Poster #933

Hemoglobin Decline During Lead-in Phase as an Early Predictor of Anemia After the Addition of Boceprevir: A Retrospective Analysis of HCV SPRINT-1

F. Poordad,[1] J. M. Vierling,[2] R. Esteban,[3] P. Y. Kwo,[4] J. Long,[5] E. I. Chaudhri,[5] L. D. Pedicone,[5] J. K. Albrecht[5]

[1]Cedars-Sinai Medical Center, Los Angeles, CA, USA; [2]Baylor College of Medicine, Houston, TX, USA; [3]Hospital Universitario Vall d'Hebron, Barcelona, Spain; [4]Indiana University School of Medicine, Indianapolis, IN, USA; [5]Merck & Co., Inc., Kenilworth, NJ, USA

Abstract

Background. SPRINT-1 is a Phase 2b trial of 595 treatment-naive patients to assess the safety and efficacy of boceprevir (BOC) 800 mg TID, an oral inhibitor of HCV-NS3 protease, plus standard of care peginterferon alfa-2b 1.5 mcg/kg/week (P) and ribavirin 400-1400 mg/day (R) compared to P/R alone in genotype 1 (G1) chronic hepatitis C (CHC) patients. Two of the study arms received P/R for 4 wks (lead-in) prior to adding BOC. R therapy is well known to decrease hemoglobin (Hgb) and addition of BOC can further decrease Hgb by 1-1.5 g/dL. The aim of this analysis was to assess the predictive value of the Hgb decline during P/R lead-in for the Hgb nadir after addition of BOC. **Methods.** Patients were randomized to 48 wks of P/R or 4 wks of P/R lead-in followed by P/R/BOC for 24 or 44 wks or P/R/BOC for 28 or 48 wks. The primary endpoint was SVR at 24 wks post-treatment (Roche TaqMan LLD<15 IU/mL). Hgb <10 g/dL was managed using protocol guidelines for R dose reduction. At the discretion of the investigator, erythropoietin (EPO) was also permitted with concomitant R dose reduction. Data from patients randomized to the 2 study arms with 4-wk P/R lead-in treatment were pooled for analysis. **Results.** Hgb nadirs were comparable in the 2 arms with 4 wk lead-in therapy, regardless of total treatment duration. Hgb nadir of <9.5 g/dL was observed in 27%-29% of patients. The magnitude of Hgb decline during the P/R lead-in period correlated with the Hgb nadir observed after addition of BOC to the P/R treatment regimen (Table). Of all the patients from the 2 arms, 17% (31/183) had Hgb <10 g/dL by TW8 and 17% received EPO by TW8. In patients with ≥3g/dL decline of Hgb within the first 4 wks of lead-in, the Hgb nadir was <10g/dL in 61% (20/33) by TW8 and 67% (22/33) were treated with EPO by TW8. **Conclusions.** P/R lead-in therapy can identify patients at risk for further declines in Hgb after the addition of BOC to the treatment regimen. Such patients may benefit from close monitoring to prevent delays in the start of EPO treatment, reductions of R dosages to ineffective levels or discontinuation of therapy for anemia. A large clinical trial evaluating the role of EPO in the management of anemia during BOC therapy is ongoing and will provide additional information.

	Hgb Decline <10 g/dL While On P/R/BOC	Hgb <10 g/dL by TW8*	EPO Start by TW8*
Hgb Decline at TW4			
<1 g/dL	8/22 (36%)	0	0
1-<2 g/dL	18/48 (38%)	7/18 (39%)	4/18 (22%)
2-<3 g/dL	23/52 (44%)	4/23 (17%)	5/23 (22%)
3-<4 g dL	18/39 (46%)	11/18 (61%)	15/18 (83%)
≥4 g/dL	15/22 (68%)	9/15 (60%)	7/15 (47%)

*TW8= 4 weeks of P/R lead-in followed by 4 weeks of P/R/BOC.

