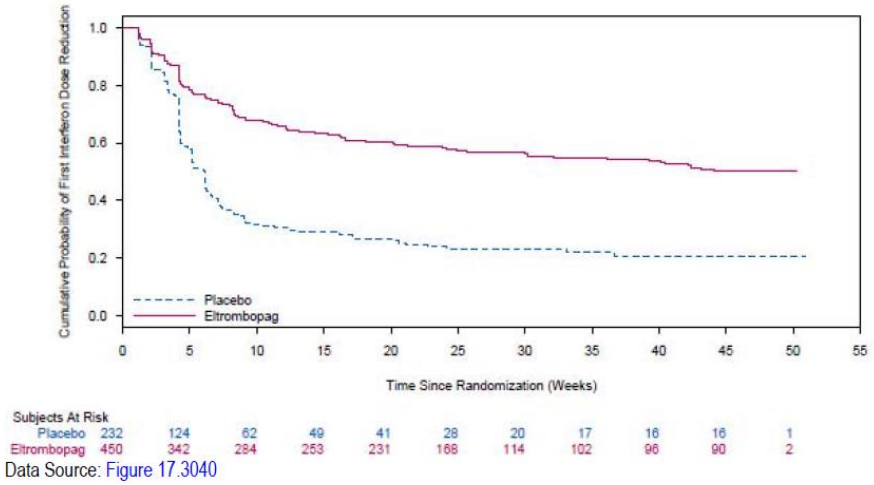
TABLE 28: ENABLE 1 AND ENABLE 2: ANTIVIRAL DOSE REDUCTIONS (INTENTION-TO-TREAT POPULATION)

Characteristic	ENABLE 1		ENABLE 2	
	ELT (N = 450)	PL (N = 232)	ELT (N = 506)	PL (N = 253)
Any dose reduction, n (%)				
0	195 (43)	65 (28)	231 (46)	68 (27)
1	93 (21)	57 (25)	101 (20)	76 (30)
2	56 (12)	55 (24)	75 (15)	40 (16)
3	49 (11)	26 (11)	47 (9)	34 (13)
> 3	57 (13)	29 (13)	52 (10)	35 (14)
P value	0.0029		< 0.0001	
Time in weeks to first RBV dose reduction				
	n = 162	n = 63	N = 189	N = 79
Mean (SD)	12.6 (9.8)	11.2 (9.2)	11.0 (9.0)	12.4 (9.7)
Median (Min–Max)	8.7 (1.3 to 44.0)	8.1 (1.1 to 40.3)	8.1 (1.0 to 45.0)	8.1 (2.0 to 40.1)
Time in weeks to first PEG-IFN dose reduction				
	n = 193	n = 163	N = 208	N = 171
Mean (SD)	9.0 (9.4)	5.8 (5.3)	10.6 (9.3)	6.6 (7.3)
Median (Min–Max)	5.1 (1.1 to 44.1)	4.3 (1.1 to 36.7)	7.3 (1.0 to 43.1)	4.1 (0.9 to 45.0)
Median time in weeks to first PEG-IFN dose reduction (Min–Max)				
From 180 to 135 mcg	4.6 (1 to 43)	4.1 (1 to 37)	NR	NR
From 180 to 90 mcg	7.9 (1 to 44)	4.3 (1 to 24)	NR	NR
From 180 to 45 mcg	-	5.6 (5 to 6)	NR	NR
From 135 to 90 mcg	10.6 (2 to 36)	9.7 (2 to 44)	NR	NR
From 135 to 45 mcg	-	10.8 (9 to 12)	NR	NR
From 90 to 45 mcg	11.1 (4 to 30)	8.1 (4 to 33)	NR	NR
≤ 25%	NR	NR	12.1 (1 to 43)	5.1 (1 to 44)
> 25% to ≤ 34%	NR	NR	7.3 (1 to 42)	8.1 (1 to 44)

Characteristic	ENABLE 1		ENABLE 2	
	ELT (N = 450)	PL (N = 232)	ELT (N = 506)	PL (N = 253)
> 34% to ≤ 50%	NR	NR	8.1 (1 to 42)	4.1 (1 to 45)
> 50%	NR	NR	12.5 (4 to 45)	7.1 (1 to 36)
Level of any PEG-IFN dose reductions, n (%)				
From 180 to 135 mcg	121 (27)	73 (31)	NR	NR
From 180 to 90 mcg	82 (18)	94 (41)	NR	NR
From 180 to 45 mcg	0	2 (< 1)	NR	NR
From 135 to 90 mcg	64 (14)	55 (24)	NR	NR
From 135 to 45 mcg	0	2 (< 1)	NR	NR
From 90 to 45 mcg	12 (3)	18 (8)	NR	NR
≤ 25%	NR	NR	89 (18)	44 (17)
> 25% to ≤ 34%	NR	NR	35 (7)	33 (13)
> 34% to ≤ 50%	NR	NR	112 (22)	115 (46)
> 50%	NR	NR	30 (6)	33 (13)

