Response-Guided Therapy with Boceprevir + Peginterferon alfa-2b/Ribavirin for Treatment-Naïve Patients with Hepatitis C Virus Genotype 1 Was Similar to a 48-Wk Fixed-Duration Regimen with Boceprevir + Peginterferon alfa-2b/Ribavirin in SPRINT-2

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Abstract

Background: In SPRINT-2, BOC added to P/R given for 44 wks or as RGT after a 4-wk lead-in (LI) treatment period with P/R significantly improved the sustained virologic response (SVR) in treatment-naive G1 patients compared to standard of care. We examined whether RGT based on the HCV RNA response during Wks 8-24 for a total duration of 28 or 48 wks (but including only 24 wks of BOC from Wks 4 to Wk 28 regardless of the Wk 8-24 HCV RNA response) produced similar results to the 4-wk LI & then BOC/P/R for 44 wks.

Methods: SPRINT-2 compared a LI treatment period with P/R, followed by (1) P/R plus placebo for 44 wks (48P/R); (2) RGT: BOC/P/R for 24 wks, with an additional 20 wks of P/R alone only if HCV RNA was detected during Wks 8-24 (LI+24BOC/P/R+/-20P/R); or (3) BOC/P/R for 44 wks (LI+44BOC/P/R). Study therapy was stopped for futility in patients with detectable HCV RNA at Wk 24. The primary efficacy endpoint was the SVR in all randomized patients treated with ≥1 dose of any study medication. Non-black (Cohort 1) & black (Cohort 2) patients were enrolled & analyzed separately per protocol.

Results: In Cohort 1, the overall SVR [95%CI] was similar for RGT (66.8%) & LI+44BOC/P/R (68.5%), with a Δ=1.7% [-5.6%, 9.0%]. For the 47% of subjects in RGT arm who achieved persistently undetectable HCV RNA during Wks 8-24, the SVR was 97% after LI+24/BOC/P/R & similar to the 96% SVR for the corresponding patients receiving LI+44BOC/P/R (Table). 31% of patients in the RGT arm discontinued treatment by 28 weeks (mostly due to the 24-wk futility rule or adverse events) & were not assigned a treatment duration. For the 22% of patients in the RGT arm with detectable HCV RNA during Wks 8-24 who received >28 wks of therapy, the SVR was 74% after LI+24BOC/P/R+20P/R & matched the 74% SVR for the corresponding patients given LI+44BOC/P/R. Generally comparable results were seen in the much smaller Cohort 2.

Conclusions: RGT with LI+24BOC/P/R+/-20P/R based upon on-treatment HCV RNA response produced SVR similar to LI+44BOC/P/R. Non-black patients achieving undetectable HCV RNA on LI+BOC/P/R from Wk 8 through Wk 24 can have their treatment duration shortened from 48 wks to 28 wks.

	Sustained Virologic Response (SVR) Rates			
	Undetectable Wks 8-24 HCV RNA		Detectable Wks 8-24 HCV RNA	
	RGT LI+24BOC/P/R	Fixed Duration LI+44BOC/P/R	RGT[1] LI+24BOC/P/R+20P/R	Fixed Duration[1] LI+44BOC/P/R
Cohort 1 N=938	143/147 (97%)	137/142 (96%)	52/70 (74%)	48/65 (74%)
Cohort 2 N=159	13/15 (87%)	18/19 (95%)	7/12 (58%)	7/8 (88%)

[1]Includes only patients continuing therapy for >28 wks

Background

- Chronic hepatitis C (CHC) genotype 1 is the least responsive subtype to standard of care treatment with peginterferon (PEG) plus ribavirin (R)
  - Sustained virologic response (SVR) rates of approximately 40% in treatment-naïve adults[1]
- Boceprevir (BOC) inhibits the NS3-protease active site
  - Phase 3 study of treatment-naive CHC genotype 1 adults (SPRINT-2) showed increased SVR rates of
    - 67-68% in non-Black patients treated with BOC + PEG alfa-2b (P) + R for up to 48 weeks compared with 40% in non-Black patients treated with PR only
    - 42-53% in Black patients treated with BOC + PR for up to 48 weeks compared with 23% in Black patients treated with PR only
    - Oral presentation of SPRINT-2 final results on Monday, Nov 1 at 5:30 pm (LB-4)

[1]McHutchison et al. *NEJM* 2009;361:580-93.

