Criteria Grid
Best Practices and Interventions for the Diagnosis and Treatment of Hepatitis C

Best Practice/Intervention:	Chang MH. et al. (2012) Boceprevir: a protease inhibitor for the treatment of hepatitis C. Clinical Therapeutics, 34(10):2021-2038.
Date of Review:	February 8, 2015
Reviewer(s):	Christine Hu

Part A

Category:	**Basic Science** ☐ **Clinical Science** ☐ **Public Health/Epidemiology** ☐ **Social Science** ☐ **Programmatic Review** ☒
Best Practice/Intervention:	**Focus:** **Hepatitis C** ☒ **Hepatitis C/HIV** ☐ **Other:** _____ **Level:** **Group** ☒ **Individual** ☐ **Other:** _____ **Target Population:** **HCV patients treated with boceprevir** **Setting:** **Health care setting/Clinic** ☒ **Home** ☐ **Other:** _____ **Country of Origin:** **United States** **Language:** **English** ☒ **French** ☐ **Other:** _____

Part B

	YES	NO	N/A	COMMENTS
Is the best practice/intervention a meta-analysis or primary research?	☐	☒	☐	Use of available data to provide an overview of the mechanism of action, pharmacologic and pharmacokinetic properties, clinical efficacy, and tolerability of boceprevir
The best practice/intervention has utilized an evidence-based approach to assess:				
Efficacy	☒	☐	☐	Treatment-naive patients: efficacy of boceprevir evaluated in a Phase II, multicenter, randomized, openlabel trial, Serine Protease Inhibitor Therapy–1 (SPRINT-1); and a Phase III, multicenter, randomized, blinded, placebo-controlled trial, Serine Protease Inhibitor Therapy-2

				(SPRINT-2) Treatment-experience patients: efficacy of boceprevir in a Phase Ib, randomized-to-sequence, openlabel, 2-dose level, crossover study; and a Phase III, multicenter, randomized, double-blinded, placebo-controlled trial: Retreatment with HCV Serine Protease Inhibitor Boceprevir and PegIntron/Rebetol 2 (RESPOND-2)
Effectiveness	☒	☐	☐	
The best practice/intervention has been evaluated in more than one patient setting to assess:				
Efficacy	☒	☐	☐	
Effectiveness	☒	☐	☐	

	YES	NO	N/A	COMMENTS
The best practice/intervention has been operationalized at a multi-country level:	☒	☐	☐	Relevant information was obtained through a search of online databases
There is evidence of capacity building to engage individuals to accept treatment/diagnosis	☐	☒	☐	
There is evidence of outreach models and case studies to improve access and availability	☐	☒	☐	
Do the methodology/results described allow the reviewer(s) to assess the generalizability of the results?	☒	☐	☐	All information were cited
Are the best practices/methodology/results described applicable in developed countries?	☒	☐	☐	
Are the best practices/methodology/results described applicable in developing countries?	☐	☒	☐	Boceprevir is a new drug; 1 of only 2 FDA-approved direct-acting antiviral agent with a high cost that may not be readily available in developing countries
Evidence of manpower requirements is indicated in the best practice/intervention	☒	☐	☐	Different clinical trials of boceprevir are done by difference group of scientists and HCV patients

Juried journal reports of this treatment, intervention, or diagnostic test have occurred	☒	☐	☐	*Clinical Therapeutics*
International guideline or protocol has been established	☐	☒	☐	
The best practice/intervention is easily accessed/available electronically	☐	☒	☐	Can be downloaded with a cost from: http://www.clinicaltherapeutics.com/
Is there evidence of a cost effective analysis? If so, what does the evidence say? ***Please go to Comments section***	☒	☐	☐	Cammà et al assessed cost-effectiveness of triple therapy for HCV (peginterferon-alfa, ribavirin, and boceprevir or telaprevir) vs SOC (peginterferon, ribavirin) dual therapy in treatment-naive patients with genotype 1 viruses - used 5 competing strategies: (1) boceprevir RGT; (2) boceprevir IL28B genotype–guided therapy; (3) boceprevir RVR-guided therapy; (4) telaprevir RGT; and (5) telaprevir IL28B genotype–guided therapy, - the most cost-effective strategies were boceprevir RVRguided therapy and telaprevir IL28B genotype–guided therapy
How is the best practice/intervention funded? ***Please got to Comments section***	☐	☐	☒	Not funded
Other relevant criteria: _____	☐	☐	☐	