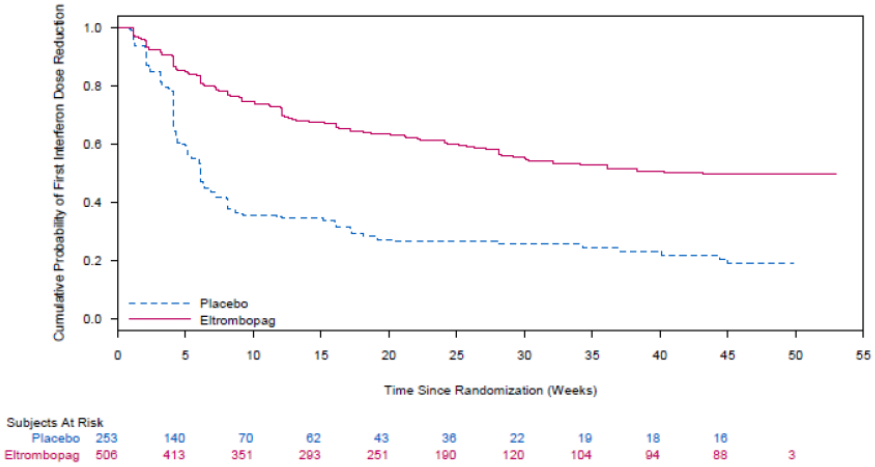
ELT = eltrombopag; ITT = intention-to-treat; mcg = microgram; Min–Max = minimum to maximum; n = number of patients with event; N = number of patients; PEG-IFN = pegylated interferon; PL = placebo; RBV = ribavirin; SD = standard deviation.

FIGURE 6: ENABLE 1: KAPLAN–MEIER ESTIMATES OF TIME TO FIRST PEGYLATED INTERFERON DOSE REDUCTION (INTENTION-TO-TREAT POPULATION)



Source: ENABLE 1.[22]

FIGURE 7: ENABLE 2: KAPLAN–MEIER ESTIMATES OF TIME TO FIRST PEGYLATED INTERFERON DOSE REDUCTION (INTENTION-TO-TREAT POPULATION)



Source: ENABLE 2.[23]

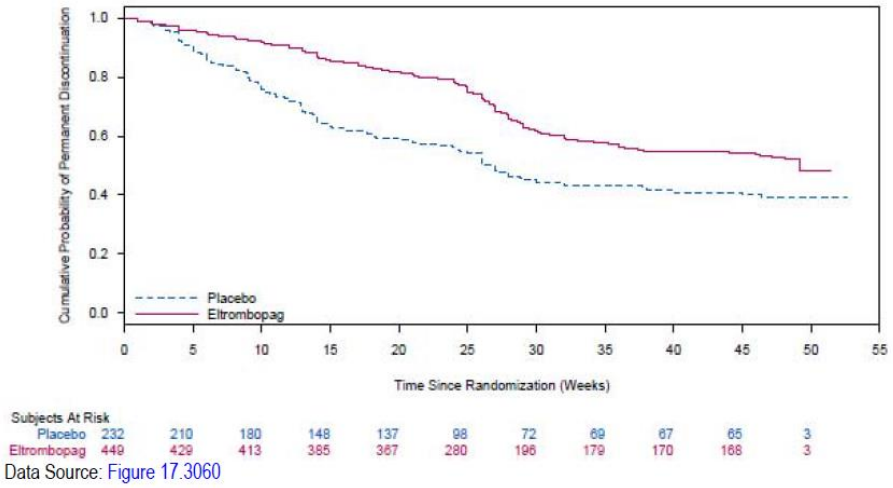
TABLE 29: ENABLE 1 AND ENABLE 2: PREMATURE DISCONTINUATION FROM ANTIVIRAL THERAPY (INTENTION-TO-TREAT POPULATION)

Characteristic	ENABLE 1		ENABLE 2	
	ELT (N = 450)	PL (N = 232)	ELT (N = 506)	PL (N = 253)
Premature DC AVT,[a] n (%)				
Yes	184 (41)	129 (56)	242 (48)	164 (65)
Per cent diff. (95% CI)	–16.0 (–23.3 to –8.6)		–16.2 (–23.1 to –9.3)	
P value	0.0001		< 0.0001	

AVT = antiviral therapy; CI = confidence interval; DC = discontinue; diff. = difference; ELT = eltrombopag; n = number of patients with event; N = number of patients; PL = placebo.

[a] Discontinuation of pegylated interferon and/or ribavirin; adjusted for actual strata: hepatitis C virus Genotype, BL Platelet Count, and HCV RNA.

