HEPATITIS WEB STUDY HEPATITIS C ONLINE

Boceprevir (*Victrelis*)

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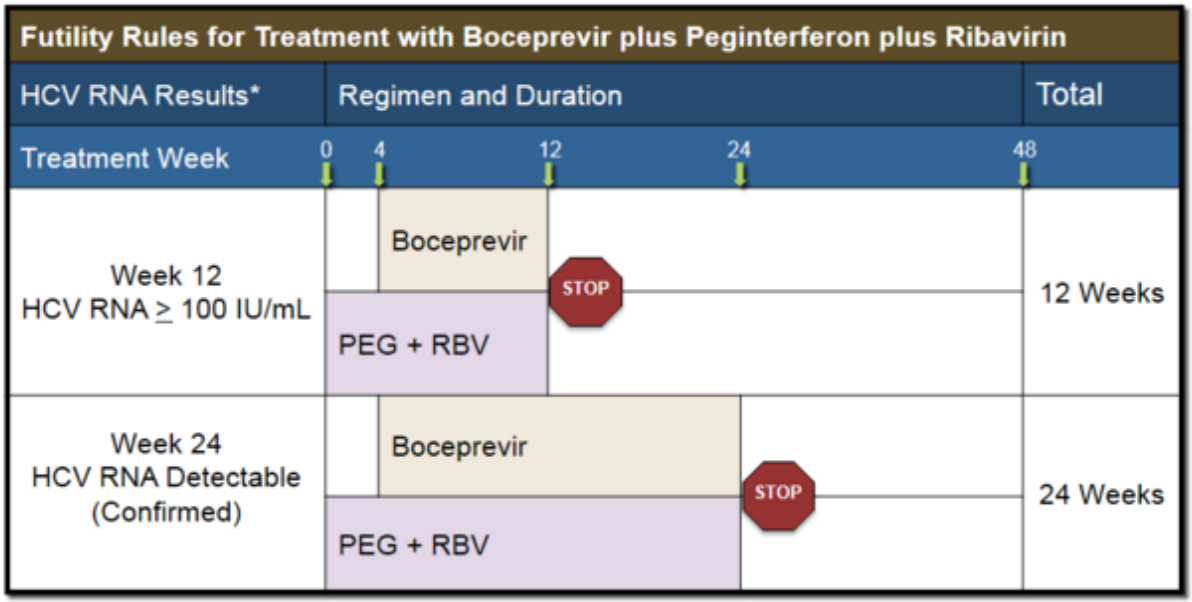
Last Updated: March 6, 2014

Hepatitis web study

Boceprevir (*Victrelis*)
Treatment Futility Rules for All Patients



*In clinical trials, HCV-RNA in plasma was measured using a Roche COBAS® TaqMan® assay with a lower limit of quantification of 25 IU/mL and a limit of detection of 9.3 IU/mL.

Source: Boceprevir (*Victrelis*) Prescribing Information. Merck & Co.

Hepatitis web study

BOCEPREVIR (*VICTRELIS*)

Adverse Effects

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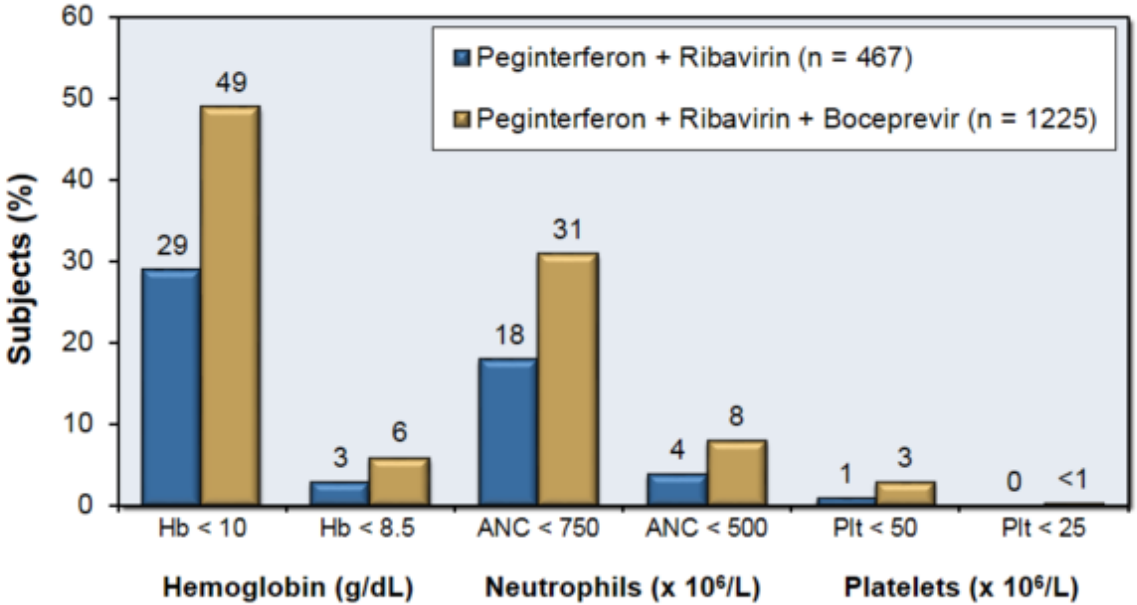
Boceprevir-Related Hematologic Adverse Effects
Previously Untreated (SPRINT-1 & SPRINT-2)



ANC = absolute neutrophil count

Source: Boceprevir (*Victrelis*) Prescribing Information. Merck & Co.

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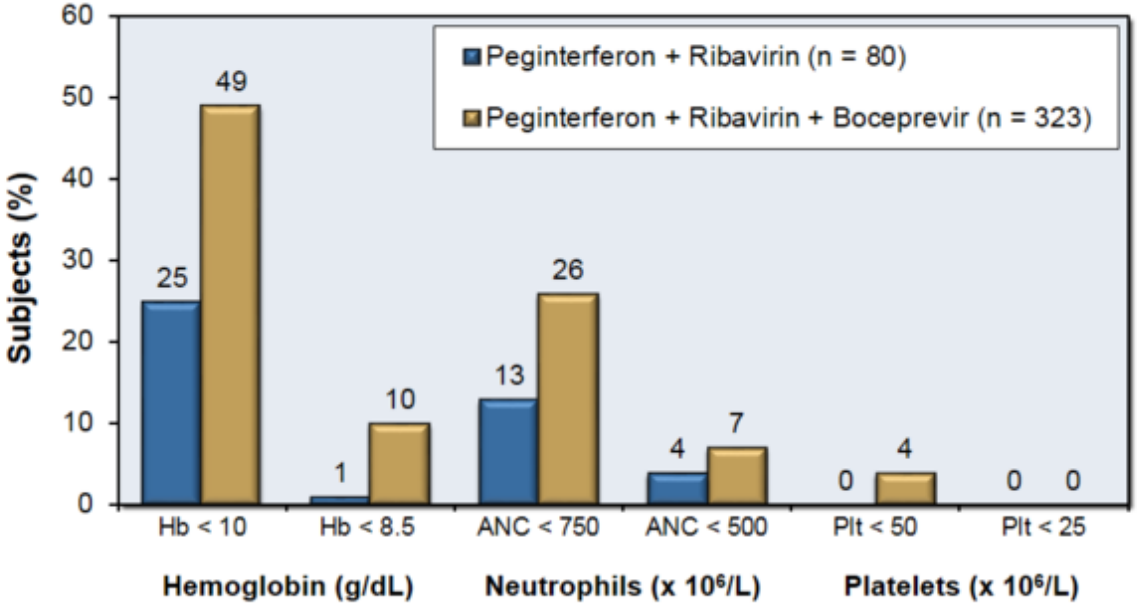
Boceprevir-Related Hematologic Adverse Effects Previously Treatment Failures (RESPOND-2)



ANC = absolute neutrophil count

Source: Boceprevir (*Victrelis*) Prescribing Information. Merck & Co.

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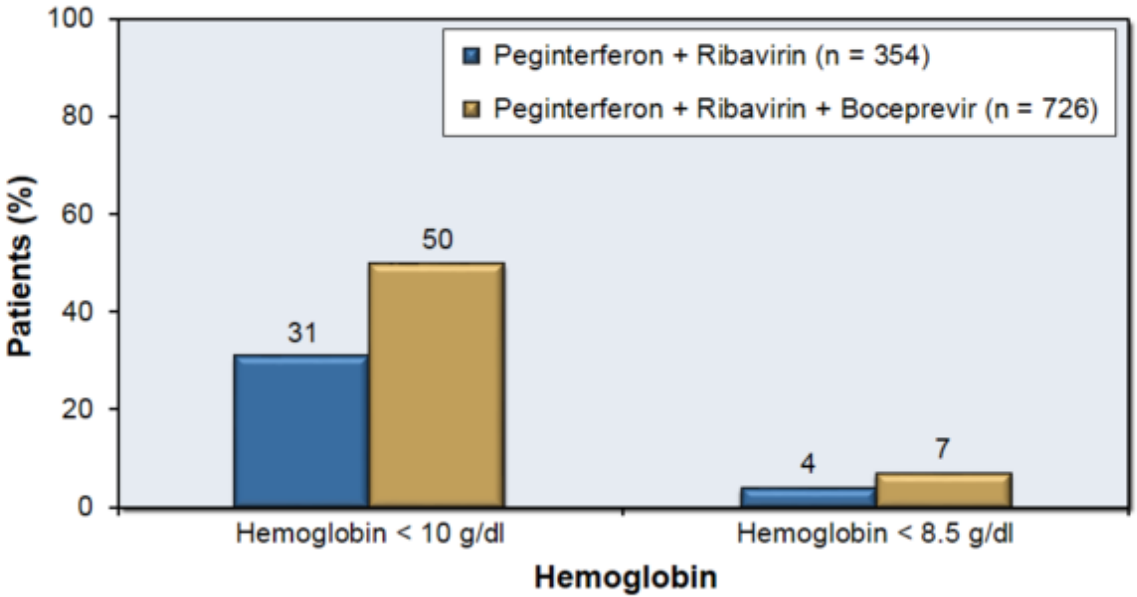
Boceprevir-Related Hematologic Adverse Effects
Previously Untreated (SPRINT-2)



ANC = absolute neutrophil count

Source: Sulkowski MS, et al. Hepatology. 2012:Oct 18 [Epub ahead of print].