New Drug Review

Boceprevir: A Protease Inhibitor for the Treatment of Hepatitis C

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ABSTRACT

Background: Boceprevir is a protease inhibitor indicated for the treatment of chronic hepatitis C virus (HCV) genotype 1 infection in combination with peginterferon and ribavirin for treatment-naive patients and those who previously failed to improve with interferon and ribavirin treatment.

Objective: This article provides an overview of the mechanism of action, pharmacologic and pharmacokinetic properties, clinical efficacy, and tolerability of boceprevir.

Methods: Relevant information was identified through a search of PubMed (1990–July 2012), EMBASE (1990–July 2012), International Pharmaceutical Abstracts (1970–July 2012), and Google Scholar using the key words *boceprevir*, *SCH 503034*, *non-structural protein 3 (NS3) serine protease inhibitor*, and *direct-acting antiviral agent (DAA)*. Additional information was obtained from the US Food and Drug Administration's Web site, review of the reference lists of identified articles, and posters and abstracts from scientific meetings.

Results: Clinical efficacy of boceprevir was assessed in 2 Phase III trials, Serine Protease Inhibitor Therapy–2 (SPRINT-2) for treatment-naive patients and Retreatment with HCV Serine Protease Inhibitor Boceprevir and PegIntron/Rebetol 2 (RESPOND-2) for treatment-experienced patients. In SPRINT-2, patients were randomized to receive peginterferon + ribavirin (PR) or peginterferon + ribavirin + boceprevir (PRB); duration of boceprevir therapy varied from 24, 32, to 44 weeks on the basis of HCV RNA results. The primary endpoint was achievement of sustained virologic response (SVR; lower limit of detection, 9.3 IU/mL). The addition of boceprevir was shown to be superior, with overall SVR rates ranging from 63% to 66% compared with 38% with PR ($P < 0.001$). Results of SVR in SPRINT-2 were also reorganized to monitor SVRs in black and non-black patients. Treatment-experienced patients were assessed in RESPOND-2; however, null responders were excluded. Patients were again randomized to PR or PRB; duration of boceprevir therapy varied from 32 to 44 weeks on the basis of HCV RNA results. SVR was significantly higher in patients receiving boceprevir (59%–66% vs 21% with PR; $P < 0.001$). This benefit was seen in both previous nonresponders (SVR, 40%–52% vs 7% with PR), as well as previous relapsers (SVR, 69%–75% vs 29% with PR). Importantly, SVR could be attained with a shortened course of therapy in almost one half of all treated patients in SPRINT-2 (44%) and RESPOND-2 (46%).

Conclusions: Boceprevir was well tolerated in clinical trials and a welcomed addition to our HCV armamentarium. (*Clin Ther.* 2012;34:2021–2038) Published by Elsevier HS Journals, Inc.

Key words: boceprevir, direct-acting antiviral agent, nonstructural protein 3 serine protease inhibitor, SCH 503034.

INTRODUCTION

After peaking in the late 1980s, the incidence of hepatitis C virus (HCV) infection steadily declined throughout the 1990s; however, since 2003, these rates have remained constant.[1] With an estimated 3.2 million people living with HCV, it is now recognized as the most common chronic bloodborne infection in the United States, accounting for 1.3% of the population.[2] The continued prevalence is largely driven by the aging population infected during the peak of new cases.[3]

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However, this number is most likely an underestimate of the true burden of the disease because many infected individuals are often asymptomatic and hence unaware of their status. Moreover, individuals who are at the highest risk for infection, intravenous drug abusers, may not access the health care system.[3,4] Approximately 70% to 85% of those acutely infected will develop a chronic infection.[2] Of these patients, 60% to 70% will develop active liver disease and 25% will develop cirrhosis; therefore, HCV-related cirrhosis accounts for ~40% of all cases of cirrhosis.[2–6] Furthermore, HCV has an estimated 5-year cumulative risk for hepatocellular carcinoma of 17%.[7] Finally, HCV remains the leading cause for liver transplantation.[2–4]