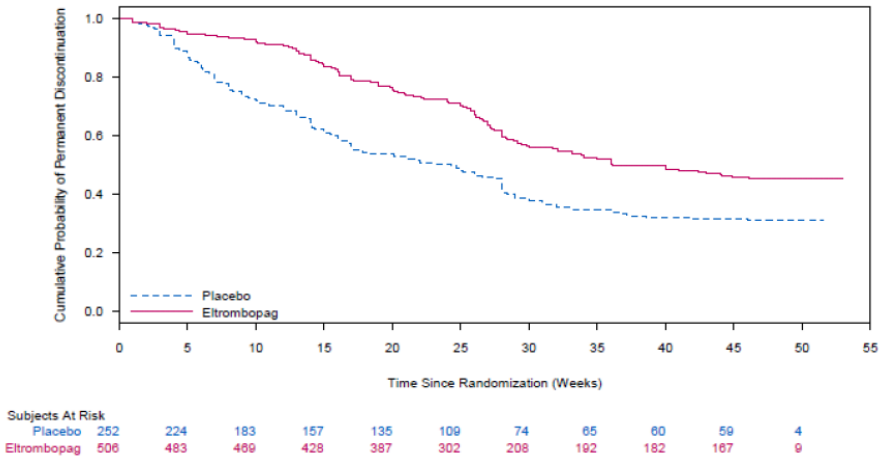
FIGURE 8: ENABLE 1: KAPLAN–MEIER ESTIMATES OF TIME TO PERMANENT PEGYLATED INTERFERON DISCONTINUATION (INTENTION-TO-TREAT POPULATION)



Data Source: Figure 17.3060

Source: ENABLE 1.[22]

FIGURE 9: ENABLE 2: KAPLAN–MEIER ESTIMATES OF TIME TO PERMANENT PEGYLATED INTERFERON DISCONTINUATION (INTENTION-TO-TREAT POPULATION)



Source: ENABLE 2.[23]

TABLE 30: TPL102357: SUMMARY OF ANTIVIRAL THERAPY DOSE REDUCTIONS (ITT POPULATION)

Outcome	ELT 30 mg (N = 14)	ELT 50 mg (N = 19)	ELT 75 mg (N = 23)	PL (N = 18)
	End of Initiation Phase (Part 1)			
No. patients entering Part 2	10	14	21	4
No. patients with 1 level of PEG-IFN dose reduction, n (%) Pegasys PegIntron	1 (10) 1 (10) 0	1 (7) 1 (7) 0	1 (5) 1 (5) 0	1 (25) 1 (25) 0
No. patients with > 1 level of PEG-IFN dose reduction, n (%) Pegasys PegIntron	1 (10) 1 (10) 0	1 (7) 1 (7) 0	0 0 0	0 0 0
No. patients DC PEG-IFN, n (%) Pegasys PegIntron	2 (20) 2 (20) 0	1 (7) 1 (7) 0	0 0 0	0 0 0
No. patients with 1 level of RBV dose reduction, n (%)	0	1 (10)	0	0
No. patients with > 1 level of RBV dose reduction, n (%)	0	1 (10)	0	0
No. patients DC RBV, n (%)	0	1 (10)	0	0

DC = discontinue; ELT = eltrombopag; ITT = intention-to-treat; mg = milligram; n = number of patients with event; N = number of patients; No. = number; PEG-IFN = pegylated interferon; PL = placebo; RBV = ribavirin.

TABLE 31: ENABLE 1 AND ENABLE 2: EVENTS SUGGESTIVE OF HEPATIC DECOMPENSATION DURING AVT PLUS 30 DAYS (EXTERNAL ADJUDICATION) (SAFETY DOUBLE-BLIND POPULATION)

Characteristic	ENABLE 1		ENABLE 2	
	ELT (N = 449)	PL (N = 232)	ELT (N = 506)	PL (N = 252)
Any event, n (%)	59 (13)	19 (8)	66 (13)	16 (6)
Ascites	28 (6)	10 (4)	27 (5)	4 (2)
Hepatic encephalopathy	11 (2)	2 (< 1)	13 (3)	2 (< 1)
Variceal hemorrhage	10 (2)	2 (< 1)	3 (< 1)	2 (< 1)
Spont. bact. peritonitis	5 (1)	2 (< 1)	3 (< 1)	0
Hepatocellular carcinoma	10 (2)	4 (2)	17 (3)	8 (3)
Other decomp. events[a]	12 (3)	1 (< 1)	3(< 1)	0
Death	8 (2)	4 (2)	15 (3)	3 (1)
Time to event (days)				
Mean (SD)	146.0 (79.6)	160.3 (99.8)	185.6 (87.7)	173.9 (77.1)
Median (Min–Max)	145 (36 to 378)	129 (37 to 401)	170.5 (50 to 427)	171.5 (53 to 297)

AVT = antiviral therapy; DB = double-blind; ELT = eltrombopag; Min–Max = minimum to maximum; n = number of patients with event; N = number of patients; PL = placebo; SD = standard deviation.

[a] Includes events with preferred terms: hepatic failure, hepatorenal syndrome, or verbatim end stage liver disease.