Aim

- To evaluate response-guided therapy [BOC RGT] based on HCV-RNA levels between treatment weeks 8-24 vs. fixed-duration therapy of 4-week lead-in with PR and boceprevir + PR for 44 weeks (BOC/PR48) in the SPRINT-2 study

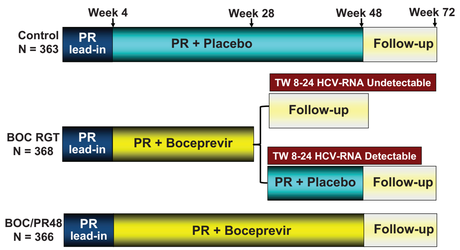
Methods

Study Design

- SPRINT-2 was a phase 3, double-blind, randomized, controlled trial conducted at 149 centers worldwide **(Figure 1)**
- Two cohorts were enrolled and analyzed separately
  - Cohort 1: 938 (86%) non-Black patients
  - Cohort 2: 159 (14%) Black patients
- Patients were randomized 1:1:1 to the 3 treatment arms and treated for up to 48 weeks
  - Patients were stratified based on screening HCV RNA level (≤400,000 vs >400,000 IU/mL) and genotype 1 subtype (1a vs 1b)
  - Patients with detectable HCV-RNA at week 24 were discontinued from treatment

Methods

Figure 1. SPRINT-2 Study Design



BOC RGT = response-guided therapy, BOC/PR48 = fixed-duration therapy of 4 weeks PR and 44 weeks boceprevir/PR.

HCV-RNA measured by the Cobas TaqMan assay (Roche).
Patients with detectable HCV-RNA (LLD=9.3 IU/mL) at week 24 were considered treatment failures.

Peginterferon alfa-2b (P) administered subcutaneously at 1.5 µg/kg once weekly; ribavirin (R) using weight-based dosing of 600-1400 mg/day in a divided twice daily dose; boceprevir (BOC) dose of 800 mg thrice daily.

N represents non-Black and Black patients combined.

Patient Population

- Treatment-naive with CHC, genotype 1 infection
- Age 18 to 70 years old
- Weight 40 to 125 kg
- Pretreatment HCV-RNA ≥10,000 IU/mL
- Compensated liver disease

Assessments

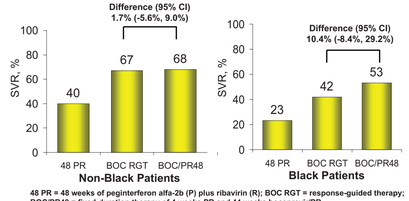
- Primary endpoint
  - SVR in all randomized patients with ≥1 dose of any study medication
- HCV RNA levels assessed at screening, treatment weeks 2, 4, 6, 8, 10, 12, 16, 20, 24, 28, 34, 40, 48 and follow-up weeks 4, 12, and 24

Results

Efficacy Results in SPRINT-2

- SVR rates in non-Black patients who received BOC RGT and BOC/PR48 were similar **(Figure 2)**
- 10% difference in the SVR rates in Black patients between the BOC RGT and BOC/PR48 groups was seen

Figure 2. SVR Rates in SPRINT-2



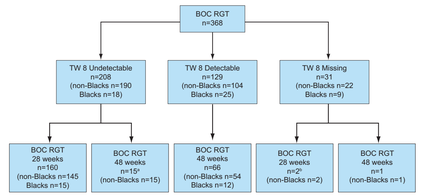
48 PR = 48 weeks of peginterferon alfa-2b (P) plus ribavirin (R); BOC RGT = response-guided therapy; BOC/PR48 = fixed-duration therapy of 4 weeks PR and 44 weeks boceprevir/PR.

