Poster #1419

A RANDOMIZED TRIAL COMPARING RIBAVIRIN DOSE REDUCTION VERSUS ERYTHROPOIETIN FOR ANEMIA MANAGEMENT IN PREVIOUSLY UNTREATED PATIENTS WITH CHRONIC HEPATITIS C RECEIVING BOCEPREVIR PLUS PEGINTERFERON/RIBAVIRIN

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Introduction

- Anemia, a common adverse event (AE) associated with peginterferon (PEG-IFN)/ribavirin (RBV) therapy for chronic hepatitis C (CHC), is increased with addition of hepatitis C virus (HCV) protease inhibitors
  - SPRINT-2: anemia was reported in 29% of patients receiving PEG-IFN alfa-2b/RBV and 49% of patients receiving boceprevir (BOC) plus PEG-IFN alfa-2b/RBV[1]
    - 13% of patients receiving PEG-IFN alfa-2b/RBV and 21% of BOC recipients required dose reduction (DR) due to anemia (hemoglobin <10 g/dL)
  - ADVANCE: anemia was reported in 37% to 39% of patients receiving telaprevir plus PEG-IFN alfa-2a/RBV, compared with 19% of those receiving PEG-IFN alfa-2a/RBV alone[2]
- RBV DR and erythropoietin (EPO) are anemia management strategies for patients receiving treatment for CHC

Study Objectives

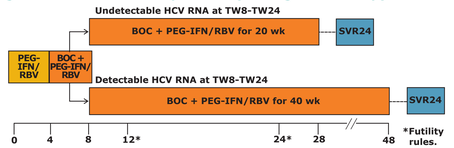
- To compare the effect on efficacy of EPO vs RBV DR for the management of anemia during the treatment of CHC genotype 1 infection with BOC plus PEG-IFN/RBV
- To determine the safety and tolerability of EPO vs RBV DR by the incidence of adverse events and discontinuation rates
- To identify predictors of sustained virologic response (SVR) by multivariate analysis

Methods

Study Design

- Treatment regimen: 4-week PEG-IFN/RBV lead-in, then BOC plus PEG-IFN/RBV
  - PEG-IFN alfa-2b 1.5 µg/kg/wk plus RBV 600-1400 mg/d
  - BOC 800 mg 3 times daily
- Cohort 1: total 48 weeks of treatment
  - PEG-IFN/RBV for 4 weeks, then BOC plus PEG-IFN/RBV for 44 weeks
- Cohort 2: response-guided therapy (**Figure 1**)
  - Short duration (28 weeks): patients with undetectable HCV RNA at treatment week (TW) 8 and all subsequent HCV RNA less than the lower limit of quantitation (LLQ) up to TW 24
  - Long duration (48 weeks): patients with detectable HCV RNA at TW 8, or patients with undetectable HCV RNA at TW 8 and any subsequent HCV RNA above the LLQ up to TW 24 (if no futility rules were met)
- 16% (111/687) of patients were enrolled/treated before a protocol amendment that allowed the response-guided therapy paradigm. Those patients were assigned a fixed-dose regimen (4 weeks PEG-IFN/RBV followed by 44 weeks of BOC plus PEG-IFN/RBV). The results for patients receiving a fixed-dose regimen (Cohort 1) vs response-guided therapy (Cohort 2) did not differ, and for the presentation the data have been combined

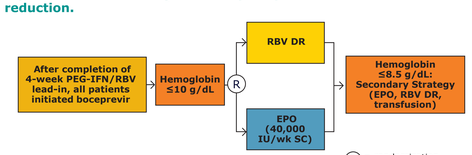
Figure 1. Treatment: boceprevir response-guided therapy.



BOC, boceprevir; PEG-IFN, peginterferon alfa-2b; RBV, ribavirin; SVR, sustained virologic response; TW, treatment week; wk, weeks. Patients with a <2-log decline at week 12 or HCV RNA above the lower limit of quantitation at week 24 met protocol futility rules and were discontinued from the study.