TABLE 32: ENABLE 1 AND ENABLE 2: ADHERENCE TO DOUBLE-BLIND STUDY DRUG (INTENTION-TO-TREAT POPULATION)

Characteristic	ENABLE 1		ENABLE 2	
	ELT (N = 450)	PL (N = 232)	ELT (N = 506)	PL (N = 253)
Adherence (%)				
Yes	246 (55)	102 (44)	261 (52)	84 (33)
No	204 (45)	130 (56)	245 (48)	169 (67)
Per cent diff. (95% CI)	11.7 (4.2 to 19.3)		17.4 (10.5 to 24.2)	
P value	0.0066		< 0.0001	

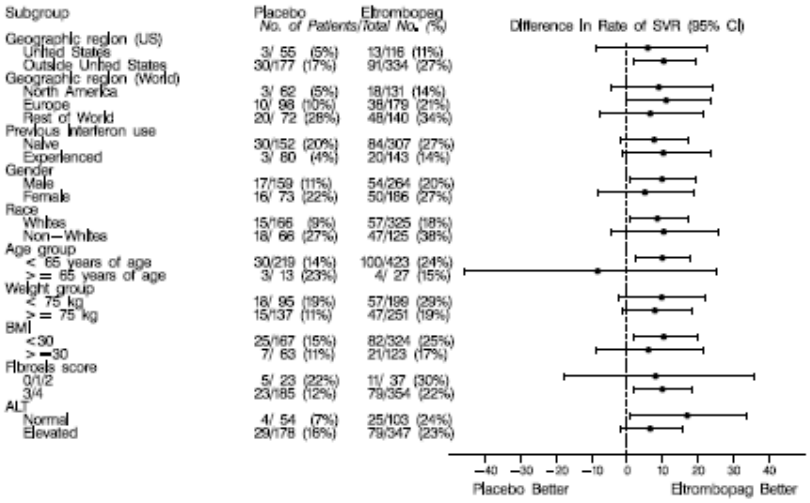
CI = confidence interval; DB = double-blind; diff. = difference; ELT = eltrombopag; ITT = intention-to-treat; N = number of patients; PL = placebo.
Note: Adherence was defined as receiving at least 80% of the investigator-prescribed dose of each of pegylated interferon and ribavirin for at least 80% of the planned duration (80-80-80 rule).

TABLE 33: ENABLE 1 AND ENABLE 2: ASSOCIATION OF ADHERENCE AND SVR (ITT POPULATION)

Characteristic	ENABLE 1		ENABLE 2	
	ELT (N = 450)	PL (N = 232)	ELT (N = 506)	PL (N = 253)
SVR, n (%)				
Adherence				
Yes	96/104 (92)	30/31 (91)	90/97 (93)	30/32 (94)
No	150/346 (43)	72/199 (36)	171/409 (42)	54/221 (24)
P value	< 0.0001		< 0.0001	

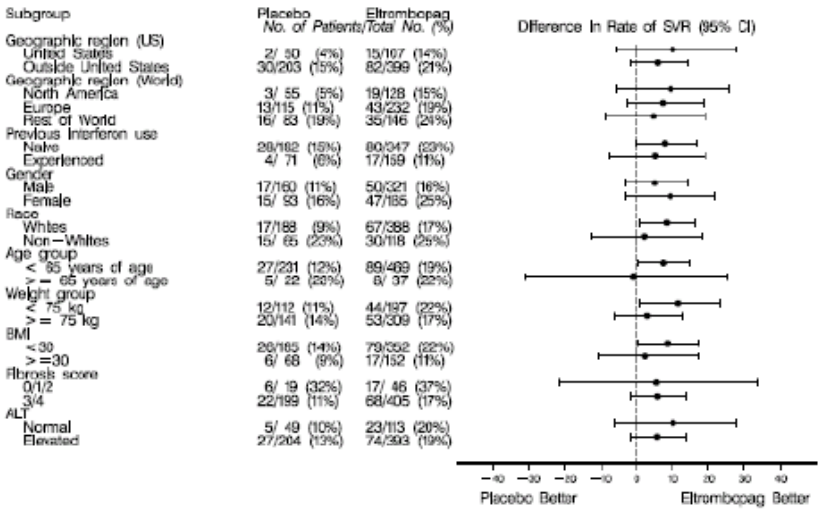
ELT = eltrombopag; ITT = intention-to-treat; n = number of patients with event; N = number of patients; PL = placebo; SVR = sustained virologic response.
Note: Adherence was defined as receiving at least 80% of the investigator-prescribed dose of each of PEG-IFN and ribavirin for at least 80% of the planned duration (80-80-80 rule).

FIGURE 10: ENABLE 1: FOREST PLOT OF DIFFERENCE IN SVR RATES (95% CI) BY SUBGROUP (ITT POPULATION)



ALT = alanine aminotransferase; BMI = body mass index; CI = confidence interval; ITT = intention-to-treat; kg = kilogram; No. = number; SVR = sustained virologic response.
Source: ENABLE 1.[22]

FIGURE 11: ENABLE 2: FOREST PLOT OF DIFFERENCE IN SVR RATES (95% CI) BY SUBGROUP (ITT POPULATION)



ALT = alanine aminotransferase; BMI = body mass index; CI = confidence interval; ITT = intention-to-treat; kg = kilogram; No. = number; SVR = sustained virologic response.
Source: ENABLE 2.[23]