Background

- Anemia is a well-described and frequent adverse event associated with peginterferon alfa (PEG-IFN) and ribavirin therapy in patients with chronic hepatitis C
  - In the IDEAL study, 26% to 28% of patients receiving PEG-IFN plus ribavirin required ribavirin dose reduction because of anemia, and 2% to 4% met protocol-defined criteria for treatment discontinuation (hemoglobin <8.5 g/dL)[1]
  - Retrospective analysis of data from IDEAL indicated that use of erythropoietin (EPO) was significantly associated with sustained virologic response (SVR) in patients with early-onset anemia (≤8 weeks of treatment) compared with those with late-onset anemia[2]
- First-generation, direct-acting antiviral drugs, such as boceprevir and telaprevir, are also associated with hemoglobin decline, and clinical trials combining these drugs with PEG-IFN and ribavirin have been shown to exacerbate treatment-induced anemia[3-5]
  - In SPRINT-1, 42% to 50% of patients receiving boceprevir plus standard-of-care therapy developed nadir hemoglobin levels of 8.5 to <10 g/dL compared with 24% of patients receiving standard-of-care therapy alone
  - SVR rates were greater in patients with nadir hemoglobin levels <10 g/dL than in those with higher hemoglobin levels

Aim

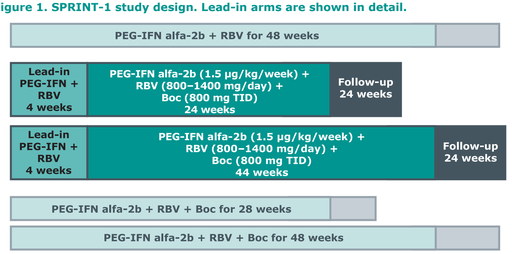
- To assess the predictive value of the hemoglobin decline during PEG-IFN plus ribavirin lead-in therapy for the hemoglobin nadir after addition of boceprevir

Patients and Methods

Study Design

- SPRINT-1 was a phase 2b, open-label, randomized trial designed to compare boceprevir (800 mg TID) plus PEG-IFN alfa-2b 1.5 µg/kg/week and ribavirin 400–1400 mg/day to PEG-IFN alfa-2b + ribavirin alone[5]
- In part 1 of the study, patients were randomized to 48 weeks of PEG-IFN alfa-2b + ribavirin (control) or 4 weeks of PEG-IFN alfa-2b + ribavirin lead-in followed by PEG-IFN alfa-2b + ribavirin + boceprevir for 24 or 44 weeks or PEG-IFN alfa-2b + ribavirin + boceprevir for 28 or 48 weeks (**Figure 1**)
- Data from patients randomized to the 2 study arms with 4-week PEG-IFN alfa-2b + ribavirin lead-in treatment were pooled for analysis

Figure 1. SPRINT-1 study design. Lead-in arms are shown in detail.



Boc = boceprevir; PEG-IFN = peginterferon; RBV = ribavirin.

- In the lead-in arms, ribavirin dosing was based on patient body weight (**Table 1**)

Table 1. Ribavirin Dosing in Part 1

Body Weight	Ribavirin Dose Schedule
≤65 kg	800 mg per day (400 mg twice daily)
66–80 kg	1000 mg per day (400 mg in the morning and 600 in the evening)
81–105 kg	1200 mg per day (600 mg twice daily)
>105 kg	1400 mg per day (600 mg in the morning and 800 in the evening)

Patients

- Previously untreated adults with genotype 1 hepatitis C virus infection, aged 18–60 years, with a liver biopsy consistent with hepatitis C infection were enrolled
- Minimum hematologic and biochemical parameters included hemoglobin of 13 g/dL in men and 12 g/dL in women, neutrophil count 1.5 × 10^9/L, platelet count 100 × 10^9/L, and bilirubin, albumin, and creatinine within normal limits
- Patients with decompensated cirrhosis, human immunodeficiency virus infection, previous organ transplantation, or cause of liver disease other than hepatitis C were excluded

Assessments

- The primary end point was SVR at 24 weeks posttreatment (Roche TaqMan LLD <15 IU/mL)
- Anemia, defined as <10 g/dL, was managed with protocol-recommended guidelines for dose reduction
  - **Ribavirin**: dose lowered by 200 mg/day except patients receiving 1400 mg/day, for whom the initial dose reduction was 400 mg/day
  - **Boceprevir**: dose lowered by 200 mg to 600 mg TID, and again to 400 mg TID at the discretion of the investigator
- EPO use was allowed with concomitant ribavirin dose reduction at the discretion of the investigator