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Boceprevir
Adverse Effects in SPRINT Trial

- **Anemia**
  - Nadir Hgb 8.5-10 g/dL
  - 52-63% in Boceprevir arms
  - 34% in Peginterferon/Ribavirin Control
  - 40% of patients used Epoetin alfa
  - Use of erythropoietin associated with treatment completion
  - Average attributable decrease in Hgb of 1 g/dL

- **Dysgeusia**
  - 21-44% in all Boceprevir arms
  - 9% in Peginterferon/Ribavirin control arm

Source: Kwo PY, et al. Lancet. 2010;376:705-16.

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BOCEPREVIR (*VICTRELIS*)

Drug Interactions

Boceprevir
Drug Interactions

- **Potential for Boceprevir to Affect Other Medications**
  - Boceprevir is strong inhibitor of CYP3A4/5 enzyme
  - Boceprevir is potential inhibitor of p-glycoprotein (P-gp)

- **Potential for Other Medications to Affect Boceprevir**
  - Boceprevir primarily metabolized by aldo-ketoreductase (AKR)
  - Boceprevir may be co-administered with aldo-ketoreductase inhibitors
  - Partially metabolized by CYP3A4/5
  - Potential for interactions with drugs that inhibit or reduce CYP3A4/5

Source: Boceprevir (*Victrelis*) Prescribing Information. Merck & Co.

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Boceprevir
Dosage Adjustment in Special Populations

- **Hepatic Impairment**
  - No dosage adjustment of Boceprevir with hepatic impairment
- **Renal Impairment/Dialysis**
  - No dose adjustment of Boceprevir with any degree of renal impairment
- **Gender**
  - No dosage adjustment of Boceprevir based on gender
- **Race**
  - No dose adjustment of Boceprevir based on race
- **Age**
  - No dosage adjustments of Boceprevir in subjects aged 19-65

Source: Boceprevir (*Victrelis*) Prescribing Information. Merck & Co.

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Boceprevir
Drug-Drug Interactions: Contraindicated Medications

Medications Contraindicated for use with Boceprevir	Last Revised 1/20/2014
Drug Class	**Medication and Interaction**
Alpha-1 Adrenoreceptor Antagonist	Alfuzosin, doxazosin, silodosin, tamsulosin
Anticonvulsants	Carbamazepine, phenobarbital, phenytoin
Antimycobacterials	Rifampin
Ergot Derivatives	Dihydroergotamine, ergonovine, ergotamine, methylergonovine
Gastrointestinal Motility Agent	Cisapride
Herbal Products	St John's wort (*Hypericum perforatum*)
HMG CoA-Reductase Inhibitors	Lovastatin, simvastatin
Neuroleptic	Pimozide
Oral Contraceptives	Drospirenone
PDE5 Inhibitor	Sildenafil or Tadalafil (dose levels for treatment of pulmonary hypertension)
Sedatives/hypnotics	Triazolam; orally administered midazolam

Source: Boceprevir (*Victrelis*) Prescribing Information. Merck & Co.

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BOCEPREVIR (*VICTRELIS*)

Background and Dosing

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Boceprevir (*Victrelis*)
Interactions with Antiretroviral Medications

Boceprevir and Interactions with HIV Antiretroviral Medications		
Medication	**Effect**	**Recommendation**
NNRTIs		
Efavirenz	↓ Boceprevir	Avoid combination
Etravirine	↓ Etravirine	The clinical significance of the reductions in etravirine pharmacokinetic parameters has not been directly assessed
Rilpivirine	↑ Rilpivirine	No dose adjustment of boceprevir or rilpivirine is recommended.
Integrase Inhibitors		
Raltegravir	↔ Raltegravir	No dose adjustment required for boceprevir or raltegravir.
Protease Inhibitors		
Atazanavir + Ritonavir	↓ Atazanavir ↓ Ritonavir	Coadministration of atazanavir/ritonavir and boceprevir is not recommended
Darunavir + Ritonavir	↓ Darunavir ↓ Ritonavir ↓ Boceprevir	Coadministration of darunavir/ritonavir and boceprevir is not recommended.
Lopinavir + Ritonavir	↓ Lopinavir ↓ Ritonavir ↓ Boceprevir	Coadministration of lopinavir/ritonavir and boceprevir is not recommended.

Source: Modified from Boceprevir (*Victrelis*) Prescribing Information. Merck & Co.

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Boceprevir (*Victrelis*)

Resistance

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Treatment Emergent NS3 Protease Domain Mutations in Boceprevir-Treated Patients who Did Not Achieve SVR

Frequency of Resistance-Associated Variants (RAVs) Detected Based on HCV Genotype		
	Subjects with HCV Genotype 1a	**Subjects with HCV Genotype 1b**
>10% of Boceprevir-Treated Subjects who did not Achieve SVR[a]	V36M, T54S, R155K	T54A, T54S, V55A, A156S, I/V170A
< 1-10% of Boceprevir-Treated Subjects who did not Achieve SVR[a]	V36A, T54A, V55A, V55I, V107I, R155T, A156S, A156T, V158I, D168N, I/V170T, I/V170F	V36A, V36M, T54C, T54G, V107I, R155K, A156T, A156V, V158I, I/V170T, M175L
[a]Data taken from SPRINT-2 and RESPOND-2 Trials		

Source: Boceprevir (*Victrelis*) Prescribing Information. Merck & Co.

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Boceprevir for Chronic HCV Infection
Resistance Among those who did not achieve SVR

- Treatment-emergent resistance-associated variants (RAVs) occurred in 53% (295) of 343 evaluable subjects from SPRINT-2 and RESPOND-2 trials who did not achieve SVR, occurring more often among black patients and poor interferon responders.

Frequency of Resistance-Associated Variants (RAVs) Detected Based on Interferon Response or Race Categories

	Subjects with samples sequenced, n	Subjects with detectable RAVs, n/N (%)
Poor Interferon Responders[a]	169	115/169 (68%)
Interferon Responders[b]	128	40/128 (31%)
Black Patients	47	30/47 (64%)
Non-Black Patients	154	81/154 (53%)

[a]Subjects with < 1-$\log_{10}$ decrease in HCV-RNA at treatment week 4 from baseline
[b]Subjects with ≥ 1-$\log_{10}$ decrease in HCV-RNA at treatment week 4 from baseline

Source: Boceprevir (*Victrelis*) Prescribing Information. Merck & Co.

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Boceprevir and Telaprevir Genotypic Resistance

Mutation	Telaprevir	Boceprevir
V36A/M	+	+
T54S/A	+	+
V55A	In vitro	+
Q80R/K	-	-
R155K/T/Q	+	+
A156S	+	+
A156T/V	+	In vitro
D168A/V/T/H	-	-
V170A/T	In vitro	+

Source: Sarrazin C, Zeuzem S. Gastroenterology. 2010;138:447-62.

Hepatitis web study

BOCEPREVIR (*VICTRELIS*)

Treatment Data

Boceprevir: Summary of Key Studies

- Treatment-Naïve Genotype-1
  - SPRINT-1: Phase 2
  - SPRINT-2: Phase 3
- Previously Treated Genotype-1
  - RESPOND-2: Phase 3
  - PROVIDE: Phase 3

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Treatment Naïve

Boceprevir with PEG + RBV in Genotype 1
SPRINT-1

Kwo PY, et al. Lancet. 2010;376:705-16.