First identified in 1989 as non-A, non-B hepatitis, HCV is a positive, single-stranded, RNA virus of the family *Flaviviridae*.[3,5,8–11] The virus exists as >6 major genotypes, which can be further classified into >70 subtypes.[9,12,13] These genotypes have varying geographical distributions, with genotype 1 being most commonly found in the United States, followed by genotypes 2 and 3.[1] Encoded in a 3000 amino acid sequence is the polyprotein that contains key structural and nonstructural proteins.[5,8,11,14] The nonstructural proteins responsible for HCV replication are activated when cleavage occurs at 4 specific sites, a process catalyzed by the nonstructural protein 3 (NS3) protease; hence, the NS3 protease is a key target in the arrest of HCV replication.[8,11,14]

Since 2001, with the pegylation of interferon, there have been no significant changes in the management of chronic HCV infection, a disheartening fact given the low cure rates in the predominant genotype seen in the United States.[4–7,13,15] The standard of care (SOC) with peginterferon and ribavirin for 48 weeks of therapy resulted in sustained virologic response (SVR) of 30% to 50%.[4–7,12,13,15] A major limitation to advances in research was the lack of a durable replication model.[10,16] Fortunately, in 1999, the chimpanzee model was exchanged for a cell culture replication model system.[8,10,11] The proof of concept paper for the NS3 protease inhibitor, BI 2061, in which HCV RNA declined by >4-$\log_{10}$, provided new hope, although it was short-lived because of cardiotoxicity associated with this compound.[10,16,17]

Ten years later, with the approval of boceprevir[18] and telaprevir[19] in 2011, the treatment of HCV is now experiencing a similar revelation in treatment options that a different viral infection, HIV, saw ~15 years ago. The paradigm has shifted to specifically targeted antiviral therapy for hepatitis C compounds, a focused approach in which therapy is targeted for various stages of the HCV life cycle, possibly resulting in the ultimate removal of peginterferon and ribavirin as the backbone of therapy.[6,20–22] Currently, there are >50 direct-acting antiviral agents (DAAs), exhibiting varying potency against HCV genotypes, at assorted stages of preclinical and clinical development.[20]

Nonetheless, this management approach brings its own set of challenges. The practitioner involved in the management of the patient with chronic HCV must become familiar with specific treatment response terminology (**Table I**) as he or she embarks on treatment or retreatment.[3] A clear understanding of such terms facilitates intraprovider communication. More importantly, response-guided therapy (RGT), in which treatment duration is decided on the basis of HCV RNA response at prespecified intervals, is the current cornerstone of HCV treatment.[20] In addition, the HCV provider must learn the complexities of baseline and on-

Table I. Virologic response during treatment of hepatitis C virus (HCV).[3]

Virologic Response	Definition
Rapid virologic response	HCV RNA negative by treatment week 4
Early virologic response	HCV RNA negative by treatment week 12
End-of-treatment response	HCV RNA negative at end of treatment period
Sustained virologic response	HCV RNA negative 24 weeks' posttreatment
Null response	Decrease in HCV RNA by <2-$\log_{10}$ from baseline by week 24
Partial response	Decrease in HCV RNA by >2-$\log_{10}$ from baseline without HCV RNA negative at week 24
Breakthrough	HCV RNA negative with reappearance of HCV RNA during treatment
Relapse	HCV RNA negative at end of treatment period with reappearance of HCV RNA 24 weeks' posttreatment

treatment resistance patterns. Unlike nonviral chronic comorbidities, HCV is a dynamic entity that quickly adapts in response to drug pressure, largely due to its prolific, yet error-prone, nature.[23] The close management of adherence, adverse drug events, and drug interactions will become increasingly important, clearing an excellent niche for specialists with expertise in this area.

