Poster LB16

Boceprevir Plus Peginterferon alfa-2b/Ribavirin for Treatment of Genotype 1 Chronic Hepatitis C in Previously Untreated Patients: Interim Results from the HCV SPRINT-1 Study

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Abstract

Background: Boceprevir (Boc) is an oral HCV-NS3 protease inhibitor being assessed in combination with peginterferon alfa-2b (P) 1.5 μg/kg/QW and ribavirin (R) for chronic hepatitis C.

Methods: HCV SPRINT-1 is a Phase 2 study in HCV-1 patients evaluating Boc 800 mg TID in three treatment regimens: 1) 4 weeks of P/R 800-1400 mg/d (lead-in) followed by addition of Boc to the combination for 24 or 44 weeks (total 28 or 48 weeks); 2) Boc in combination with P/R (800-1400 mg/d) for 28 or 48 weeks; 3) Boc in combination with P/low-dose R (400-1000 mg/d) for 48 weeks, compared to P (1.5 μg/kg QW)/R (800-1400 mg/d) for 48 weeks. The primary endpoint of the study is sustained virologic response (SVR) at 24 weeks of follow-up (Roche Cobas Taqman: LLD 15 IU/mL).

Results: 595 patients treated: 77% US, 16% Black, 7% cirrhotic, 89% >600,000 IU/mL. Regimens 1, 2 and P/R control results from a planned interim analysis are reported. Addition of Boc markedly increased SVR with 28 and 48 week regimens compared to P/R control. SVR was higher with a 4-week P/R lead-in for the 48 week regimen, while a decrease in viral breakthrough was observed with both 28 and 48-week lead-in regimens. As with P/R, rapid virologic response (RVR) and early virologic response (EVR) were highly predictive of response with the Boc combinations. The most common adverse events reported in the Boc arms were fatigue, anemia, nausea and headache. Incidence of rash-related AEs was similar in boceprevir-containing regimens and P/R control. Treatment discontinuations due to adverse events were between 9 to 19% for patients in Boc arms, compared to 8% in control arm.

Conclusions: In this study, boceprevir when combined with P/R is safe for use up to 48 weeks and substantially improves SVR rates with 28 weeks of therapy and can nearly double the SVR compared to the current P/R standard of care (48 weeks) in this trial. Use of a 4-week lead-in with P/R prior to the addition of boceprevir appears to reduce the incidence of viral breakthrough.

Treatment Arm	Sustained Virologic Response, % (n/N)*			Viral‡ Breakthrough, %
	All Patients	Patients with RVR†	Patients with EVR†	
No lead-in, 28 weeks	55 (59/107)	74 (32/43)	69 (59/85)	7
Lead-in, 28 weeks	56 (58/103)	82 (54/66)	68 (58/85)	4
No lead-in, 48 weeks	66 (68/103)	82 (31/38)	83 (67/81)	11
Lead-in, 48 weeks	74 (76/103)	92 (61/66)	89 (76/85)	5
P/R control, 48 weeks	38 (39/104)	100 (8/8)	86 (32/37)	0

* SVR 12 48-week arms; SVR 24 28-week arms.
† RVR: undetectable HCV-RNA on or before 4 weeks of Boc treatment; EVR: undetectable HCV-RNA on or before 12 weeks of Boc treatment.
‡ Persistent ≥ 2 $\log_{10}$ increase from nadir and ≥ 50,000 IU/mL.

Background

- Combination therapy with pegylated interferon-alfa and weight-based ribavirin is the standard of care (SOC) for the treatment of chronic hepatitis C (CHC) patients infected with HCV genotype 1
  - However, only approximately 40%[1,2] of these patients achieve sustained virologic response (SVR) with SOC
- Boceprevir inhibits the HCV-NS3 protease, thereby preventing viral replication
  - A new mechanism of action compared with both pegylated interferon-alfa and ribavirin
- Boceprevir may improve virologic response and shorten treatment duration when added to the current SOC regimen
- Previous studies with SOC have shown that patients who achieve rapid virologic response (RVR) and early virologic response (EVR), defined as undetectable HCV-RNA in plasma at Week 4 and Week 12 of treatment, respectively, are more likely to attain SVR
- The addition of boceprevir to SOC may lead to a greater proportion of subjects achieving RVR and EVR
- Four weeks of PegIntron and ribavirin lead-in treatment should allow
  - Achievement of steady-state drug levels
  - Alpha interferon-mediated immune system activation
  - Lower HCV burden
- This lead-in strategy may reduce the emergence of viral resistance by decreasing the pool of pre-existing viral quasi-species