Hepatitis web study

Boceprevir for Treatment-Naïve HCV Genotype 1
SPRINT-1 Trial: Part 1

SPRINT-1: Features

- N = 520 HCV-monoinfected patients
- Randomized, open label, phase 2 trial, with Part 1 and Part 2
- All with chronic HCV genotype 1and treatment naïve
- Eligible if 18 to 60 years of age
- Setting: 67 sites (US, Canada, and Europe)
- 90% with HCV RNA $\geq$ 600,000 IU/ml
- Part 1 (n = 520): Randomized to one of five arms
- Part 2 (n = 75): Randomized to one of two arms based on ribavirin dose

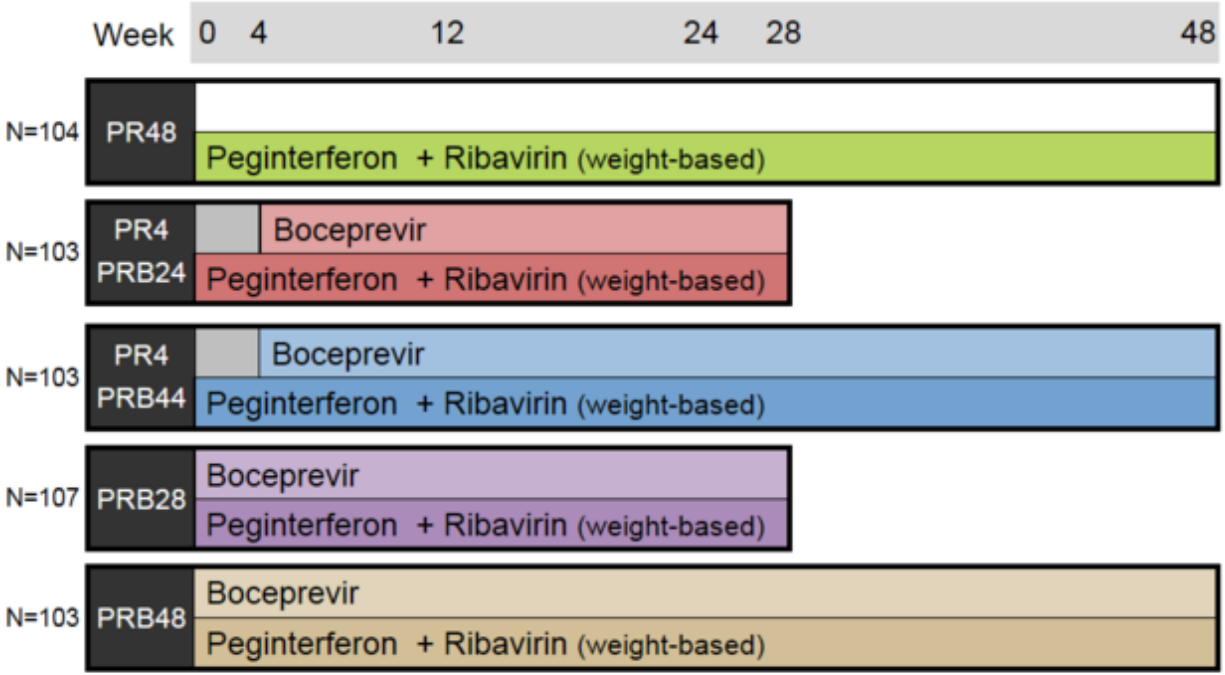
Drug Dosing

Boceprevir = 800 mg three times daily
Peginterferon alfa-2b = 1.5 µg/kg once weekly
Ribavirin = 800-1400 mg/day (based on weight)
Ribavirin = 400-1000 mg/day (low dose)

Source: Kwo PY, et al. Lancet. 2010;376:705-16.

Hepatitis web study

Boceprevir for Treatment-Naïve HCV Genotype 1
SPRINT-1 Trial, Part 1: Design



Source: Kwo PY, et al. Lancet. 2010;376:705-16.

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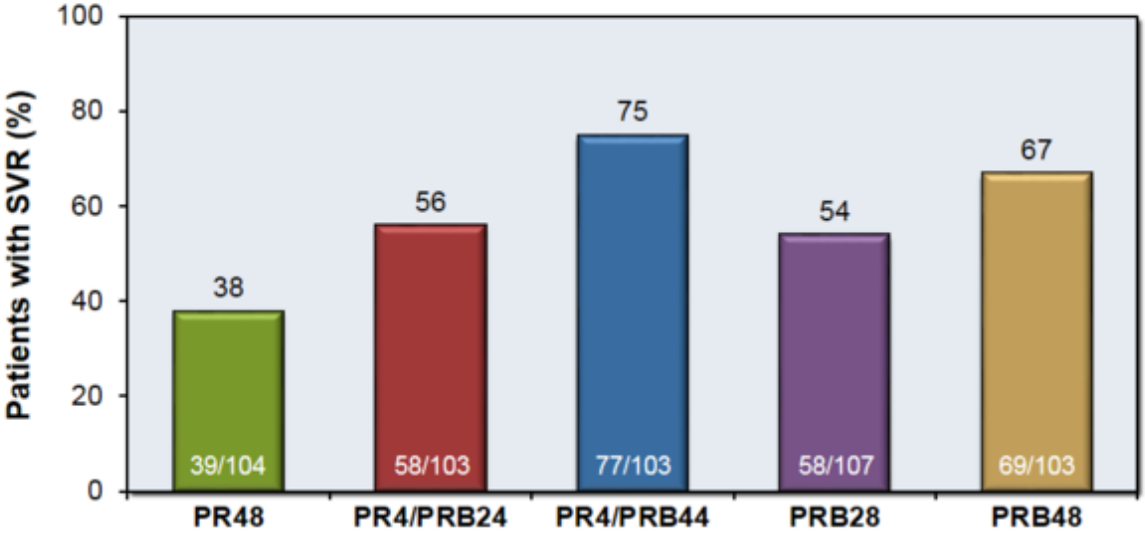
Boceprevir (*Victrelis*) Summary

- **Approval**: FDA Approved May 13, 2011
- **Indications**
  - Genotype 1 chronic HCV in combination with peginterferon-alfa and ribavirin
  - Adults (≥ 18 years of age) with compensated liver disease, including cirrhosis
  - Treatment-naïve or failed prior interferon and ribavirin therapy
- **Dosing**
  - Available in 200 mg capsules
  - 800 mg three times daily (every 7 to 9 hours) with food (meal or light snack)
  - Boceprevir given for 24-44 weeks
  - Treat with PR for 28-48 weeks based on HCV RNA results (week 8 & 24)
- **Adverse Effects**
  - Anemia, nausea, and dysgeusia

Source: Boceprevir (*Victrelis*) Prescribing Information. Merck & Co.

Boceprevir for Treatment-Naïve HCV Genotype 1
SPRINT-1 Trial, Part 1: Results

SPRINT-1, Part 1: SVR 24 by Regimen



B = Boceprevir; PR = Peginterferon + Ribavirin

Source: Kwo PY, et al. Lancet. 2010;376:705-16.

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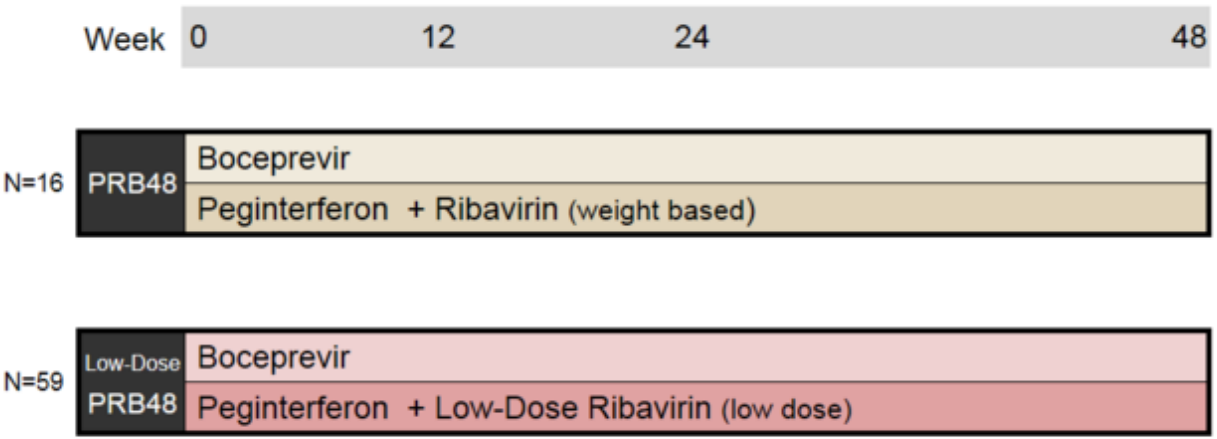
Boceprevir and Peginterferon plus Ribavirin for Chronic HCV
SPRINT-1 Trial, Part 2: Design



Source: Kwo PY, et al. Lancet. 2010;376:705-16.