APPENDIX 4: EXCLUDED STUDIES

TABLE 34: EXCLUDED STUDIES

Reference	Reason for Exclusion
Zekry A, et al., 2008[27]	Inappropriate study design
Mondelli MU, 2008[28]	Inappropriate study design
Kawaguchi T, et al., 2012[29]	Inappropriate study design
Afdhal NH, et al., 2007[11]	Inappropriate study design
Afdhal NH, et al., 2012[7]	Different indication and patient population

APPENDIX 5: VALIDITY OF OUTCOME MEASURES: CHRONIC LIVER DISEASE QUESTIONNAIRE–HEPATITIS C VIRUS

Aim

To provide background information on the Chronic Liver Disease Questionnaire–Hepatitis C Virus (CLDQ-HCV) as a health-related quality of life (HRQoL) instrument in patients with hepatitis C virus (HCV) infection.

Findings

The CLDQ-HCV is a disease-specific HRQoL instrument developed for patients with chronic hepatitis C (CHC).[30] The CLDQ-HCV is an item-selection questionnaire comprising 29 questions covering four domains: activity/energy, emotions, systemic symptoms, and worry. A total CLDQ-HCV score can be derived from the domain scores. The questionnaire was developed by Younossi et al., using a variety of sources including available generic and liver-specific instruments (mainly the Chronic Liver Disease Questionnaire [CLDQ]), interviews, and focus groups with hepatitis C patients.[31] The final instrument was derived from administering an initial questionnaire containing 77 items to 72 patients with CHC, and eliminating redundancies following Impact Scores and Factor Analysis. Approximately half of the questions in the CLDQ-HCV also occur in the CLDQ, with the remaining questions focusing on symptoms and issues unique to HCV. Both the CLDQ-HCV and the CLDQ are anchored on a two-week recall period. Each item on the CLDQ-HCV questionnaire is open-ended and may be answered with one of seven response options rated on a Likert scale from 1 to 7. A score of 1 means the symptom being assessed is "present always" while a score of 7 means the symptom is "never present". Therefore, a higher score corresponds to a better HRQoL while a lower score corresponds to a worse HRQoL. The questions in each domain have a range of factor loads indicative of their impact, and a clinically important difference is defined as a score change of 0.5.[30,31] The CLDQ-HCV instrument has been demonstrated to have a good internal consistency through psychometric testing carried out using Cronbach alpha.[31] The CLDQ-HCV is a widely validated tool to detect HRQoL issues related to CHC.[30,32,33] Its overall and domain scores show high correlation with the Short-Form (36) Health Survey (SF-36) scale score, particularly the physical subscale.[32]

Conclusion

The CLDQ-HCV is a validated tool with demonstrated ability to detect HRQoL issues related to CHC and is used in clinical trials of new drugs for HCV. Its overall and domain scores are highly correlated with the SF-36 scale score. A clinically important difference is defined as a change in score of 0.5.

APPENDIX 6: APPRAISAL OF MANUFACTURER-SUBMITTED STUDY OF THE BURDEN OF ILLNESS OF HCV IN QUEBEC

Aim

To appraise the results of a study of the burden of illness of hepatitis C (HCV) in Quebec (referred to hereafter as the BIQ study).

Methods

The BIQ study was a retrospective chart review study conducted on a random sample of patients selected from five treatment sites in Quebec with high HCV patient volume, using patient data such as patient demographics, comorbidities, concomitant medication use, treatments for HCV, laboratory test results, HCV genotype, and HCV viral counts.

Populations

The study population comprised patients diagnosed with HCV between January 1, 2001 and the time of data extraction. A subpopulation of patients with thrombocytopenia (TCP) was also analyzed.

Intervention and Comparators

The patients were treated with interferon/peg-interferon and ribavirin (IFN/RBV) dual therapy, or a triple therapy that included a protease (PI) (IFN/RBV + PI).

Outcomes

Complete treatment was defined as 48 weeks (two-week window allowed) of treatment with IFN/RBV for patients with genotypes 1, 4, 5, and 6 and 24 weeks (2-week window allowed) of treatment for patients with genotypes 2 and 3. For patients on IFN/RBV + PI, completed treatment was considered as 48 weeks (two-week window allowed) of treatment regardless of genotype.
The primary end points of the BIQ study were:

Treatment responses were defined as per the 2012 Canadian consensus guidelines for the management of chronic HCV presented in Table 35.

This appraisal focuses on SVR following complete treatment with IFN/RBV versus incomplete treatment with IFN/RBV.

TABLE 35: DEFINITION OF TREATMENT RESPONSES

Response	Definition
RVR	Undetectable HCV RNA negative at 4 weeks of therapy
Extended rapid virological response	Undetectable HCV RNA at weeks 4 and 12 of therapy in patients treated with telaprevir-based triple therapy
EVR	≥ 2 Log_{10} decrease in HCV RNA at 12 weeks compared with baseline
ETR	Undetectable HCV RNA at the end of treatment
SVR	Undetectable HCV RNA at least 24 weeks after end of treatment
Null response	< 2 Log_{10} decrease in HCV RNA at week 12 compared with baseline in patients treated with pegylated interferon and ribavirin-based therapy
Partial response	≥ 2 Log_{10} decrease in HCV RNA but still detectable at week 12 in patients treated with pegylated interferon and ribavirin-based therapy

ETR = end-of-treatment virological response; EVR = early virological response; HCV = hepatitis C virus; RNA = ribonucleic acid; RVR = rapid virological response; SVR = sustained virologic response.