Aims

- Evaluate the safety and efficacy of boceprevir in combination with PegIntron 1.5 μg/kg plus ribavirin in previously untreated adults with genotype 1 CHC
- Assess the relationship between RVR and EVR to SVR
- Assess the effect of the 4-week lead-in with PegIntron and ribavirin on SVR
- Assess the effect of duration of treatment with boceprevir on SVR

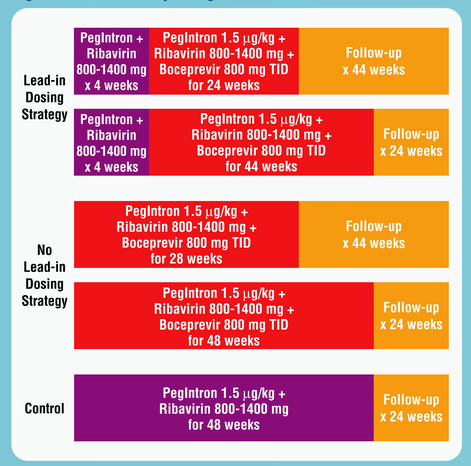
Methods

- This is an open-label randomized trial conducted in two parts
- Part 1 has 5 treatment arms, randomized 1:1:1:1:1, and compares
  - PegIntron and ribavirin for 4 weeks followed by PegIntron, ribavirin, and boceprevir for 44 weeks (Arm 5)
  - PegIntron, ribavirin, and boceprevir for 48 weeks (Arm 4)
  - PegIntron and ribavirin for 4 weeks followed by PegIntron, ribavirin, and boceprevir for 24 weeks (Arm 3)
  - PegIntron, ribavirin, and boceprevir for 28 weeks (Arm 2)
  - PegIntron and ribavirin for 48 weeks (Control Arm 1)

  Note: Ribavirin dosing for Part 1 is weight based, 800 to 1400 mg/d
- Part 2 enrolled after Part 1 and has 2 treatment arms randomized 1:4 and compares
  - PegIntron, ribavirin (800 to 1400 mg/d), and boceprevir for 48 weeks (Arm 6)
  - PegIntron, ribavirin (400 to 1000 mg/d), and boceprevir for 48 weeks (Arm 7)

  Note: Data for Part 2 not available at the time of this interim analysis
- Patients at baseline
  - CHC genotype 1; treatment naïve; liver biopsy (all histologic grades including cirrhosis), aged 18-60 years, 45-125 kg
- Efficacy assessments
  - Proportion of patients with undetectable HCV-RNA using Roche COBAS TaqMan LLD 15 IU/mL
  - SVR 12 for 48-week arms
  - SVR 24 for 28-week arms