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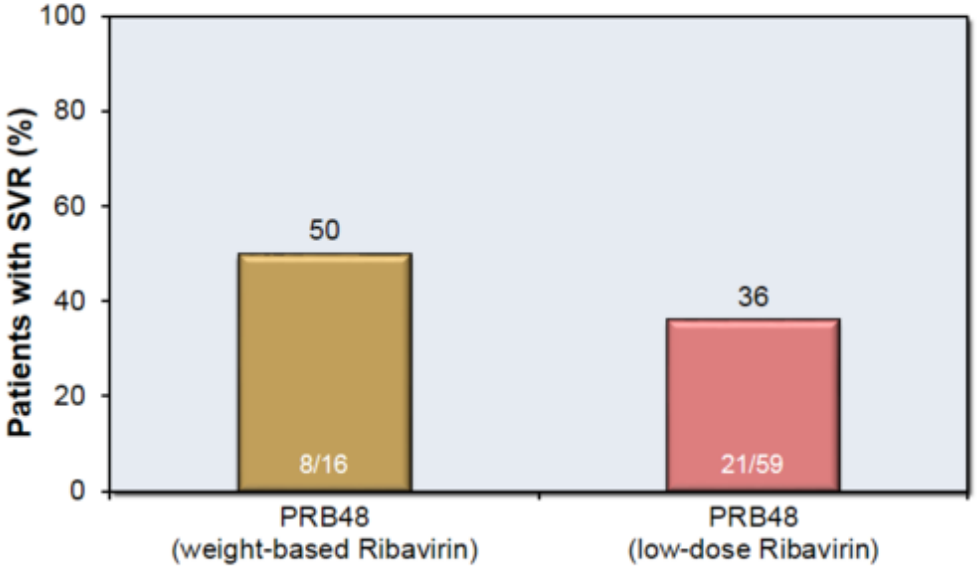
Boceprevir and Peginterferon plus Ribavirin for Chronic HCV
SPRINT-1 Trial, Part 2,: Results

SPRINT-1: SVR 24 by Ribavirin Dosing



P = Peginterferon; R = Ribavirin; B = Boceprevir

Source: Kwo PY, et al. Lancet. 2010;376:705-16.

Hepatitis web study

Boceprevir and Peginterferon plus Ribavirin for Chronic HCV
SPRINT-1 Trial: Conclusions

Interpretation: "In patients with untreated genotype 1 chronic hepatitis C infection, the addition of the direct-acting antiviral agent boceprevir to standard treatment with peginterferon and ribavirin after a 4-week lead-in seems to have the potential to double the sustained response rate compared with that recorded with standard treatment alone."

Source: Kwo PY, et al. Lancet. 2010;376:705-16.

Hepatitis web study

Treatment Naïve

Boceprevir in Treatment Naive
SPRINT-2

Poordad F, et al. N Engl J Med. 2011;364:1195-206.

Hepatitis web study

Boceprevir for Treatment-Naïve HCV Genotype 1
SPRINT-2 Trial: Study Design

SPRINT-2: Study Features

- N = 1097 HCV-monoinfected patients (159 black)
- Randomized, double-blind, placebo-controlled, phase 3 study
- All with chronic HCV and genotype 1 and treatment naïve
- Setting: multiple sites in United States and Europe
- HCV RNA ≥ 10,000 IU/ml
- Mean age 50; 14.5% black
- Randomized to 3 arms (1:1:1)

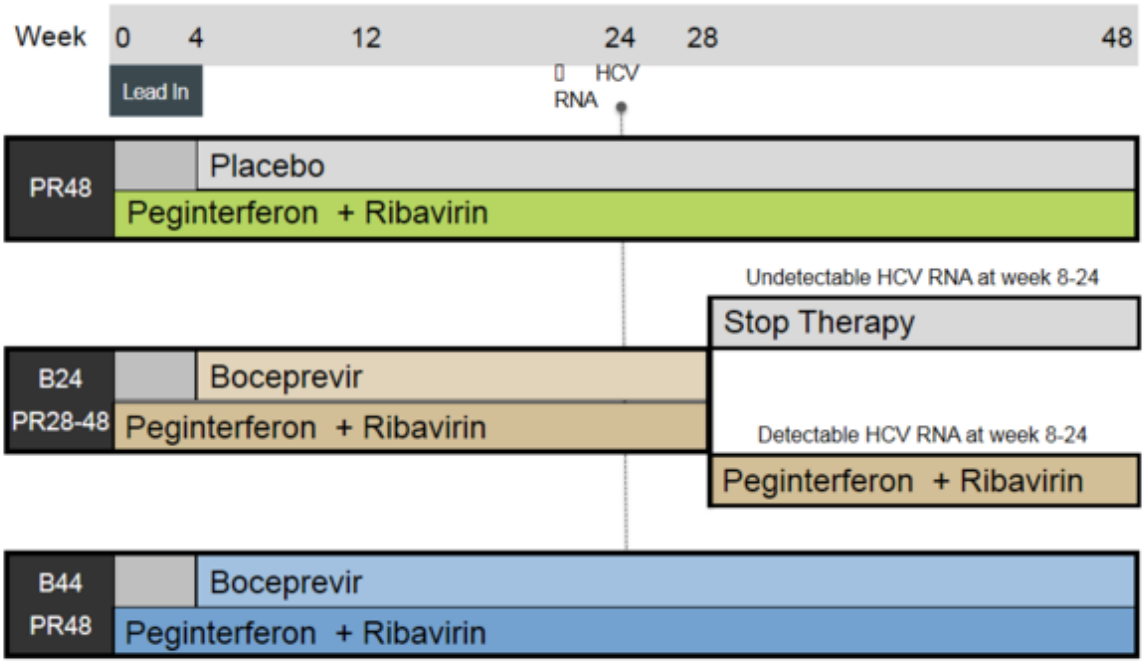
Drug Dosing

Boceprevir = 800 mg three times daily
Peginterferon alfa-2b = 1.5 µg/kg once weekly
Ribavirin = 600-1400 mg/day (based on weight)

Source: Poordad F, et al. N Engl J Med. 2011;364:1195-206.

Hepatitis web study

Boceprevir for Treatment-Naïve HCV Genotype 1 SPRINT-2 Trial: Treatment Regimens

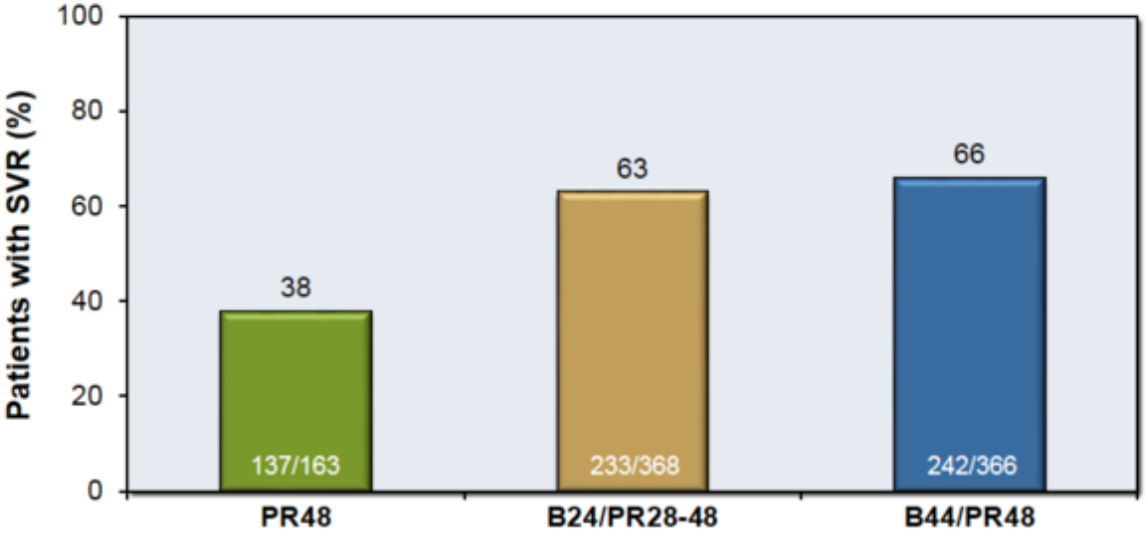


Source: Poordad F, et al. N Engl J Med. 2011;364:1195-206.

Hepatitis web study

Boceprevir for Treatment-Naïve HCV Genotype 1
SPRINT-2 Trial: Treatment Regimens

SPRINT-2: SVR 24 by Regimen



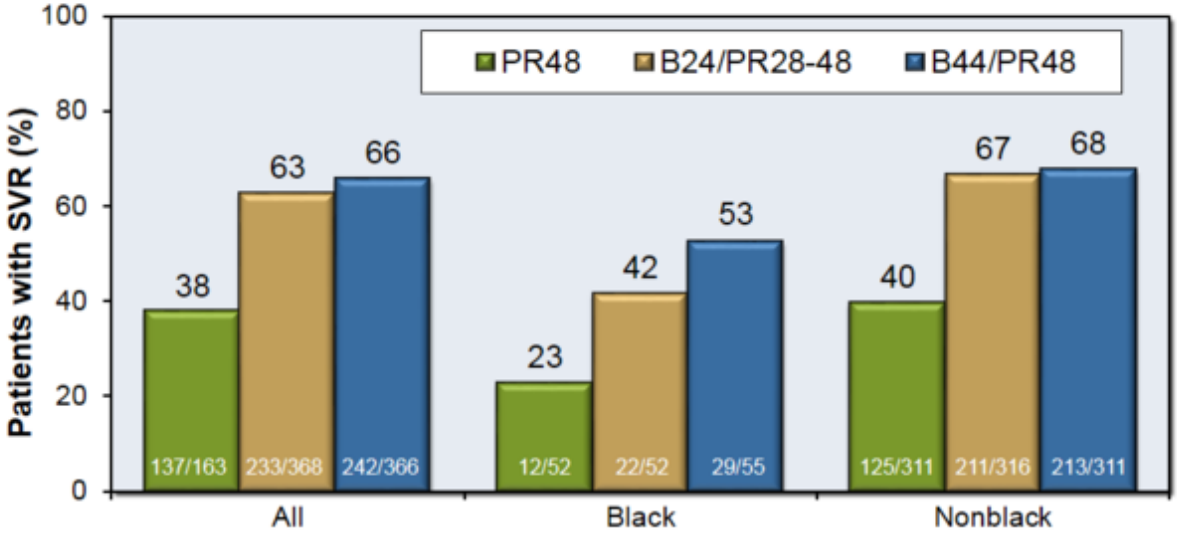
B = Boceprevir; PR = Peginterferon + Ribavirin

Source: Poordad F, et al. N Engl J Med. 2011;364:1195-206.