- Patients were randomly assigned when hemoglobin approximately ≤10 g/dL (stratification: black vs nonblack, anemia onset ≤16 weeks vs >16 weeks from the start of the lead-in treatment; **Figure 2**)
  - RBV DR by 200-400 mg/d with a follow-up assessment at 2 weeks
    - If further DR was required, a second or third level of DR (by 200 mg/d) could be used
  - EPO 40,000 IU/wk
- Secondary anemia management was permitted when hemoglobin ≤8.5 g/dL
  - Discontinuation: hemoglobin ≤7.5 g/dL
- During the monitoring for the development of anemia, if the pattern of hemoglobin decline suggested that the value would be ≤10 g/dL before the next protocol-specified visit and the value was <11 g/dL, then the patient could be randomly assigned
- Patients with hemoglobin >10 g/dL throughout the study remained in the pending randomization arm

Figure 2. Anemia management: erythropoietin vs ribavirin dose reduction.



DR, dose reduction; EPO, erythropoietin; PEG-IFN, peginterferon; RBV, ribavirin; SC, subcutaneously.

Inclusion/Exclusion Criteria

- Adult patients were required to be ≥18 years old with CHC genotype 1 infection
- All patients were required to have a hemoglobin concentration of 12-15 g/dL (female) or 13-15 g/dL (male) and a liver biopsy consistent with CHC and no other etiology
  - Patients with bridging fibrosis (F3) or cirrhosis (F4) were required to have a sonogram with no findings suspicious for hepatocellular carcinoma
- Patients with previous treatment for HCV, coinfection with HIV or hepatitis B virus, or decompensated liver disease were excluded

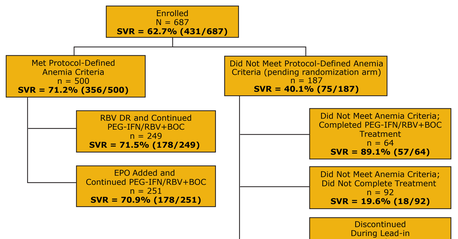
Assessments

- Intent-to-treat population: patients randomized to either anemia management strategy
- Primary efficacy end point: SVR, defined as undetectable HCV RNA 24 weeks post-treatment
- Primary efficacy analysis: a modified Koch method used to calculate the stratum-adjusted difference (EPO vs RBV DR) in SVR rates and corresponding 95% confidence intervals
- Primary efficacy analysis was conducted on the full analysis set (all randomized patients)
- HCV RNA was assessed using Taqman (LLQ = 25 IU/mL; lower limit of detection = 9.3 IU/mL)
- Hemoglobin was measured every 2 weeks from TW 0 to 20 and every 4 to 8 weeks thereafter

Results

- 73% (500/687) of patients met the protocol-defined definition of anemia and were randomly assigned to RBV DR (n = 249) or EPO (n = 251; **Figure 3**)
- Baseline demographic and disease characteristics were well balanced between the treatment arms. The majority of patients in the RBV DR and EPO groups were female (69% and 65%, respectively), were nonblack (82% and 81%, respectively), and had a baseline hemoglobin >13 g/dL (85% and 82%, respectively)

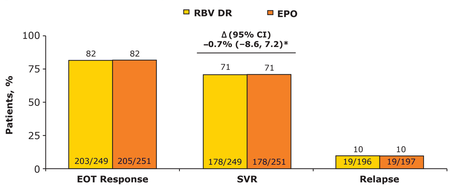
Figure 3. Patient disposition and outcome.



BOC, boceprevir; DR, dose reduction; EPO, erythropoietin; PEG-IFN, peginterferon; RBV, ribavirin; SVR, sustained virologic response.

- End-of-treatment response, relapse, and SVR were comparable between RBV DR and EPO arms (**Figure 4**)

Figure 4. Primary and key efficacy end points.



CI, confidence interval; DR, dose reduction; EOT, end of treatment; EPO, erythropoietin; RBV, ribavirin; SVR, sustained virologic response.
*The stratum-adjusted difference (EPO vs RBV DR) in SVR rates, adjusted for stratification factors and protocol cohort.