In the future, questions will need to be addressed regarding the approach of patients with varying failed responses to a regimen containing peginterferon, ribavirin, and DAA or even regimens containing multiple DAAs.[24] Further research efforts must still be pursued in difficult-to-treat patients, such as those of African-American ethnicity or with advanced fibrosis, decompensated cirrhosis, reinfection of liver transplant, and coinfection with HIV.[7,25,26] Aside from the clinical concerns mentioned here, another looming issue remains how the health care system will absolve the increase in health care costs.[23] In a phenomenon called "warehousing," many patients have been waiting, and will continue to wait, to start therapy with regimens containing newly approved agents promising improved cure rates.[22] As new treatments become available, difficult decisions must be made regarding who to treat first: patients who may benefit the most due to advanced liver disease but may not tolerate therapy to completion or patients who have multiple positive prognostic factors, and hence an increased likelihood of achieving an SVR in a shortened treatment cycle?[3]

Boceprevir is a novel DAA, specifically a NS3 protease inhibitor, that was approved by the US Food and Drug Administration (FDA) on May 13, 2011, for the treatment of chronic HCV genotype 1 infection in combination with peginterferon and ribavirin.[18] Currently, it is 1 of only 2 FDA-approved DAAs available to treat adult (age ≥18 years) patients with compensated liver diseases who are either treatment naive or previously failed to improve with SOC therapy.[18,19] It is not indicated for monotherapy due to resistance issues.[18] The current article provides an overview of the mechanism of action, pharmacologic and pharmacokinetic properties, clinical efficacy, and tolerability of boceprevir.

METHODS

A search of PubMed (1990–July 2012), EMBASE (1990–July 2012), International Pharmaceutical Abstracts (1970–July 2012), and Google Scholar using the key words *boceprevir*, *SCH 503034*, *non-structural protein 3 (NS3) serine protease inhibitor*, and *direct-acting antiviral agent (DAA)* identified relevant information pertaining to boceprevir. To retrieve all available information on boceprevir, neither limits nor inclusion/exclusion criteria were applied. Additional information was obtained from the FDA Web site and by a thorough review of the reference lists of identified articles. Posters and abstracts from meetings of the American Association for the Study of Liver Diseases, European Association for the Study of the Liver, Infectious Diseases Society of America, American Society for Microbiology, Conference on Retroviruses and Opportunistic Infections, and the European Society of Clinical Microbiology and Infectious Diseases from 2000 to 2011 were also consulted.

RESULTS

Chemical Structure

Boceprevir (**Figure**) is a NS3 serine protease inhibitor of HCV.[8,18] Chemically, it is (1R,5S)-N-[3-Amino-1-(cyclobutylmethyl)-2,3-dioxopropyl]-3-[2(S)-[[[(1,1-dimethylethyl)amino]carbonyl]amino]-3,3-dimethyl-1-oxobutyl]-6,6-dimethyl-3-azabicyclo[3.1.0]hexan-2(S)-carboxamide.[18] The empirical formula for boceprevir is $C_{27}H_{45}N_5O_5$, with a molecular weight of 519.7 daltons.[18] It is manufactured as a white to off-white amorphous powder containing a mixture of 2 diastereomers, in which the S-configuration is the active isomer.[18,27]

Mechanism of Action

The NS3 serine protease is vital to the life cycle of HCV, without which the virus will not be able to replicate inside the host cell.[8,27] This virally encoded protease is responsible for cleaving the polyprotein gener-

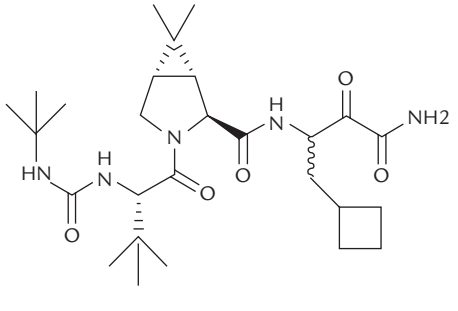

Figure. Structural formula of boceprevir.[8,18]

ated from the HCV genome template. Cleavage allows for the release of functional proteins and generation of mature proteins. Boceprevir is a covalent reversible inhibitor of the HCV NS3 serine protease, binding at the active site through an α-ketoamide functional group.[8,18,27] Inhibition of the NS3 protease will suppress RNA replication and ultimately the production of virions.[8,27] As such, boceprevir is described as a DAA.