Statistical Analysis

Data were analyzed using descriptive statistics including estimates of the mean, median, standard deviation, and 95% confidence interval (CI) of the mean for continuous variables and frequency distributions for categorical variables. One-way analysis of variance (ANOVA) and the independent samples t-test, as required, were used to assess between-group differences for statistical significance for continuous variables, and the chi-square test was used for categorical variables. Relative risk and associated 95% CI were used to assess the differences in SVR achievement between relevant patient subgroups.

Findings

Eighty-five (85) patients completed treatment, 57 discontinued (described as reduced treatment) and data for 12 were reported as missing. Patients who discontinued treatment early were less likely to achieve SVR compared with patients completing treatment [relative risk (RR) (95% CI) = 0.58 (0.38 to 0.90); *P* = 0.008] (Table 36). Similarly, reduced rate of SVR [RR (95% CI) = 0.57 (0.29 to 1.11); *P* = 0.068] was reported in the subgroup of chronic HCV (chronic HCV) patients with TCP (Table 37).

TABLE 36: SUSTAINED VIROLOGIC RESPONSE BY TREATMENT COMPLETION — INTERFERON/RIBAVIRIN SUBGROUP ANALYSIS

		SVR		Total
		No	Yes	
Treatment discontinued	Count	39	18	57
	% within treatment completed	68.4	31.6	100.0
	% Within SVR	50.0	28.1	40.1
Treatment completed	Count	39	46	85
	% within treatment completed	45.9	54.1	100.0
	% Within SVR	50.0	71.9	59.9
Total	Count	78	64	142
	% within treatment completed	54.9	45.1	100.0
	% Within SVR	100.0	100.0	100.0

SVR = sustained virologic response.
Note: Relative risk of [redacted] associated with the reduced treatment duration can be calculated using data from the highlighted cells as
$RR = \frac{31.6}{54.1} =$ [redacted].

TABLE 37: SUSTAINED VIROLOGIC RESPONSE BY TREATMENT COMPLETION — INTERFERON/RIBAVIRIN SUBGROUP ANALYSIS (PATIENTS WITH THROMBOCYTOPENIA)[A]

		SVR		Total
		No	Yes	
Treatment discontinued	Count	15	7	22
	% within treatment completed	68.2	31.8	100.0
	% within SVR	42.9	21.9	32.8
Treatment completed	Count	20	25	45
	% within treatment completed	44.4	55.6	100.0
	% within SVR	57.1	78.1	67.2
Total	Count	35	32	67
	% within treatment completed	52.2	47.8	100.0
	% within SVR	100.0	100.0	100.0

SVR = sustained virologic response.
[a] Relative risk of 0.572 associated with the reduced treatment duration can be calculated using data from the highlighted cells as $RR = \frac{31.8}{55.6} = 0.0572$.

Interpretation of Results

The results of the BIQ study provide evidence that real-world treatment of chronic HCV in Quebec with IFN/RBV is significantly less effective in patients who discontinue treatment early versus those who complete the full treatment course. Specifically, patients who discontinued IFN/RBV treatment prematurely were significantly less likely to achieve SVR compared with patients who completed treatment (RR [95% CI] = 0.58 [0.38 to 0.90]; *P* = 0.008). This finding likely applies irrespective of whether patients have TCP, because the relative risk for this subpopulation in the BIQ study (RR [95% CI] = 0.57 [0.29 to 1.11]; *P* = 0.068) was very similar to that obtained for the full population. The lack of statistical significance for the RR in the TCP subpopulation likely reflects the lack of statistical power due to a small sample size. Although the manufacturer has referred to “reduced dose” treatment in the

pharmacoeconomic (PE) submission (with regard to treatment strategy 4 in the PE model), there was no indication that patients who did not complete treatment in the BIQ study were treated with a lower dose of IFN/RBV; rather, "reduced dose" with respect to the BIQ study refers to patients who did not complete a full course of treatment (i.e., reduced duration of treatment).

The BIQ study was retrospective and relied on data from patient chart, which possibly had incomplete information with respect to treatments used or the incidence of TCP, and therefore raises the potential for misclassification of exposure. In addition, the study was conducted at only five sites in one province (Quebec) and had a relatively small sample size (n = 175). Therefore, the precise magnitude of the differences in outcomes for patients who complete the full course of IFN/RBV therapy compared with those who discontinue treatment prematurely is uncertain, and might be greater or less than an RR of 0.58.

The strengths of the study include the use of a standardized protocol for patient identification and data collection to minimize bias due to data acquisition errors. Secondly, it likely reflected real-life clinical practice in terms of assessment of patient management and treatment effectiveness because of its observational nature.