- SVR rates were similar with RBV DR and EPO management strategies, regardless of race, sex, body weight, fibrosis score, and IL28B genotype (**Table 1**)
  - Multivariate logistic regression analyses for SVR revealed that treatment differences (EPO vs RBV DR) were not statistically significant for subgroups, including sex (female vs male, $P = 0.20$), age (≤40 y vs >40 y; $P = 0.40$), fibrosis score (F0/1/2 vs F3/4, $P = 0.39$), baseline hemoglobin (≤13 g/dL vs >13 g/dL, $P = 0.098$), and time to anemia onset (≤16 weeks vs >16 weeks, $P = 0.17$; ≤8 weeks vs >8 weeks, $P = 0.22$)

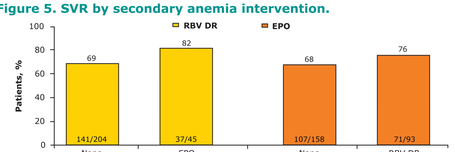
Table 1. SVR According to Baseline Characteristics

Subgroup	Category	RBV DR n = 249	EPO n = 251
Race, n/N (%)	Black	24/45 (53)	23/47 (49)
	Nonblack	154/204 (75)	155/204 (76)
Sex, n/N (%)	Male	60/78 (77)	60/87 (69)
	Female	118/171 (69)	118/164 (72)
Weight, kg, n/N (%)	<75	76/106 (72)	74/106 (70)
	≥75	102/143 (71)	104/145 (72)
Fibrosis score, n/N (%)*	F0/1/2	156/211 (74)	147/203 (72)
	F3/4	19/33 (58)	26/39 (67)
IL28B genotype, n/N (%)	CC	61/78 (78)	63/77 (82)
	CT	86/123 (70)	89/133 (67)
	TT	30/46 (65)	24/37 (65)

*Assessed by central pathologist.

- 82% of patients randomly assigned to RBV DR and 62% of patients randomly assigned to EPO did not receive secondary anemia management intervention
- SVR rates in patients receiving only primary anemia management were similar in the RBV DR (69%) and EPO (68%) groups (**Figure 5**)
- Patients who received additional secondary intervention had a numerically higher SVR rate than those who only received primary intervention: 82% and 76% for the RBV DR and EPO groups, respectively (**Figure 5**)

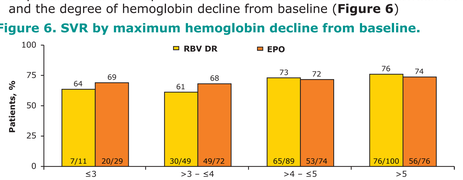
Figure 5. SVR by secondary anemia intervention.



DR, dose reduction; EPO, erythropoietin; RBV, ribavirin; SVR, sustained virologic response.

- Multivariate logistic regression analysis showed no difference between RBV DR and EPO use ($P = 0.769$) on the probability of SVR. Meanwhile, IL28B CC (vs TT) genotype ($P = 0.011$), normal (vs elevated) alanine aminotransferase ($P = 0.015$), nonblack race ($P < 0.0001$), genotype 1b infection ($P = 0.009$), and platelet count ≥200,000 cells/mm^3 ($P = 0.003$) were significantly associated with an increased likelihood of SVR
  - There was also a borderline association between male sex and higher SVR ($P = 0.048$)
- In patients who developed anemia there was no association between SVR and the degree of hemoglobin decline from baseline (**Figure 6**)

Figure 6. SVR by maximum hemoglobin decline from baseline.



DR, dose reduction; EPO, erythropoietin; RBV, ribavirin; SVR, sustained virologic response.