Figure 1. Part 1 Study Design



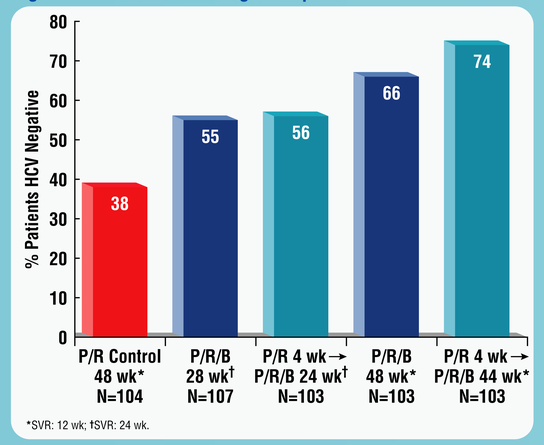
Results

Table 1. Baseline Characteristics

	P/R Control N=104	P/R/B 28 wk N=107	P/R Lead-in → P/R/B 28 wk N=103*	P/R/B 48 wk N=103	P/R Lead-in → P/R/B 48 wk N=103*
Gender					
Male (%)	67	59	50	61	56
Race					
Caucasian (%)	80	80	83	84	83
Mean Age (years)	48.3	46.4	47.7	46.7	47.6
Mean Weight (kg)	83.4	83.4	79.9	80.0	78.4
HCV Subtype (%)					
1a	51	63	51	53	58
1b	40	28	36	35	34
1 (no subtype)	9	9	13	12	8
Viral Load Mean ($\log_{10}$ IU/mL)	6.5	6.6	6.5	6.5	6.5
HCV-RNA >600,000 IU/mL (%)	90	92	87	91	90
Cirrhosis (%)	8	7	7	9	6

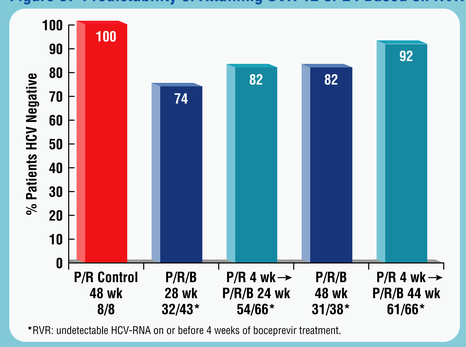
*Boceprevir added to treatment regimen after 4-week lead-in of PEG-IFN α-2b + ribavirin.

Figure 2. Sustained Virologic Response



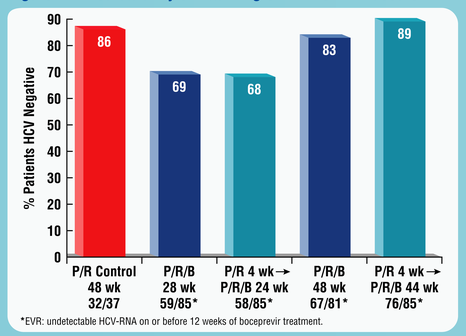
*SVR: 12 wk; †SVR: 24 wk.

Figure 3. Predictability of Attaining SVR 12 or 24 Based on RVR



*RVR: undetectable HCV-RNA on or before 4 weeks of boceprevir treatment.

Figure 4. Predictability of Attaining SVR 12 or 24 Based on EVR



*EVR: undetectable HCV-RNA on or before 12 weeks of boceprevir treatment.

- The addition of boceprevir markedly increased SVR with 28- and 48-week regimens compared with P/R control
- SVR was higher with a 4-week P/R lead-in for the 48-week regimen
- RVR and EVR in boceprevir-containing arms very predictive of SVR

Table 2. Common Adverse Events*

	P/R 48 wk N=104 N (%)	P/R/B 28 wk N=107 N (%)	Lead-in P/R/B 28 wk N=103 N (%)	P/R/B 48 wk N=103 N (%)	Lead-in P/R/B 48 wk N=103 N (%)
Fatigue	57 (55)	65 (61)	70 (68)	51 (50)	73 (71)
Headache	45 (43)	52 (49)	41 (40)	44 (43)	54 (52)
Nausea	44 (42)	41 (38)	42 (41)	56 (54)	48 (47)
Anemia	35 (34)	60 (56)	55 (53)	54 (52)	58 (56)
Neutropenia	12 (12)	25 (23)	17 (17)	26 (25)	31 (30)
Chills	35 (34)	31 (29)	31 (30)	33 (32)	34 (33)
Alopecia	27 (26)	36 (34)	30 (29)	30 (29)	35 (34)
Pyrexia	35 (34)	28 (26)	27 (26)	41 (40)	35 (34)
Insomnia	39 (38)	36 (34)	29 (28)	40 (39)	41 (40)
Diarrhea	24 (23)	28 (26)	27 (26)	25 (24)	29 (28)
Dysgeusia	9 (9)	23 (21)	27 (26)	33 (32)	28 (27)
Arthralgia	20 (19)	14 (13)	22 (21)	20 (19)	19 (18)
Myalgia	17 (16)	31 (29)	20 (19)	21 (20)	27 (26)
Flu-like Illness	25 (24)	24 (22)	21 (20)	19 (18)	15 (15)
Depression	22 (21)	21 (20)	20 (19)	29 (28)	20 (19)
Irritability	23 (22)	25 (23)	24 (23)	15 (15)	27 (26)
Pruritus	16 (15)	19 (18)	19 (18)	23 (22)	19 (18)