In Vitro Activity

The in vitro activity of boceprevir was evaluated by using 2 biological assays, the enzyme assay and the cell-based replicon assay.[8,27] The assays are used to assess the potency of inhibition and subsequent efficacy of HCV protease inhibitors. In the HCV NS3 biochemical assay against genotype 1a and 1b, boceprevir was shown to be a potent inhibitor with an average binding constant K_i of 14 nM.[18,27,28] The values for the boceprevir concentration at which the reaction of an organism was 50% or 90% less than the control value were ~200 and 400 nM, respectively, in a 72-hour cell-based replicon assay consisting of only genotype 1b.[8,18,27,28] In addition, the cross-reactivity of boceprevir was tested in vitro against a broad number of other serine proteases and general enzymes, and showed no cross-reactivity or identification of no major issues.[8,27] Final results all indicated that boceprevir was highly selective toward the HCV NS3 protease inhibitor.[8,18,27,28]

Pharmacokinetics and Pharmacodynamics

In preclinical studies in rats and dogs, boceprevir demonstrated good oral bioavailabilities of 26% and 30%, respectively.[8,27,28] Based on target organ analysis in rats, boceprevir was also found to concentrate well in the liver, with a 30-fold liver/plasma concentration ratio. [8,27,28]

In humans, single-dose and multiple ascending-dose pharmacokinetic studies have been conducted in healthy volunteers, patients, and those with varying degrees of hepatic and renal impairment.[29–33] In trials with healthy volunteers, pharmacokinetic results were obtained from subjects who received 800 mg of boceprevir monotherapy 3 TID.[18,29] On oral administration, boceprevir was rapidly absorbed, with a median T_{max} of 2 hours, C_{max} of 1723 ng/mL, C_{min} of 88 ng/mL, and AUC_{0-8} of 5408 ng · h/mL. Additional dose studies indicated that AUC, C_{max}, and C_{min} values at steady state did not increase proportionally to doses, whereas exposures for individual subjects overlapped at 800 and 1200 mg, indicating diminished absorption at higher doses. Compared with the fasting state, food increased the AUC of boceprevir by 65%. The type of meal (high-fat vs low-fat) and timing of meal did not make a difference in drug exposure. Currently, all doses are advised to be taken with a meal or a light snack to enhance the exposure of boceprevir.[18] At 800 mg TID, steady state was achieved after 1 day with minimal accumulation, 0.8-fold to 1.5-fold.[18] The volume of distribution was ~772 L at steady state with 75% bound to plasma protein.[18,29] Boceprevir primarily undergoes metabolism via the aldo-keto reductase pathway to inactive ketone-reduced metabolites.[18,34] To a lesser extent, it also undergoes oxidative metabolism via cytochrome P450 (CYP) 3A4 and 3A5.[18,34] After a single 800-mg radiocarbon dose of boceprevir, ~79% of the dose was excreted in the feces and 9% in the urine.[34] Of these amounts, only 8% (feces) and 3% (urine) were eliminated as boceprevir, suggesting that the liver is the primary elimination route. Elimination $t_{½}$ values ranged from 7 to 15 hours across a total daily dose range of 50 to 1200 mg.[29] The mean plasma $t_{½}$ is ~3.4 hours.[18] These values found in healthy volunteers were similar to those obtained from patients and are summarized in **Table II**.[18,29–33] No significant differences were found in any pharmacokinetic parameters in studies conducted in patients with genotype 1 infection who were nonresponders to interferon with or without ribavirin and patients with varying degrees of hepatic and renal impairment.[30–33]

Table II. Pharmacokinetic parameters* of boceprevir.[18,29]

Variable	Value
C_{max}	1723 ng/mL
C_{min}	88 ng/mL
T_{max}	2 h
V_{dss}	772 L
$t_{½}$	3.4 h
AUC_{0-8}	5408 ng · h/mL

V_{dss} = apparent volume of distribution at steady state.
*Values based on healthy volunteers who received 800 mg of boceprevir TID.