Conclusion

The results of the BIQ study of 175 patients with chronic HCV in Quebec suggest that patients who discontinue IFN/RBV treatment prematurely are significantly less likely to achieve SVR compared with patients who complete a full course of treatment.

REFERENCES

1. Louie KS, Micallef JM, Pimenta JM, Forssen UM. Prevalence of thrombocytopenia among patients with chronic hepatitis C: a systematic review. J Viral Hepat. 2011 Jan;18(1):1-7.
2. Dienstag JL, Ghany MG, Morgan TR, Di Bisceglie AM, Bonkovsky HL, Kim HY, et al. A prospective study of the rate of progression in compensated, histologically advanced chronic hepatitis C. Hepatology [Internet]. 2011 Aug [cited 2014 Nov 21];54(2):396-405. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3144992
3. Giannini EG. Eltrombopag in patients with chronic hepatitis C and thrombocytopenia. Future Virology. 2014;9(1):9-20.
4. McHutchison JG, Manns M, Patel K, Poynard T, Lindsay KL, Trepo C, et al. Adherence to combination therapy enhances sustained response in genotype-1-infected patients with chronic hepatitis C. Gastroenterology. 2002 Oct;123(4):1061-9.
5. [Pr]Revolade® (eltrombopag olamine): 25 mg, 50 mg, and 75 mg eltrombopag tablets [product monograph]. Mississauga (ON): GlaxoSmithKline; 2014 Mar 27.
6. Myers RP, Ramji A, Bilodeau M, Wong S, Feld JJ. An update on the management of hepatitis C: consensus guidelines from the Canadian Association for the Study of the Liver. Can J Gastroenterol [Internet]. 2012 Jun [cited 2014 Nov 21];26(6):359-75. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3378284/
7. Afdhal NH, Giannini EG, Tayyab G, Mohsin A, Lee JW, Andriulli A, et al. Eltrombopag before procedures in patients with cirrhosis and thrombocytopenia. N Engl J Med. 2012 Aug 23;367(8):716-24.
8. Remis RS. Modelling the incidence and prevalence of hepatitis C infection and its sequelae in Canada, 2007 [Internet]. Ottawa: Public Health Agency of Canada; 2007. [cited 2014 Nov 21]. Available from: http://www.phac-aspc.gc.ca/sti-its-surv-epi/model/pdf/model07-eng.pdf
9. Giannini EG, Savarino V. Thrombocytopenia in liver disease. Curr Opin Hematol. 2008 Sep;15(5):473-80.
10. Giannini EG, Afdhal NH. Eltrombopag in patients with chronic liver disease. Expert Opin Pharmacother. 2013 Apr;14(5):669-78.
11. Afdhal NH, McHutchison JG. Review article: pharmacological approaches for the treatment of thrombocytopenia in patients with chronic liver disease and hepatitis C infection. Aliment Pharmacol Ther. 2007 Nov;26(Suppl 1):29-39.
12. [Pr]PEGETRON® (ribavirin plus peginterferon alfa-2b) [product monograph]. Kirkland (QC): Merck Canada Inc.; 2013.
13. [Pr]Pegasys® (peginterferon alfa-2a injection) [product monograph] [Internet]. Mississauga (ON): Hoffman - La Roche Canada Limited; 2014. [cited 2014 Nov 21]. Available from: http://www.rochecanada.com/fmfiles/re7234008/Research/ClinicalTrialsForms/Products/ConsumerInformation/MonographsandPublicAdvisories/Pegasys/Pegasys_PM_E.pdf
14. Lin KH, Hsu PI, Yu HC, Lin CK, Tsai WL, Chen WC, et al. Factors linked to severe thrombocytopenia during antiviral therapy in patients with chronic hepatitis c and pretreatment low platelet counts. BMC Gastroenterol [Internet]. 2012 [cited 2014 Nov 21];12:7. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3275508
15. Tripodi A, Primignani M, Chantarangkul V, Lemma L, Jovani M, Rebulla P, et al. Global hemostasis tests in patients with cirrhosis before and after prophylactic platelet transfusion. Liver Int. 2013 Mar;33(3):362-7.

16. Stroncek DF, Rebulla P. Platelet transfusions. Lancet. 2007 Aug 4;370(9585):427-38.

17. Ikeda N, Imanishi H, Aizawa N, Tanaka H, Iwata Y, Enomoto H, et al. Nationwide survey in Japan regarding splenectomy/partial splenic embolization for interferon treatment targeting hepatitis C virus-related chronic liver disease in patients with low platelet count. Hepatol Res. 2014 Aug;44(8):829-36.

18. Akahoshi T, Tomikawa M, Kawanaka H, Furusyo N, Kinjo N, Tsutsumi N, et al. Laparoscopic splenectomy with interferon therapy in 100 hepatitis-C-virus-cirrhotic patients with hypersplenism and thrombocytopenia. J Gastroenterol Hepatol. 2012 Feb;27(2):286-90.