Hepatitis web study

Boceprevir for Treatment-Naïve HCV Genotype 1
SPRINT-2 Trial: Results

SPRINT-2: SVR 24 by Regimen



SVR = Sustained Virologic Response; B = Boceprevir; PR = Peginterferon + Ribavirin

Source: Poordad F, et al. N Engl J Med. 2011;364:1195-206.

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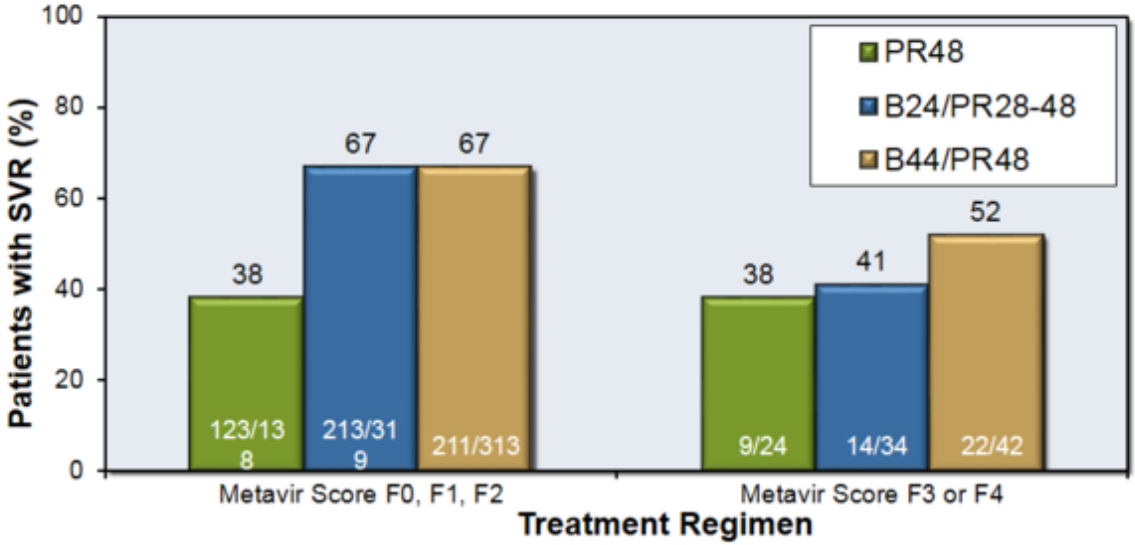
Boceprevir for Treatment-Naïve HCV Genotype 1
SPRINT-2 Trial: SVR by Liver Histology

SPRINT-2: SVR 24 by Degree of Fibrosis



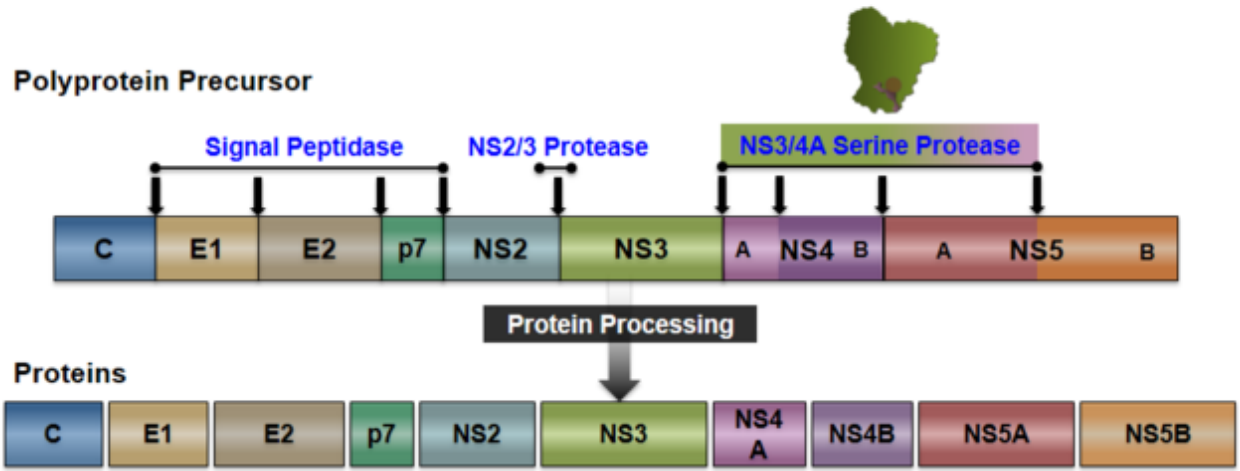
PR48 = Peginteron/Ribavirin x 48 weeks

SVR = Sustained Virologic Response; B = Boceprevir; PR = Peginterferon + Ribavirin

Source: Poordad F, et al. N Engl J Med. 2011;364:1195-206.

Hepatitis web study

HCV Protein Processing
Role of Role of NS3/4A Serine Protease



Hepatitis web study

Boceprevir for Treatment-Naïve HCV Genotype 1
SPRINT-2 Trial: Conclusions

Conclusions: "The addition of boceprevir to standard therapy with peginterferon–ribavirin, as compared with standard therapy alone, significantly increased the rates of sustained virologic response in previously untreated adults with chronic HCV genotype 1 infection. The rates were similar with 24 weeks and 44 weeks of boceprevir."

Source: Poordad F, et al. N Engl J Med. 2011;364:1195-206.

Hepatitis web study

Treatment Experienced

Boceprevir in Treatment Experienced
RESPOND-2

Bacon BR, et al. N Engl J Med. 2011;364:1207-17.

Hepatitis web study

Boceprevir for Retreatment of HCV Genotype 1 Infection
RESPOND-2 Trial: Study Design

RESPOND-2: Study Features

- N = 403 HCV-monoinfected, treatment-experienced patients
- Randomized, double-blind, placebo-controlled, phase 3 study
- All with chronic HCV and genotype 1
- Previously responded to treatment but did not obtain SVR
- Previous null responders excluded
- Mean Age = 53
- 88% with HCV RNA > 800,000 IU/mL
- Randomized to 3 arms (1:2:2)

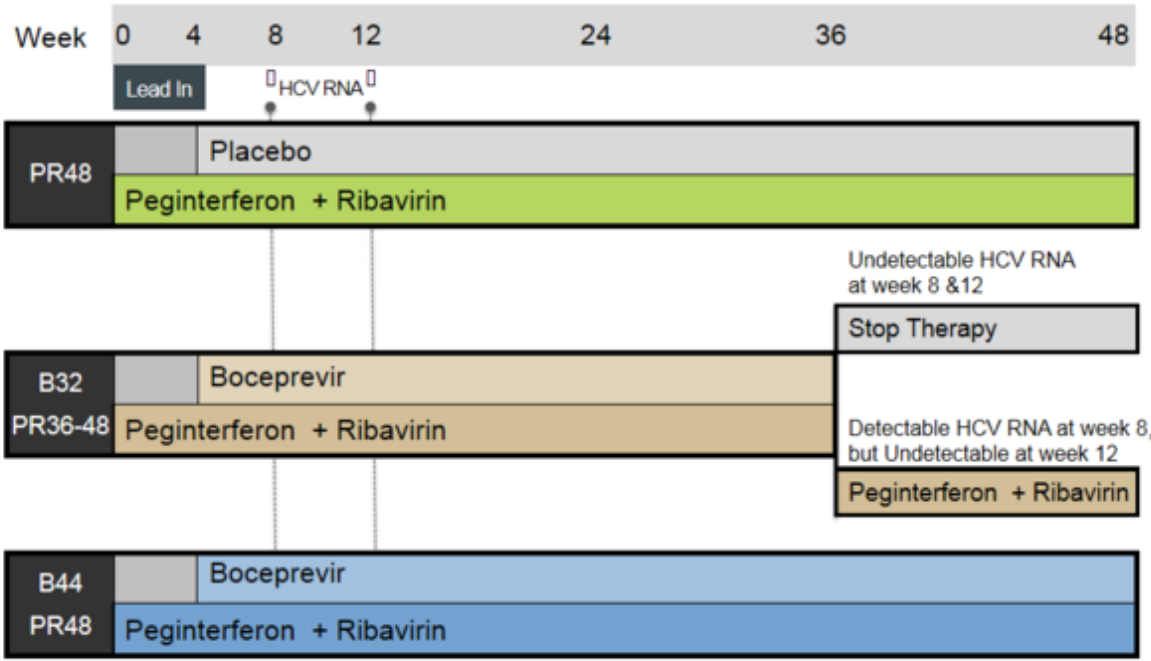
Drug Dosing

Boceprevir = 800 mg three times daily
Peginterferon alfa-2b = 1.5 µg/kg once weekly
Ribavirin = 600-1400 mg/day (based on weight)

Source: Bacon BR, et al. N Engl J Med. 2011;364:1207-17.