*Based upon reports for all treatment groups combined.

- Common adverse events (AEs) in boceprevir-containing arms
  - Mostly constitutional symptoms
  - Comparable to P/R control
- Pruritus comparable to P/R control
- Higher incidence of dysgeusia and anemia in boceprevir-containing arms

Table 3. Severity of Skin and Subcutaneous Disorders*

Severity	P/R 48 wk N=104 N (%)	P/R/B 28 wk N=107 N (%)	Lead-in P/R/B 28 wk N=103 N (%)	P/R/B 48 wk N=103 N (%)	Lead-in P/R/B 48 wk N=103 N (%)
All	39 (38)	36 (34)	38 (37)	46 (45)	40 (39)
Mild	31 (30)	31 (29)	29 (28)	32 (31)	33 (32)
Moderate	8 (8)	5 (5)	8 (8)	13 (13)	7 (7)
Severe	0	0	1 (1)†	1 (1)‡	0

*Skin and subcutaneous disorders include adverse event terms of dermatitis, eczema, erythema, exfoliative rash, photosensitivity reaction, rash erythematous, rash generalized, rash maculo-papular, rash papular, rash pruritic, skin exfoliation, and skin irritation.
† Severe erythema: Patient was in P/R lead-in; never received boceprevir.
‡ Severe eczema: Patient treated with prednisone and topical steroids.

- Incidence of rash-related AEs was similar in boceprevir-containing regimens and P/R control

Table 4. Treatment Discontinuations

	P/R Control N=104 (%)	P/R/B 28 wk N=107 (%)	P/R Lead-in → P/R/B 28 wk N=103 (%)‡	P/R/B 48 wk N=103 (%)	P/R Lead-in → P/R/B 48 wk N=103 (%)‡
Total Discontinued	16 (15)	30 (28)	27 (26)	39 (38)	27 (26)
Adverse Events	8 (8)	12 (11)	15 (15)	20 (19)	9 (9)
Viral Breakthrough*	0	7 (7)	4 (4)	11 (11)	5 (5)
Other†	8 (8)	11 (10)	8 (8)	8 (8)	13 (13)

*Persistent ≥ 2 $\log_{10}$ increase from nadir and ≥ 50,000 IU/mL.
†Lost to follow-up, subject did not wish to continue, non-compliance with protocol.
‡Boceprevir added to treatment regimen after 4-week lead-in of PEG-IFN α-2b + ribavirin.

- Treatment discontinuations due to AEs were between 9 to 19% in boceprevir-containing arms
- Less viral breakthrough in lead-in arms

Summary

- In this study, boceprevir when combined with P/R is safe for use up to 48 weeks
- Boceprevir substantially improves SVR rates with 28 weeks of therapy and nearly doubles the SVR compared to the current P/R SOC for 48 weeks
- Use of a 4-week lead-in with P/R prior to the addition of boceprevir appears to reduce the incidence of viral breakthrough regardless of treatment duration and may improve SVR over a 48-week treatment duration
- Further follow-up of this cohort and a large phase 3 trial examining the role of boceprevir will help define the optimal treatment paradigm for the incorporation of boceprevir to P/R in the treatment of genotype 1 HCV infected individuals