Results

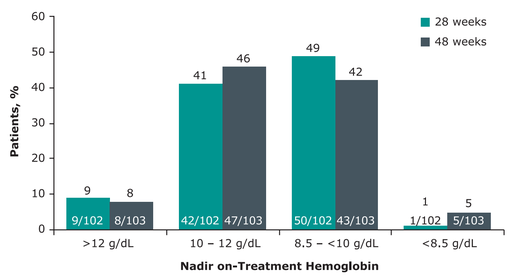
- 595 treatment-naive patients were enrolled in SPRINT-1
  - 206 patients were randomized to the PEG-IFN alfa-2b + ribavirin lead-in arms (n = 103 in each arm)
- Patient demographics are shown in **Table 2**

Table 2. Patient Demographics and Characteristics

	PEG-IFN alfa-2b + RBV Lead-in for 4 Weeks	
	PEG-IFN alfa-2b + RBV + Boceprevir for 24 Weeks (n = 103)	PEG-IFN alfa-2b + RBV + Boceprevir for 44 Weeks (n = 103)
Gender, n (%)		
Male	52 (50)	45 (44)
Female	51 (50)	58 (56)
Race, n (%)		
White	85 (83)	85 (83)
Black	15 (15)	15 (15)
Other	3 (3)	3 (3)
Age, years (SD)	47.7 (7.4)	47.6 (8.3)
Weight, kg (SD)	79.9 (14.2)	78.4 (16.5)
Genotype, n (%)		
1a	53 (51)	60 (58)
1b	37 (36)	35 (34)
No subtype	13 (13)	8 (8)
Baseline HCV RNA		
Log of geometric mean	6.53	6.53
>600,000 IU/mL, n (%)	90 (87)	93 (90)
Cirrhosis, n (%)	7 (7)	6 (6)

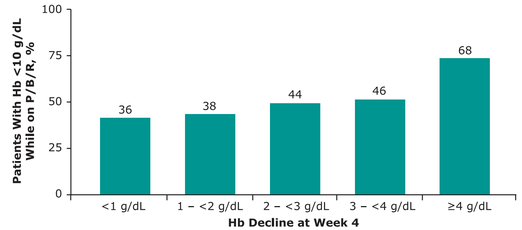
- Nadir hemoglobin levels were comparable in both study arms that incorporated a 4-week, lead-in phase, regardless of total treatment duration (**Figure 2**)
- Over the full duration of treatment, nadir hemoglobin <9.5 g/dL was observed in 27% to 29% of patients
  - Nadir hemoglobin <9.5 g/dL during the first 4 weeks of treatment was observed in 5% and 8% of patients in the 28- and 48-week treatment arms, respectively

Figure 2. Nadir hemoglobin levels.



- The magnitude of hemoglobin decline during the lead-in period correlated with the hemoglobin nadir observed after addition of boceprevir to the PEG-IFN alfa-2b + ribavirin regimen (**Figure 3**)

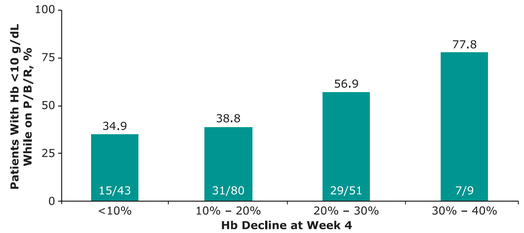
Figure 3. Association between hemoglobin decline at end of lead-in phase and nadir hemoglobin level during therapy with boceprevir plus PEG-IFN alfa-2b + ribavirin.



B = boceprevir; Hb = hemoglobin; P = peginterferon alfa-2b; R = ribavirin.