Response-guided Therapy Duration Assignment

- 44% (162/368) of patients had persistently undetectable HCV-RNA levels during weeks 8 through 24 and were assigned the shorter duration of 28 weeks of BOC RGT **(Figure 3)**
- 22% (82/368) of patients had detectable HCV-RNA levels from week 8 up to 24, and were assigned the longer duration of 48 weeks of BOC RGT (4 week lead-in with PR, 24 weeks of boceprevir/PR and 20 weeks of PR)

Results

Figure 3. Response-guided Therapy Duration Assignment by week 8 HCV-RNA level



BOC RGT = response-guided therapy.
[a]14 of the 15 patients were originally reported to have low detectable HCV-RNA level(s) between weeks 8-24 and assigned 48-week treatment duration, although two repeat tests on the detectable sample confirmed undetectable HCV-RNA.
[b]Undetectable week 8 HCV-RNA 1 day outside week 8 visit window.

Baseline Characteristics

- Baseline demographics and disease characteristics between those who received BOC RGT and BOC/PR48 were similar in non-Black and Black patients
- Among patients who received the 28-week vs 48-week BOC RGT, there were the following differences:
  - Among non-Black patients, more males, younger patients, more patients with genotype 1b received the shorter duration (28 weeks) of BOC RGT compared with those who received 48 weeks of BOC RGT **(Table 1)**
  - Given the small sample size in each group, differences in the Black patients who received a shorter duration of BOC RGT compared to those who received 48 weeks were small **(Table 2)**

Table 1. Baseline Characteristics – Non-Black Patients

	BOC Response-Guided Therapy			BOC/PR48
	28 weeks n=147	48 weeks n=70	Other[a] n=99	48 weeks n=311
Males	67%	59%	62%	60%
Race				
Caucasian	97%	93%	97%	95%
Asian	1%	1%	1%	3%
Hispanic/Latino ethnicity	10%	9%	8%	13%
Age, years, mean (SD)	47.9 (9.5)	51.4 (8.6)	50.2 (9.6)	48.5 (9.0)
Weight, kg, mean (SD)	82 (16)	82 (19)	80 (18)	80 (17)
BMI, kg/m^2, mean (SD)	28 (4)	29 (6)	27 (5)	27 (5)
Baseline HCV RNA >400,000 IU/mL	90%	96%	89%	93%
Genotype 1 subtype[b]				
1a	58%	64%	66%	63%
1b	39%	34%	30%	33%
METAVIR fibrosis score				
F0/1/2	92%	86%	85%	85%
F3/4	7%	9%	9%	12%

BOC = boceprevir, P=peginterferon alfa-2b, R=ribavirin.
[a]Discontinued prior to BOC RGT 28- or 48-week assignment.
[b]Subtyping performed by NS5B sequencing (Virco, Mechelen, Belgium).

Table 2. Baseline Characteristics – Black Patients

	BOC Response-Guided Therapy			BOC/PR48
	28 weeks n=15	48 weeks n=12	Other[a] n=25	48 weeks n=55
Males	53%	75%	48%	60%
Race				
Black or African American	100%	100%	100%	100%
Age, years, mean (SD)	51.9 (6.0)	50.7 (5.8)	53.4 (9.7)	50.9 (7.0)
Weight, kg, mean (SD)	87 (16)	88 (10)	85 (17)	91 (18)
BMI, kg/m^2, mean (SD)	29 (5)	29 (3)	30 (6)	31 (6)
Baseline HCV RNA >400,000 IU/mL	87%	100%	96%	96%
Genotype 1 subtype[b]				
1a	73%	75%	76%	73%
1b	27%	25%	24%	24%
METAVIR fibrosis score				
F0/1/2	80%	83%	72%	87%
F3/4	7%	17%	20%	11%

BOC = boceprevir, P=peginterferon alfa-2b, R=ribavirin.
[a]Discontinued prior to BOC RGT 28- or 48-week assignment.
[b]Subtyping performed by NS5B sequencing (Virco, Mechelen, Belgium).