Hepatitis web study

Boceprevir for Retreatment of HCV Genotype 1 Infection
RESPOND-2 Trial: Treatment Regimens

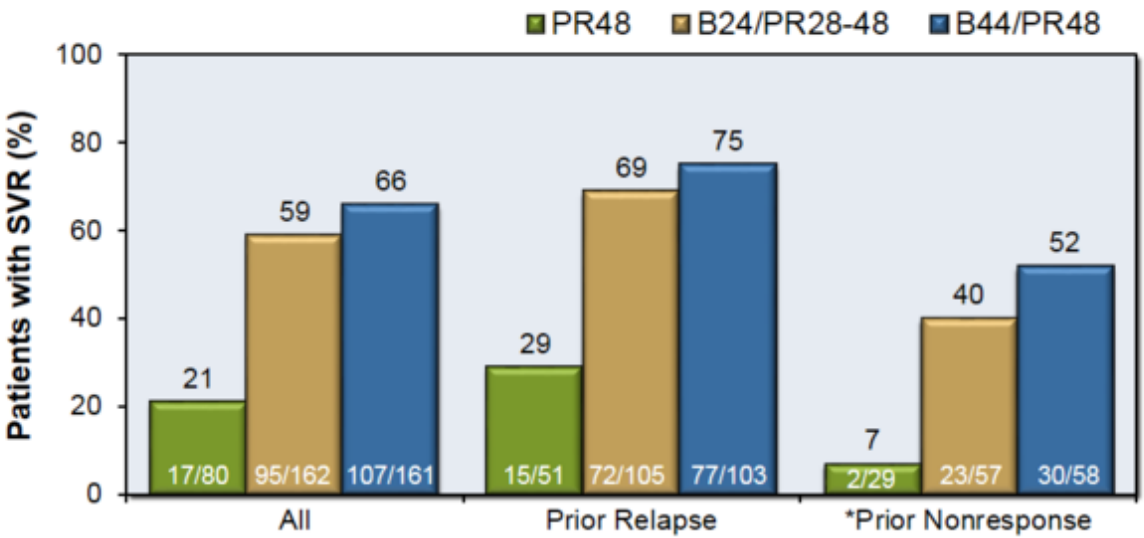


Source: Bacon BR, et al. N Engl J Med. 2011;364:1207-17.

Hepatitis web study

Boceprevir for Retreatment of HCV Genotype 1 Infection
RESPOND-2 Trial: Results

RESPOND-2: SVR 24 by Prior Response and Regimen



*Prior Nonresponse = decrease in HCV RNA of at least 2 logs by week 12, but detectable HCV RNA level during therapy period

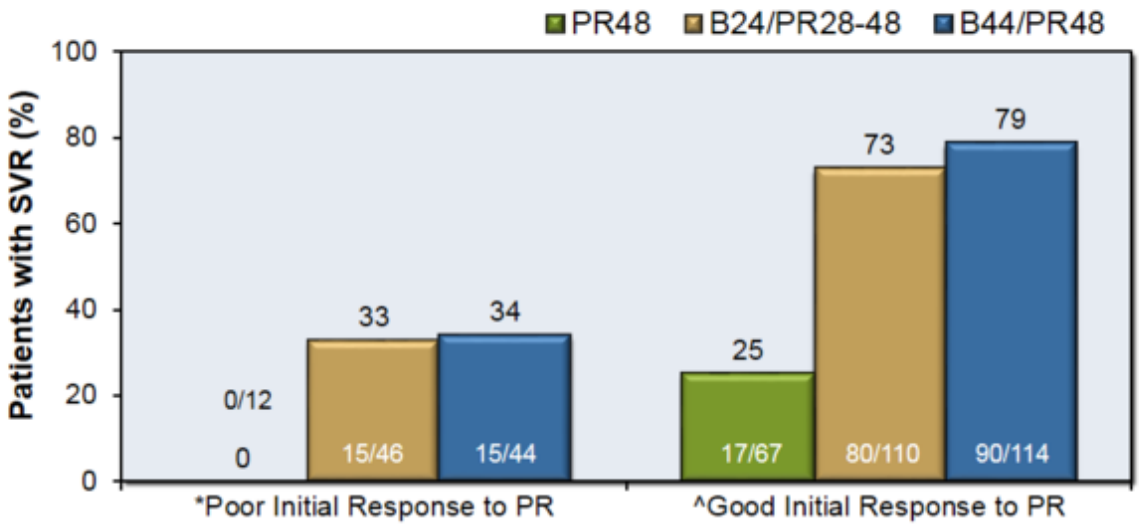
SVR = Sustained Virologic Response; B = Boceprevir; PR = Peginterferon + Ribavirin

Source: Bacon BR, et al. N Engl J Med. 2011;364:1207-17.

Hepatitis web study

Boceprevir for Retreatment of HCV Genotype 1 Infection
RESPOND-2 Trial: Results Based on Initial Week 4 Response

RESPOND-2: SVR 24, by Initial Response and Regimen



*Poor Initial Response to PR = decrease in HCV RNA level < 1 $\log_{10}$ IU/ml after 4 week lead in
^Good Initial Response to PR = decrease in HCV RNA level ≥ 1 $\log_{10}$ IU/ml after 4 week lead in
SVR = Sustained Virologic Response; B = Boceprevir; PR = Peginterferon + Ribavirin

Source: Bacon BR, et al. N Engl J Med. 2011;364:1207-17.

Hepatitis web study

Boceprevir for Retreatment of HCV Genotype 1 Infection
RESPOND-2 Trial: Conclusions

Conclusions: "The addition of boceprevir to peginterferon–ribavirin resulted in significantly higher rates of sustained virologic response in previously treated patients with chronic HCV genotype 1 infection, as compared with peginterferon–ribavirin alone."

Source: Bacon BR, et al. N Engl J Med. 2011;364:1207-17.

Hepatitis web study

Treatment Experienced

Boceprevir for Patients with Prior Failure to PEG + RIB

PROVIDE

Vierling JM, et al. J Hepatol. 2013;Dec 19 [Epub ahead of print].

Hepatitis web study

Boceprevir for Patients with Prior Failure to PEG + RIB
PROVIDE Study: Features

PROVIDE: Study Features

- N = 168 HCV-monoinfected, treatment-experienced patients
- Prior treatment failure to peginterferon + ribavirin
- Single arm, phase 3, multicenter, rollover study at 80 sites
- All with chronic HCV and genotype 1
- Mean Age = 53
- Genotype: GT1a = 68%; GT1b = 38%
- Race: 84% white; 13% black
- Fibrosis: 16% with Metavir F3 or F4
- Prior Response: Null (31%), Partial (51%), Relapse (17%)
- All retreated with Boceprevir + Peginterferon alfa-2b + Ribavirin

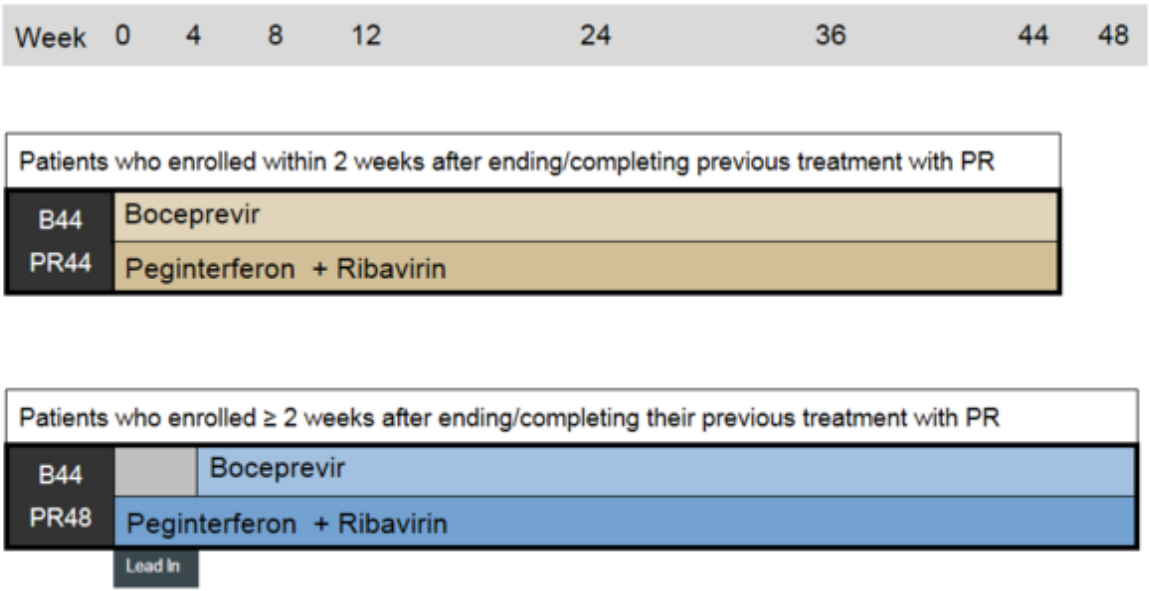
Drug Dosing

Boceprevir = 800 mg three times daily
Peginterferon alfa-2b = 1.5 µg/kg once weekly
Ribavirin = 600-1400 mg/day (based on weight)

Source: Vierling JM, et al. J Hepatol. 2013;Dec 19 [Epub ahead of print].