References

1. Fried M, et al. *N Engl J Med.* 2002;347:975-82.
2. Manns M, et al. *Lancet.* 2001;358:958-65.

Disclosures

Paul Kwo:Yes conflict of interest; Indenix:Salary:Grant/Research Support; Human Genome Sciences:Salary:Grant/Research Support; Merck:Salary:Grant/Research Support; Novartis:Salary:Grant/Research Support; Novartis:Consulting fee:Speaking & Teaching; Schering-Plough:Salary:Grant/Research Support; Schering-Plough:Salary:Advisory Committees or Review Panels; Schering-Plough:Salary:Speaking & Teaching; Vertex:Salary:Advisory Committees or Review Panels; Vertex:Salary: Grant/Research Support; Eric Lawitz: Yes conflict of interest; Achillion:Grant/Research Support; Bristol-Myers Squibb:Ownership interest (e.g. stocks, stock options):Grant/Research Support; Coley:Grant/Research Support; Gilead:Grant/Research Support; GlaxoSmithKline: Grant/Research Support; Human Genome Sciences:Grant/Research Support; Indenix:Grant/Research Support; Merck:Grant/Research Support; Novartis:OGrant/Research Support; Roche:Grant/Research Support; Schering-Plough:Grant/Research Support. Jonathan McCone: Yes conflict of interest; Schering-Plough:Consulting fee:Speaking & Teaching; Roche:Consulting fee:Speaking & Teaching. Eugene Schiff: Yes conflict of interest; Grant/Research Support. John Vierling:Yes conflict of interest; Abbott:Consulting fee:Advisory Committees or Review Panels; Axcan:Consulting fee:Speaking & Teaching; Bristol-Myers Squibb:Consulting fee; Advisory Committees or Review Panels; Bristol-Myers Squibb:Consulting fee:Speaking & Teaching; Gilead:Consulting fee:Advisory Committees or Review Panels; Indenix:Consulting fee:Grant/Research Support; Novartis:Consulting fee:Grant/Research Support; Roche:Consulting fee:Advisory Committees or Review Panels; Roche:Consulting fee: Grant/Research Support; Salix:Consulting fee:Advisory Committees or Review Panels; Schering-Plough:Consulting fee:Advisory Committees or Review Panels; Schering-Plough:Consulting fee:Grant/Research Support; Vertex:Consulting fee:Advisory Committees or Review Panels; Vertex:Consulting fee:Grant/Research Support; Wyeth:Consulting fee. David Pound:No conflict of interest; Mitchell Davis:Yes conflict of interest; Schering-Plough:Grant/Research Support; Speaking & Teaching; Consulting; Advisory Committees or Review Panels. Joseph Galati:No conflict of interest.Stuart Gordon:Yes, conflict of interest; Bayer:Grant/Research Support; Bristol-Myers Squibb:Advisory Committees or Review Panels; Gilead:Advisory Committees or Review Panels; GlaxoSmithKline: Grant/Research Support; Human Genome Sciences:Grant/Research Support; Merck: Grant/Research Support; Roche: Speaking & Teaching; Schering-Plough: Speaking & Teaching; Vertex:Grant/Research Support; Speaking & Teaching; Natarajan Ravendhran:Yes conflict of interest; Schering-Plough:Grant/Research Support. Lorenzo Rossaro:Yes conflict of interest; Schering-Plough: Consulting fee:Advisory Committees or Review Panels; Roche:Consulting fee:Advisory Committees or Review Panels. Frank Anderson:No conflict of interest; Ira Jacobson:Boehringer Ingelheim:Consulting; Bristol-Myers Squibb:Consulting; Gilead:Consulting; Human Genome Sciences:Consulting; Merck:Consulting; Pfizer:Consulting; Roche:Grant/Research Support; Schering-Plough: Consulting; Valeant:Grant/Research Support; Vertex:Consulting; Raymond Rubin:No conflict of interest; Kenneth Koury:Yes conflict of interest; Schering-Plough:Salary:Employment; Eirum Chaudhri:Yes conflict of interest; Schering-Plough: Salary:Employment. Janice Albrecht:Yes conflict of interest; Schering-Plough:Salary:Employment

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