Virologic Response Rates in the BOC RGT and BOC/PR48 Groups

- SVR rates in non-Black patients with undetectable HCV-RNA levels from week 8 through week 24 were >95% in both the BOC RGT and BOC/PR48 groups **(Figures 4 and 5)**
  - Although the SVR rate in patients with detectable HCV-RNA at any visit from week 8 to 24 were lower, the BOC RGT and BOC/PR48 groups had similar SVR rates
- Relapse rates were low among the groups
  - Relapse rates were slightly higher among Black patients with undetectable week 8 HCV-RNA levels with the shorter duration of therapy, although the sample size was small
  - Non-Black patients with detectable HCV-RNA at any visit from week 8 up to 24 had higher relapse rates

Figure 4. Virologic Response Rates for Patients with Undetectable HCV-RNA Levels Weeks 8-24

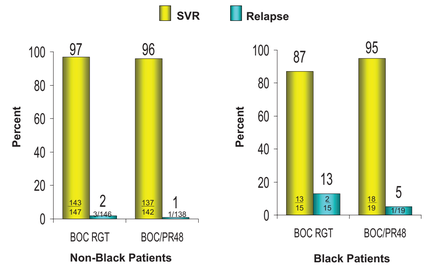
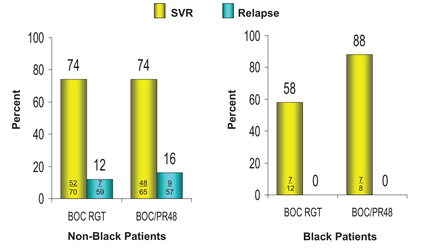


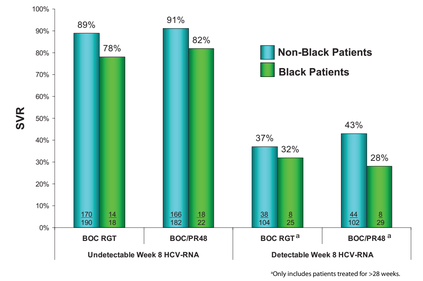
Figure 5. Virologic Response Rates for Patients with Detectable HCV-RNA Level(s) at Any Visit from Week 8 up to 24



SVR Rates Based on Week 8 HCV-RNA

- 57% (208/368) of patients in the BOC RGT arm had undetectable week 8 HCV-RNA
  - 60% (190/316) non-Black patients
  - 35% (18/52) Black patients
- SVR rates based on week 8 HCV-RNA level alone were similar between those treated with BOC RGT and those treated with BOC/PR48 in both non-Black and Black patients **(Figure 6)**

Figure 6. SVR Rates Based on Week 8 HCV-RNA



[a]Only includes patients treated for >28 weeks.

Summary

- In treatment-naive patients with CHC genotype 1 infection, addition of boceprevir to PR improved SVR rates over the current standard of care
  - Both boceprevir regimens were significantly more efficacious than PR alone in non-Black and Black patients
- Using BOC RGT, undetectable HCV RNA from weeks 8-24 identified patients who could be successfully treated with shorter courses of therapy
  - Boceprevir for 24 wks in BOC RGT was equivalent to boceprevir for 44 wks in BOC/PR48 in non-Black patients
  - Numbers were too small to draw firm conclusion in Black patients regarding BOC RGT vs. BOC/PR48

Conclusions

- RGT paradigm yielded high responses equal to those with the BOC/PR48 regimen
  - BOC RGT minimizes boceprevir exposure for all patients
    - Week 8 is a good timepoint to assess whether a patient should receive 28-week or 48-week BOC RGT since it is a good predictor of SVR
    - Approximately 60% of patients would be eligible for the shortened treatment duration of 28 weeks of boceprevir + PR

Disclosure

Dr. Bronowicki reports receiving consulting and lecture fees from Roche, Merck, Tibotec Pharmaceuticals, Vertex Pharmaceuticals, Gilead, BMS, Novartis, Boehringer Ingelheim, and Bayer.