Hepatitis web study

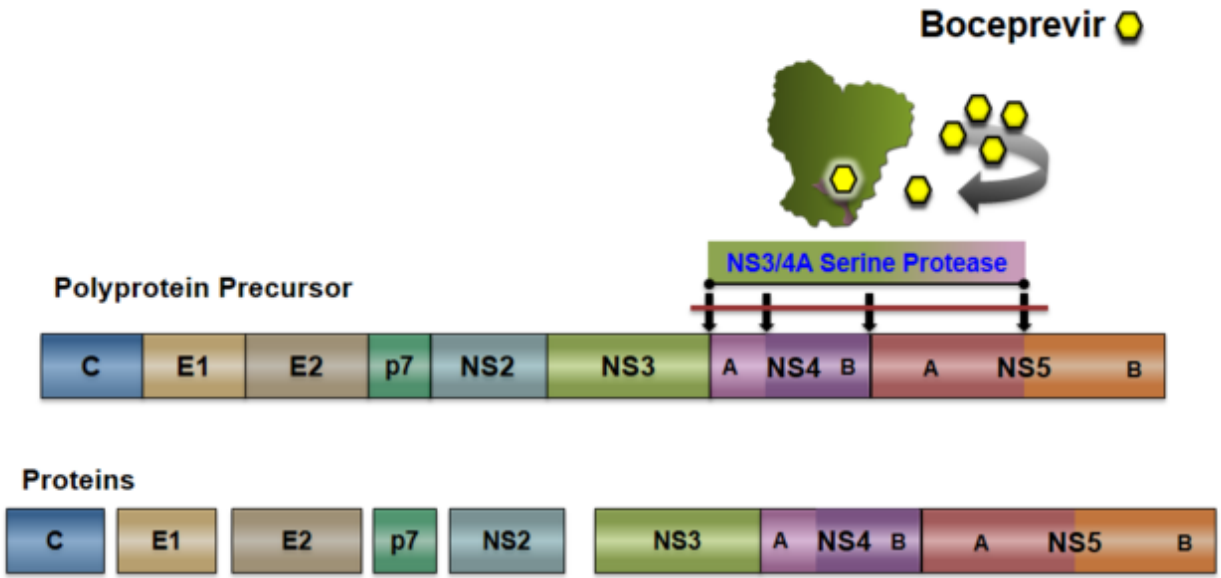
Boceprevir for Patients with Prior Failure to PEG + RIB
PROVIDE Study: Treatment Regimens



Source: Vierling JM, et al. J Hepatol. 2013;Dec 19 [Epub ahead of print].

Hepatitis web study

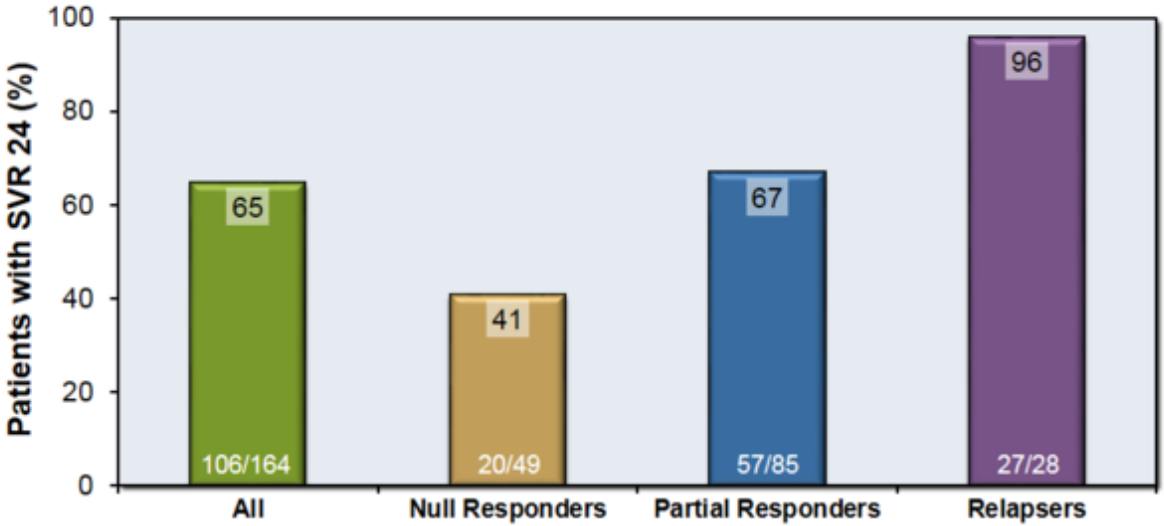
HCV Protein Processing
NS3/4A Serine Protease Inhibition



Hepatitis
web study

Boceprevir for Patients with Prior Failure to PEG + RIB
PROVIDE Study: Results

PROVIDE: SVR 24 by Prior Response (mITT)



SVR = Sustained Virologic Response; mITT = modfied intent to treat analysis

Source: Vierling JM, et al. J Hepatol. 2013;Dec 19 [Epub ahead of print].

Hepatitis web study

Boceprevir for Patients with Prior Failure to PEG + RIB
PROVIDE Study: Conclusions

Conclusions: "Re-treatment with boceprevir with peginterferon/ribavirin (BOC/PR) improved SVR rates in all patient subgroups, including those with prior null response."

Source: Vierling JM, et al. J Hepatol. 2013;Dec 19 [Epub ahead of print].

Hepatitis web study

Phase 3

Treatment Naïve and Treatment Experienced

Factors Predicting Response to Boceprevir in GT-1 SPRINT-2 and RESPOND-2 Trials

Poordad F, et al. Gastroenterology. 2012:143:608-18.

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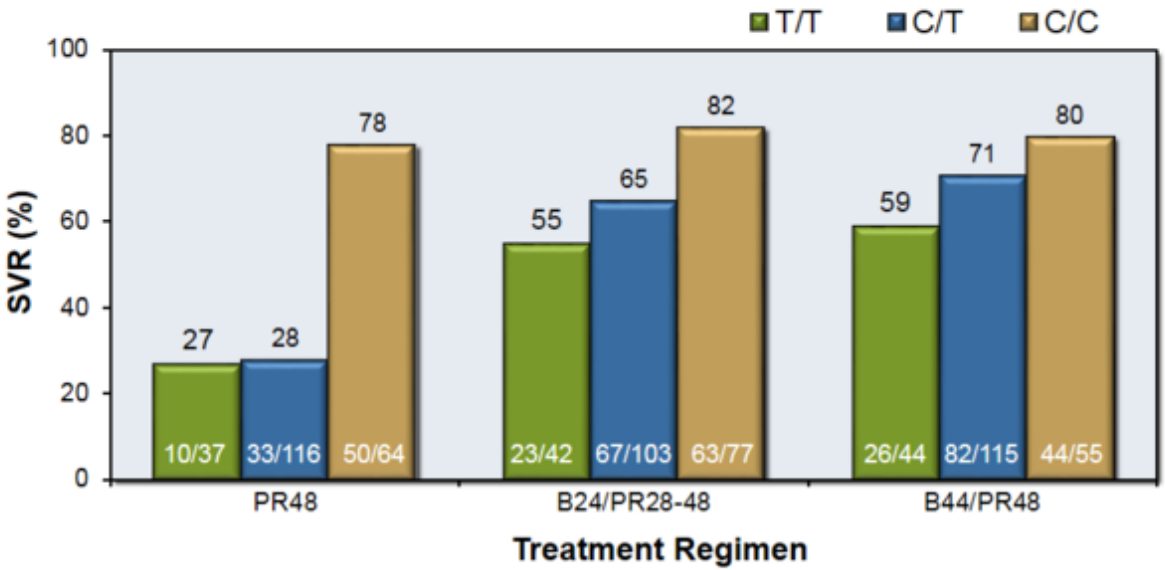
Boceprevir for Treatment-Naïve HCV Genotype 1
SPRINT-2: SVR Rates by *IL28B rs12979860* Genotype

SPRINT-2: SVR 24 by *rs12979860* Genotype



SVR = Sustained Virologic Response; RGT = Response Guided Therapy
PR = Peginterferon + Ribavirin; PRB = Peginterferon + Ribavirin + Boceprevir;

Source: Poordad F, et al. Gastroenterology. 2012:143:608-18.