19. Common Drug Review. CDEC final recommendation: eltrombopag olamine (Revolade, GlaxoSmithKline Inc.). Indication: chronic immune (idiopathic) thrombocytopenic purpura [Internet]. Ottawa: Canadian Agency for Drugs and Technologies in Health; 2014. [cited 2014 Nov 21]. Available from: http://www.cadth.ca/media/cdr/complete/cdr_complete_Revolade_Oct-26-11_e.pdf

20. Afdhal NH, Dusheiko GM, Giannini EG, Chen PJ, Han KH, Mohsin A, et al. Eltrombopag increases platelet numbers in thrombocytopenic patients with HCV infection and cirrhosis, allowing for effective antiviral therapy. Gastroenterology. 2014 Feb;146(2):442-52.

21. McHutchison JG, Dusheiko G, Shiffman ML, Rodriguez-Torres M, Sigal S, Bourliere M, et al. Eltrombopag for thrombocytopenia in patients with cirrhosis associated with hepatitis C. N Engl J Med. 2007 Nov 29;357(22):2227-36.

22. Clinical study report: TPL103922. Randomised, placebo-controlled, multicentre study to assess the efficacy and safety of eltrombopag in thrombocytopenic subjects with hepatitis C virus (HCV) infection who are otherwise eligible to initiate antiviral therapy (peginterferon alfa-2a plus ribavirin) - ENABLE 1 (Eltrombopag to INitiate and Maintain Interferon Antiviral treatment to Benefit Subjects with Hepatitis C Related Liver DiseasE) [**CONFIDENTIAL** internal manufacturer's report]. [Brentford, United Kingdom]: GlaxoSmithKline; 2012.

23. Clinical study report: TPL108390. Randomised, placebo-controlled, multicentre study to assess the efficacy and safety of eltrombopag in thrombocytopenic subjects with hepatitis C virus (HCV) infection who are otherwise eligible to initiate antiviral therapy (peginterferon alfa-2b plus ribavirin) - ENABLE 2 (Eltrombopag to INitiate and Maintain Interferon Antiviral treatment to Benefit Subjects with Hepatitis C Related Liver DiseasE) [**CONFIDENTIAL** internal manufacturer's report]. [Brentford, United Kingdom]: GlaxoSmithKline; 2012.

24. Clinical study report: TPL102357. A double-blind, randomized, placebo-controlled, multi-centre, dose-ranging, parallel group, phase II study to assess efficacy, safety/tolerability, and pharmacokinetics of a thrombopoietin receptor agonist, SB-497115-GR (eltrombopag), when administered as 30, 50, and 75mg once daily for 16 weeks in subjects with chronic hepatitis C-related thrombocytopenia who are potential candidates for antiviral treatment with pegylated interferon and ribavirin [**CONFIDENTIAL** internal manufacturer's report]. [Brentford, United Kingdom]: GlaxoSmithKline; 2007.

25. CDR submission: Revolade® (eltrombopag olamine), 25mg, 50mg, and 75 mg tablets. Company: GlaxoSmithKline Inc. [**CONFIDENTIAL** manufacturer's submission]. Mississauga (ON): GlaxoSmithKline; 2014 Mar 31.

26. Health Canada reviewer's report: Revolade® (eltrombopag) [**CONFIDENTIAL** internal report]. Ottawa: Therapeutics Products Directorate, Health Canada; 2014 Feb 27.

27. Zekry A, Freiman J. Eltrombopag: Is this "24 karat gold platelet" treatment for thrombocytopenia in cirrhosis associated with hepatitis C? Hepatology. 2008;47(4):1418-21.

28. Mondelli MU. Eltrombopag: An effective remedy for thrombocytopaenia? J Hepatol. 2008;48(6):1030-2.

29. Kawaguchi T, Komori A, Seike M, Fujiyama S, Watanabe H, Tanaka M, et al. Efficacy and safety of eltrombopag in Japanese patients with chronic liver disease and thrombocytopenia: a randomized, open-label, phase II study. J Gastroenterol [Internet]. 2012 Dec [cited 2014 Oct 14];47(12):1342-51. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3523116

30. Loria A, Escheik C, Gerber L, Price JK, Younossi ZM. The chronic liver disease questionnaire-hepatitis C (CLDQ-HCV): a sensitive and valid health related. Hepatology. 2012;56 Suppl 1:646A.

31. Younossi Z, Boparai N, McCormick M. A disease-specific health-related quality of life intrument for chronic hepatitis C: CLDQ-HCV. Hepatology. 2000;32(4 Pt.2):369A.

32. Escheik C, Gerber L, Rover L, Arsalla Z, Otgonsuren M, Younossi Z. Validation of CLDQ-HCV as a health related quality of life (HRQL) instrument for patients with chronic hepatitis C (CH-C). Am J Gastroenterol. 2012;107 Suppl 1:S159.

33. Moon J, Kallman J, Younoszai Z, Winter PM, Fang Y, Gerber L, et al. Validation of chronic liver disease-HCV version (CLDQ-HCV) with fatigue severity scale. Gastroenterology. 2010;138(5 Suppl 1):S833.