Acknowledgements

The authors would like to thank the patients, study nurses and investigators: **Argentina:** L. Colombato, J. Curciarello, M. Silva, H. Tanno, R. Terg; **Belgium:** M. Adler, P. Langlet, L. Lasser, F. Nevens; **Canada:** F. Anderson, R. Bailey, M. Bilodeau, C. Cooper, S.V. Feinman, J. Heathcote, M. Levstik, A. Ramji, M. Sherman, S. Shafran, E. Yoshida; **France:** A. Achim, S. Ben Ali, M-A. Bigard, C. Bonny, M. Bourliere, N. Boyer-Darrigrand, J-P. Bronowicki, V. Canva, P. Couzigou, V. De Ledinghen, D. Guyader, C. Hezode, D. Larrey, M. Latournerie, P. Marcellin, P. Mathurin, M. Maynard–Muet, J. Moussalli, R. Poupon, T. Poynard, L. Serfaty, A. Tran, C. Trepo, R. Truchi, J-P. Zarski; **Germany:** T. Berg , N. Dikopoulos, C. Eisenbach, P. R. Galle, G. Gerken, T. Goeser, M. Gregor, D. Klass, M. R. Kraus, C. Niederau, J. F. Schlaak, R. Schmid, P. Thies, K. Schmidt, R. Thimme, H. Weidenbach, S. Zeuzem; **Italy:** M. Angelico, S. Bruno, G. Carosi, A. Craxi, A. Mangia, M. Pirisi, M. Rizzetto, G. Taliani, A.L. Zignego; **Netherlands:** H.W. Reesink; **Portugal:** F. Serejo; **Puerto Rico:** A. Reymunde, B. Rosado, E. Torres; **Spain:** R. Barcena Marugan, M. De La Mata, J.L. Calleja, G. Castellano, M. Diago, R. Esteban, C. Fernandez, J. Sanchez Tapias, M.A. Serra Desfilis; **United States:** N. Afdhal, A. Al-Osaimi, B. Bacon, L. Balart, M. Bennett, D. Bernstein, M. Black, C. Bowlus, T. Boyer, D. Dalke, C. Davis, G. Davis, M. Davis, G. Everson, F. Felizarta, S. Flamm, B. Freilich, J. Galati, G. Galler, R. Ghalib, A. Gibas, E. Godofsky, F. Gordon, S. Gordon, J. Gross, S. Harrison, J. Herrera, S. Herrine, K-Q. Hu, J. Imperial, I. Jacobson, D. Jones, A. Kilby, J. King, A. Koch, K. Kowdley, E. Krawitt, P. Kwo, L. Lambiase, E. Lawitz, W. Lee, J. Levin, R. Levine, X. Li, A. Lok, V. Luketic, M. Malliard, J. McCone, J. McHutchison, D. Mikolich, T. Morgan, A. Muir, Don. Nelson, F. Nunes, A. Nyberg, L. Nyberg, P. Pandya, M.P. Pauly, C. Peine, G. Poleynard, F. Poordad, D. Pound, J. Poulos, M. Rabinovitz, N. Ravendhran, J. Ready, K. Reddy, R. Reindollar, A. Reuben, T. Riley, L. Rossaro, R. Rubin, M. Ryan, J. Santoro, E. Schiff, T. Sepe, K. Sherman, M. Shiffman, M. Sjogren, R. Sjogren, C. Smith, L. Stein, R. Strauss, M. Sulkowski, R. Szyjkowski, H. Vargas, J. Vierling, D. Witt, R. Yapp, Z. Younes.