Clinical Efficacy

The safety and efficacy of boceprevir was evaluated in previously untreated patients as well as in previously treated genotype 1 patients with chronic HCV infection.

Treatment-Naive Patients

Kwo et al evaluated the safety and efficacy of boceprevir in a Phase II, multicenter, randomized, open-label trial, Serine Protease Inhibitor Therapy–1 (SPRINT-1).[4,26] A total of 520 patients were randomized in a 1:1:1:1:1 ratio to the following treatment groups: PR48 (SOC, peginterferon alfa-2b 1.5 μg/kg weekly + ribavirin 800–1400 mg/d, dosed according to weight, for 48 weeks), PRB28 (SOC + boceprevir 800 mg TID, for 28 weeks), PR4B24 (SOC lead-in; 4 weeks and SOC + boceprevir 800 mg TID, 24 additional weeks), PRB48 (SOC + boceprevir 800 mg TID, for 48 weeks), and PR4B44 (SOC lead-in; 4 weeks and SOC + boceprevir 800 mg TID, 44 additional weeks).[4,10,16,26,35–38] Patients were stratified according to race (black vs non-black) and cirrhosis status (present vs not present) as determined by results of biopsy within the previous 5 years.[4,10,26] A separate second part of the study evaluated the influence of ribavirin dose on efficacy, comparing a control group who received SOC + boceprevir 800 mg TID for 48 weeks with a treatment group who received peginterferon alfa-2b 1.5 μg/kg weekly + low-dose ribavirin 400 to 1000 mg/d, dosed according to weight + boceprevir 800 mg TID for 48 weeks.[4,10,26]

The primary efficacy endpoint in SPRINT-1, and subsequent trials, was SVR, defined as patients with undetectable HCV RNA (lower limit of detection, 15 IU/mL) at 24 weeks after completion of therapy.[26] The addition of boceprevir demonstrated significant improvement in rates of SVR over SOC, ranging from 54% to 75% compared with 38% with SOC (*P* values, 0.013 to < 0.0001).[4,5,10,16,21,26,35–37,39] Moreover, the rates of SVR were better in boceprevir treatment groups that included the SOC 4-week lead-in (56% and 75% vs 54% and 67%, respectively). Attainment of SVR was highly associated with a rapid virologic response (RVR), defined as HCV RNA undetectable by treatment week 4.[10,26,37] Attainment of SVR was also positively associated with a >1.5-$\log_{10}$ reduction after the SOC lead-in.[7,26] Of patients who attained an RVR, 74% to 100% in each treatment group achieved eventual SVR, with a large number of those patients in the boceprevir treatment arms (180 of 416 vs 8 of 104 in the SOC arm) and especially the 2 boceprevir arms that included SOC lead-in (116/221).[10,26,37] Overall, of the 373 who attained undetectable HCV RNA levels by treatment week 12, almost 80% (78.6%) achieved SVR.[10,26] Conversely, if HCV RNA was detectable after week 12, the addition of boceprevir did not provide a clinical advantage, with only 1 additional patient in the PRB48 group achieving SVR. The probability of attaining SVR was highest if there was a >4-$\log_{10}$ decrease in HCV RNA at week 4 and lowest if there was a <1.5-$\log_{10}$ decrease in HCV RNA at week 4 regardless of treatment duration.[40] These benefits were seen in difficult-to-treat patients, such as black patients (SVR rates ranging from 29% to 53% with boceprevir compared with 13% with SOC) and cirrhotic patients (SVR rates ranging from 57% to 78% with boceprevir compared with 25% with SOC), albeit in a small sample size.[10,26] Results from previous clinical trials had shown that blacks and cirrhotics achieved lower SVR rates as compared to non-blacks and non-cirrhotics.[25,26]

In part 2 of SPRINT-1, the researchers demonstrated that standard ribavirin dosing was necessary for optimal treatment efficacy. SVR was 50% with standard ribavirin dosing compared with 36% with low-dose ribavirin dosing.[4,5] There was also a higher relapse rate associated with the decreased ribavirin dose (22% with low-dosing vs 11% with standard dosing).