Safety

- Serious AEs and study discontinuations occurred at a similar rate, regardless of anemia management strategy (**Table 2**)

Table 2. Safety and Tolerability

Event, n (%)	RBV DR n = 249	EPO n = 251
Treatment-emergent AE	248 (100)	248 (99)
Serious AE	39 (16)	33 (13)
Anemia	4 (2)	2 (1)
Death	1* (<1)	0
Life-threatening treatment-emergent AE	6 (2)	5 (2)
Study drug discontinuation due to AE	27 (11)	32 (13)
Discontinuation due to anemia	5 (2)	6 (2)
PRBC transfusion	10 (4)	5 (2)

AE, adverse event; DR, dose reduction; EPO, erythropoietin; PRBC, packed red blood cell; RBV, ribavirin.
*Sudden cardiac death 3 weeks after completion of treatment.

- The most common AEs (≥30% in either group) were anemia, neutropenia, diarrhea, dysgeusia, nausea, chills, fatigue, headache, insomnia, and alopecia
- There was no difference in the incidence of AEs between the RBV DR and EPO treatment arms, including influenza-like symptoms (27% vs 27%), fatigue (70% vs 71%), depression, (20% vs 21%), anxiety (12% vs 12%), dyspnea (19% vs 21%), and cardiovascular events (14% vs 13%)
- To examine potential associations of EPO with AEs potentially attributed to its use, treatment-emergent AEs with MedDRA terms that most closely matched the AEs listed in the EPO product label were examined
  - AEs potentially attributable to EPO were rare and occurred with comparable frequency between the RBV DR and EPO arms

Conclusions

- An SVR rate of 71% was achieved in anemic patients receiving BOC plus PEG-IFN/RBV using either RBV DR or EPO
- RBV DR has no impact on SVR and is an appropriate first strategy for anemia management in patients receiving BOC
- Safety profiles were similar regardless of anemia management strategy

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References

1. Poordad F, et al. *N Engl J Med*. 2011;364(13):1195-1206.
2. Jacobson IM, et al. *N Engl J Med*. 2011;364(25):2405-2416.

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*Former employee of Merck Sharp & Dohme Corp., Whitehouse Station, NJ, USA.

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ONLINE EXPERT POSTER REVIEW AND DISCUSSION

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Sustained Virologic Response (SVR) in Prior PegInterferon/Ribavirin (PR) Treatment Failures After Retreatment with Boceprevir (BOC) + PR: PROVIDE Study Interim Results

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Abstract #11

Methods

- Study Design: Open-label, single-arm, multicenter rollover study
- Patient Population:
  - Subjects from control arm of Phase 2/3 BOC studies who received ≥12 weeks of PR treatment AND failed to achieve SVR due to:
    - Futility, defined as detectable HCV RNA (Roche TaqMan, LLD = 9.3 IU/mL) at TW12 (treatment-experienced patients) or TW24 (previously untreated patients)
    - Virologic breakthrough
    - Relapse after end of treatment (EOT) response
  - Patients were enrolled in PROVIDE at the discretion of the site investigators
- PROVIDE study enabled observation of historic Null responders

Goal

- To define the SVR rate of well-documented null responders to prior P/R therapy when retreated with boceprevir in combination with peginterferon and ribavirin.

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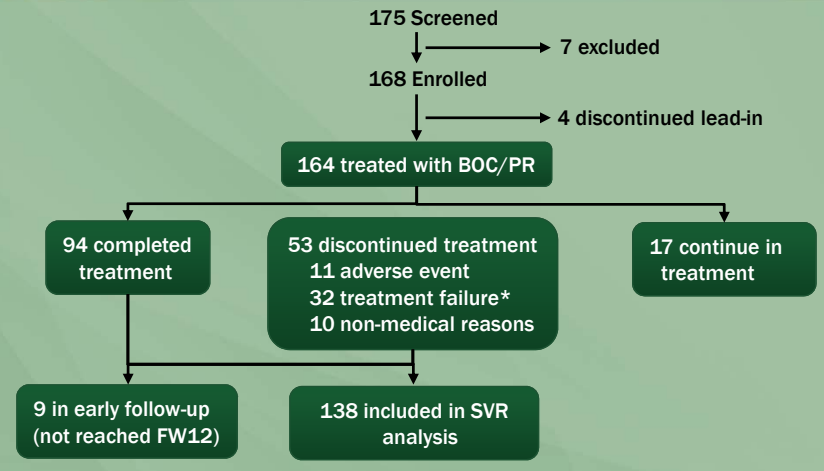
Study Flow (Interim Analysis)



* Includes subjects who discontinued due to futility at TW12 or had virologic breakthrough or incomplete virologic response.