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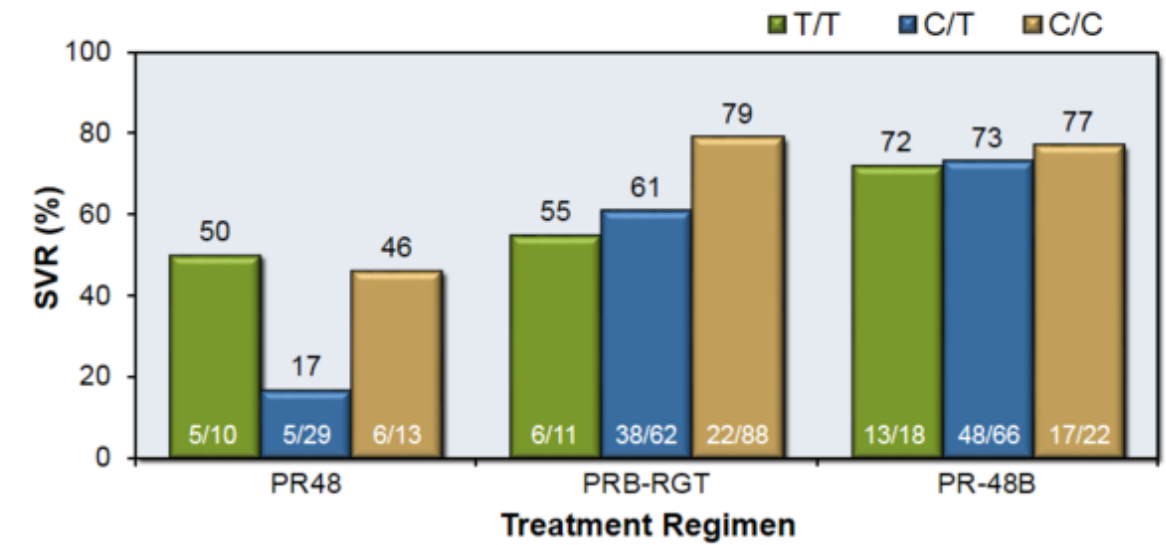
Boceprevir for Retreatment of HCV Genotype 1 Infection

RESPOND-2: SVR Rates by *IL28B rs12979860* Genotype

RESPOND-2: SVR12 by *rs12979860* Genotype



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Source: Poordad F, et al. Gastroenterology. 2012:143:608-18.

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Boceprevir for Treatment-Naïve HCV Genotype 1
SPRINT-2 Trial: Conclusions

Conclusions: "The CC polymorphism at *IL-28B* rs12979860 is associated with response to triple therapy and can identify candidates for shorter treatment durations. A ≥1 $\log_{10}$ decrease in HCV RNA at week 4 of therapy is the strongest predictor of a SVR, regardless of polymorphisms in *IL-28B*."

Source: Poordad F, et al. Gastroenterology. 2012:143:608-18.

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This slide deck is from the University of Washington's *Hepatitis C Online* and *Hepatitis Web Study* projects.

Hepatitis C Online
www.hepatitisc.uw.edu

Hepatitis Web Study
http://depts.washington.edu/hepstudy/

Funded by a grant from the Centers for Disease Control and Prevention.

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Boceprevir
Treatment-Related HCV RNA Monitoring

- **Scheduled HCV RNA Monitoring**
  - Pretreatment
  - Weeks 4, 8, 12, 24, at end of treatment, & during treatment follow-up
- **Recommended HCV RNA Assay***
  - Use sensitive real-time reverse transcriptase PCR assay
  - Lower limit of HCV **quantification**: ≤ 25 IU/ml
  - Lower limit of HCV **detection**: approximately 9.3-15 IU/ml

*For the purposes of assessing Response Guided Therapy milestones, a confirmed "detectable but below limit of quantification" HCV-RNA result should not be considered equivalent to an "undetectable" HCV-RNA result.

Source: Boceprevir (*Victrelis*) Prescribing Information. Merck & Co.

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Boceprevir for Genotype 1 HCV
Duration of Therapy

	HCV-RNA Results		Regimen and Duration
	At Treatment Week 8	At Treatment Week 24	At Treatment Week: 0 4 28 36 48
Previously Untreated	Early Responder		Boceprevir-24 / PEG + Ribavirin-28
	Not detected	Not detected	
	Late Responder		Boceprevir-32 / PEG + Ribavirin-48
	Detected	Not detected	
Previous Partial Responders or Relapsers	Early Responder		Boceprevir-32 / PEG + Ribavirin-36
	Not detected	Not detected	
	Late Responder		Boceprevir-32 / PEG + Ribavirin-48
	Detected	Not detected	
*Previous Null Responder	Detected or Not detected	Not detected	Boceprevir-44 / PEG + Ribavirin-48

*Patients with compensated cirrhosis have same treatment schedule as Previous Null Responder

Source: Boceprevir (*Victrelis*) Prescribing Information. Merck & Co.

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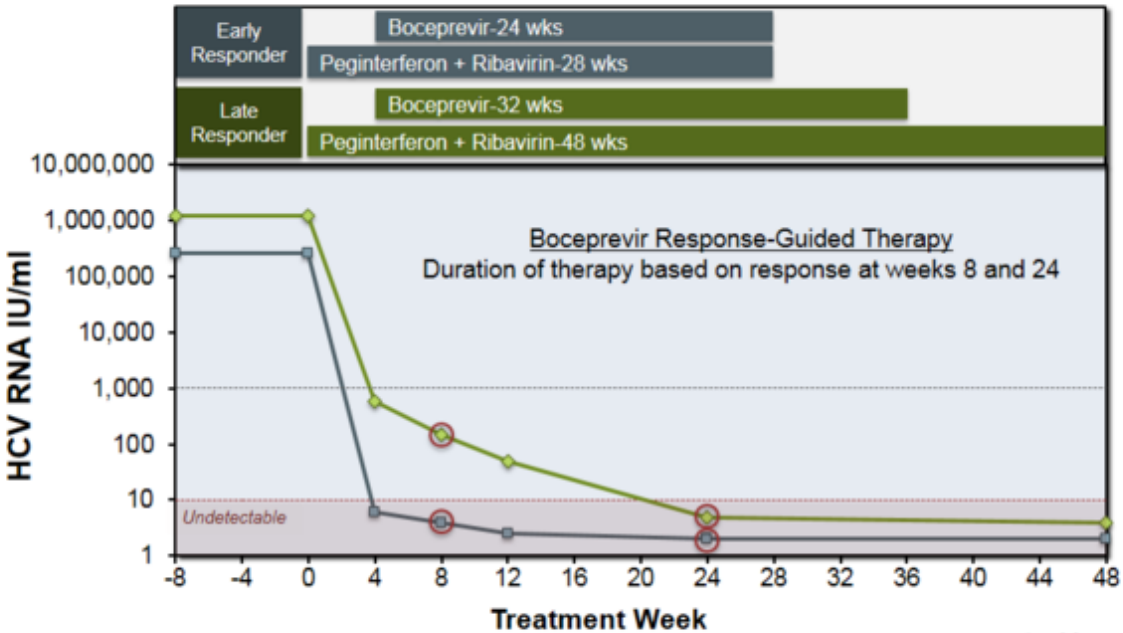
Boceprevir Response-Guided Therapy
Previously Untreated Patients

Boceprevir: Response Guided Therapy (RGT) for Previously Untreated Patients



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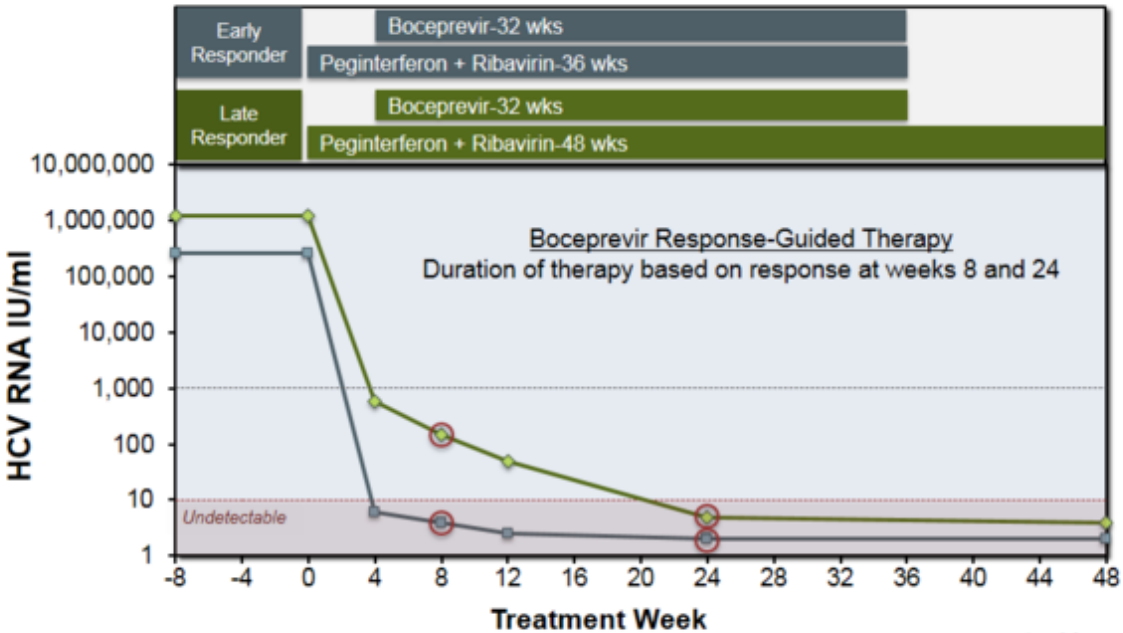
Boceprevir Response-Guided Therapy
Previous Partial Responders or Relapsers

Boceprevir: Response Guided Therapy (RGT) for Previous Partial Responders or Relapsers



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