- The magnitude of hemoglobin decline during the lead-in period, expressed as a percentage of baseline hemoglobin, also correlated with the hemoglobin nadir observed after addition of boceprevir to the PEG-IFN alfa-2b + ribavirin regimen (**Figure 4**)

Figure 4. Association between percentage hemoglobin decline at end of lead-in phase and nadir hemoglobin level during therapy with boceprevir plus PEG-IFN alfa-2b + ribavirin.



B = boceprevir; Hb = hemoglobin; P = peginterferon alfa-2b; R = ribavirin.

- The magnitude of decline in hemoglobin during the PEG-IFN alfa-2b + ribavirin lead-in correlated with the development of anemia after the addition of boceprevir, and this correlation was unaffected by patient age, gender, or ethnicity (**Table 3**)

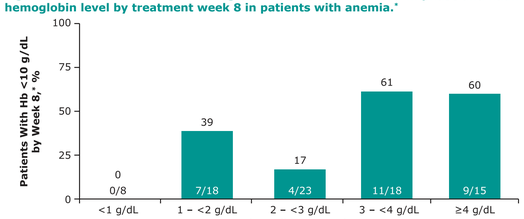
Table 3. Percentage Decline in Hemoglobin During the PEG-IFN alfa-2b + Ribavirin Lead-in as a Predictor of Anemia After the Addition of Boceprevir According to Selected Patient Subgroups

	Decline in Hemoglobin From Baseline at Week 4, %			
	<10 (n = 43)	10 – <20 (n = 80)	20 – <30 (n = 51)	30 – <40 (n = 9)
Anemia During P/R/B, % (n/N)				
All patients	35 (15/43)	39 (31/80)	57 (29/51)	78 (7/9)
Age, years				
<50	34 (11/32)	38 (14/37)	52 (14/27)	100 (3/3)
≥50	36 (4/11)	40 (17/43)	63 (15/24)	67 (4/6)
Gender				
Female	44 (11/25)	52 (17/33)	81 (17/21)	67 (2/3)
Male	22 (4/18)	30 (14/47)	40 (12/30)	83 (5/6)
Ethnicity				
Nonwhite	25 (3/12)	19 (3/16)	50 (2/4)	0 (0/1)
White	39 (12/31)	44 (28/64)	57 (27/47)	88 (7/8)

B = boceprevir; Hb = hemoglobin; P = peginterferon alfa-2b; R = ribavirin.

- 17% (31/183) of patients from both lead-in arms developed anemia (hemoglobin <10 g/dL) by treatment week 8, and 27.9% (51/183) first developed anemia after treatment week 8; the remaining 101 patients did not develop anemia (**Figure 5**)
- Early anemia (hemoglobin <10 g/dL before week 8) occurred in 61% (20/33) of patients with ≥3-g/dL decline of hemoglobin within the first 4 weeks of lead-in

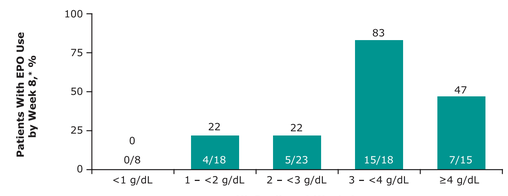
Figure 5. Association between hemoglobin decline at end of lead-in phase and nadir hemoglobin level by treatment week 8 in patients with anemia.*



Hb = hemoglobin.
*Treatment week 8 = 4 weeks of PEG-IFN alfa-2b + ribavirin lead-in followed by 4 weeks of PEG-IFN alfa-2b + ribavirin + boceprevir.

- In total, 17% of all patients from both lead-in arms received EPO by treatment week 8
- 67% (22/33) of patients with ≥3 g/dL decline in hemoglobin within the first 4 weeks of lead-in had received EPO by treatment week 8 (**Figure 6**)

Figure 6. Association between hemoglobin decline at end of lead-in phase and initiation of EPO by treatment week 8 in patients with anemia.*

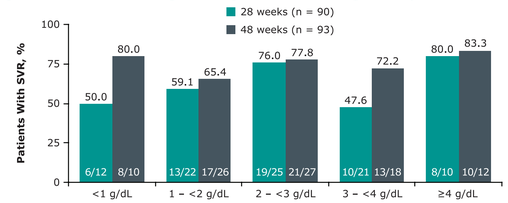


EPO = erythropoietin; Hb = hemoglobin.
*Treatment week 8 = 4 weeks of PEG-IFN alfa-2b + ribavirin lead-in followed by 4 weeks of PEG-IFN alfa-2b + ribavirin + boceprevir.