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Baseline Patient Characteristics

	Prior Null Response (N = 52)	Prior Partial Response (N = 85)	Prior Relapse (N = 26)
Male, n (%)	33 (63)	60 (71)	17 (65)
White, n (%)	36 (69)	74 (87)	26 (100)
Age (y), mean ± SD	51.3 ± 7.7	52.6 ±8.4	53.9 ± 6.6
BMI† (kg/m²), mean ± SD	26.8 ± 3.8	28.7 ±4.7	27.4 ± 4.3
VL >800,000 IU/mL, n (%)	46 (88)	68 (80)	16 (62)
HCV subtype§, n (%): 1a	34 (65)	47 (55)	18 (69)
1b	18 (35)	36 (42)	8 (31)
Metavir Score§, n (%): F0-2	46 (88)	63 (74)	22 (85)
F3-4	5 (10)	19 (22)	2 (8)
missing	1 (2)	3 (4)	2 (8)

Does not include 5 patients whose prior non-response could not be classified as null, partial, or relapse.
† using height from parent study, weight at entry in PROVIDE.
§measured at entry in parent study; HCV subtype missing for 2 patients with prior partial response.

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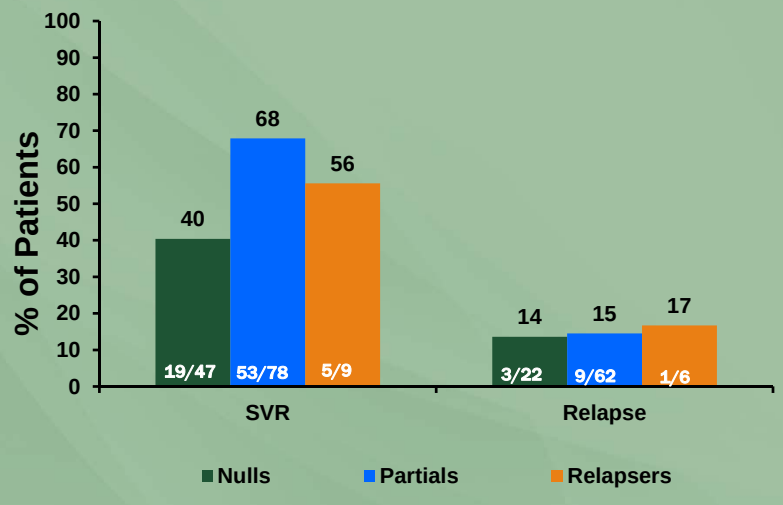
SVR and Relapse Rates, by Prior Treatment Response



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SVR by Baseline Characteristics and Prior Treatment Response

	SVR, n/m (%)		
	Prior Null Response	Prior Partial Response	Prior Relapse
VL ≤800,000	4/6 (67)	13/17 (76)	2/3 (67)
VL >800,000	15/41 (37)	40/61 (66)	3/6 (50)
F0/1/2	17/41 (41)	37/56 (66)	3/6 (50)
F3/4	2/5 (40)	15/19 (79)	1/1 (100)
HCV G1a‡	14/31 (45)	31/43 (72)	4/8 (50)
HCV G1b‡	5/16 (31)	21/34 (62)	1/1 (100)
Platelets <200,000	2/12 (17)	19/35 (54)	1/3 (33)
Platelets ≥200,000	17/34 (50)	34/43 (79)	4/6 (67)

‡ HCV subtype in referring study as determined by Janssen (Virco) assay based on sequencing of domain p329bp in the NS5B polymerase gene.

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