Association of Anemia and EPO Use With SVR

- In patients who developed anemia (n = 82), there was no significant difference in rate of SVR between patients receiving EPO and patients not receiving EPO (82.4% vs 78.6%; difference, 3.8%; 95% confidence interval, −14.3%, 31.4%)
- Because of the limited number of patients per group, it is difficult to determine whether hemoglobin decline during the lead-in phase can be used as an early predictor of SVR (**Figure 7**)

Figure 7. SVR rates according to hemoglobin decline during lead-in phase.



Hb = hemoglobin; SVR = sustained virologic response.

Conclusions

- PEG-IFN alfa-2b + ribavirin lead-in therapy can identify patients at risk for further decline in hemoglobin after the addition of boceprevir
- Patients with hemoglobin decline greater than 3 g/dL by week 4 are most likely to have hemoglobin levels <10 g/dL at week 8
- These patients may benefit from close monitoring in order to consider ribavirin dose reduction and/or use of EPO to prevent discontinuation of hepatitis C treatment due to anemia
- A large clinical trial evaluating different management strategies for anemia (use of EPO vs ribavirin dose reductions) during boceprevir therapy is ongoing and will provide additional information

- The SPRINT-1 study is registered with ClinicalTrials.gov, number NCT00423670.

Acknowledgments

Writing assistance was provided by T. Ibbotson, PhD, and C. Knight, PharmD. This assistance was funded by Merck & Co., Inc., Whitehouse Station, NJ, USA.

References

1. McHutchison JG, et al. *N Engl J Med*. 2009;361(6):580-93.
2. Sulkowski M, et al. *Gastroenterology*. 2010 Aug 16. [Epub ahead of print] doi:10.1053/j.gastro.2010.07.059
3. McHutchison JG, et al. *N Engl J Med*. 2009;360(18):1827-38.
4. Hezode C, et al. *N Engl J Med*. 2009;360(18):1839-50.
5. Kwo PY, et al, *Lancet*. 2010;376:705-16.

Disclosures

F. Poordad has disclosed that he has been an advisor/consultant and has received research grants from Abbott, Genentech, Gilead, Idenix, Merck & Co., Inc., Salix, Vertex, and has also received research grants from Pharmassett and Bristol-Myers Squibb, and has received speaker honoraria from Gilead, Genentech, and Salix. J. M. Vierling has received grant and research support from Abbott, Bristol-Myers Squibb, Conatus, Excalenz, Gilead, Globeimmune, Hyperion, Idenix-Novartis, Intercept, Novartis, Ocera, Pharmassett, Pfizer (pending), Roche, Merck & Co., Inc., Sundise, Vertex, and Zymogenetics and serves on speaker bureaus for Bristol-Meyers Squibb, Chronic Liver Disease Foundation, and Merck & Co., Inc. R. Esteban has received grants for development of educational presentations (including speaker bureau) from Merck & Co., Inc. P. Y. Kwo has received research grants, honoraria, consultancy fees, and travel grants from Merck & Co., Inc., and research grants from Abbott, Bristol-Myers Squibb, Gilead, GlaxoSmithKline, Human Genome Sciences, Idenix, Roche, Tibotec, Valeant, and Vertex, and he has served on advisory boards for Abbott, Anadys, Gilead, Human Genome Sciences, Novartis, and Vertex and is on speaker bureaus for Bristol-Myers Squibb, Gilead, Merck & Co., Inc., and Roche. J. Long, E. Chaudhri, L. D. Pedicone, and J. K. Albrecht are employees of Merck Research Institute, and E. Chaudhri, L. D. Pedicone, and J. K. Albrecht are stockholders of Merck & Co., Inc.

Presented at the 61st Annual Meeting of the American Association for the Study of Liver Diseases, October 29–November 2, 2010, Boston, MA.

Supported by Merck & Co., Inc., Whitehouse Station, NJ, USA.