Poordad et al[25] evaluated the safety and efficacy of boceprevir in a Phase III, multicenter, randomized, blinded, placebo-controlled trial, Serine Protease Inhibitor Therapy–2 (SPRINT-2). A total of 1097 patients were separated into 2 cohorts (157 black patients vs 940 non-black patients) and then randomized in a 1:1:1 ratio to the following treatment groups: PR48 (SOC, peginterferon alfa-2b 1.5 μg/kg weekly + ribavirin 800–1400 mg/d, dosed according to weight; for 48 weeks and matching placebo), PR4B24 (SOC lead-in; 4 weeks and SOC + boceprevir 800 mg TID; 24 additional weeks ± SOC/placebo; 20 additional weeks if HCV RNA detectable after treatment week 8), and PR4B44 (SOC lead-in; 4 weeks and SOC + boceprevir 800 mg TID; 44 additional weeks).[4,25] In all 3 groups, treatment was stopped according to a standard futility rule, defined as detectable HCV RNA at week 24. Patients were stratified according to baseline HCV RNA (≤400,000 vs >400,000 IU/mL) and genotype 1 subtype (1a vs 1b).[25]

The primary endpoint of SVR (lower limit of detection, 9.3 IU/mL) allowed HCV RNA measurements from posttreatment week 12 to be carried forward if posttreatment week 24 measurements were unavailable.[25] The addition of boceprevir was shown to be superior over SOC, resulting in overall SVR rates ranging from 63% to 66% compared with 38% with SOC ($P < 0.001$).[4,10,25,36,37,41,42] Rates of SVR were significantly higher in both cohorts (67%–68% compared with 40% with SOC in non-black patients, $P < 0.001$; 42%–53% compared with 23% with SOC in black patients, $P = 0.04$ for PR4B24 and $P = 0.004$ for PR4B44).[4,5,7,10,16,24,25,37,38,43–45] Overall rates of SVR were also significantly higher in patients with mild to moderate fibrosis (F0–F2), with an exception in black patients with mild to moderate fibrosis not quite reaching statistical significance ($P = 0.03$).[25] Importantly, SVR could be attained with a shortened course of therapy in almost one half of all treated patients (44%).[7,16,46] An important exception was seen in treatment-experienced patients with cirrhosis who had a higher rate of SVR with an entire year of treatment (42% vs 31%).[25]

Attainment of SVR was highly associated with an RVR (≥89%) regardless of treatment group or race.[25] However, SVR was also positively associated with a >1-$\log_{10}$ reduction after the SOC lead-in (SVR 82% compared with 39% in those with a <1-$\log_{10}$ reduction).[20] This finding held especially true for patients with advanced fibrosis (F3–F4). Attainment of SVR was also highly associated with undetectable HCV RNA at treatment week 8 (week 4 of boceprevir or matching placebo) (≥75%) regardless of treatment group or race.[25] However, a larger number of patients met these criteria if treated with boceprevir (368 of 734 vs 51 of 363 in the SOC arm). Moreover, for patients who did not achieve RVR, the addition of boceprevir significantly increased overall rates of SVR (65%–66% with boceprevir vs 34%). Even in those with <1-$\log_{10}$ reduction (poor interferon responsiveness) after SOC lead-in, the addition of boceprevir resulted in significantly increased rates of SVR (28%–38% vs 4% with SOC). This was similarly significant in patients with mild to moderate, but not advanced, fibrosis ($P <$ 0.001 versus P values: 0.31 – 1.00, respectively). Results from SPRINT-2 are summarized in **Table III**.[25]

Table III. Serine Protease Inhibitor Therapy–2: sustained virologic response rates (intention-to-treat).[25]

Variable	Combined			Non-Black Patients			Blacks Patients		
	PR48	PR4B24	PR4B44	PR48	PR4B24	PR4B44	PR48	PR4B24	PR4B44
Overall	137/363 (38%)	233/368 (63%)*	242/366 (66%)*	125/311 (40%)	211/316 (67%)*	213/311 (68%)*	12/52 (23%)	22/52 (42%)*	29/55 (53%)*
HCV RNA ND at week 4	29/30 (97%)	17/19 (89%)	18/20 (90%)	27/28 (96%)	16/18 (89%)	18/20 (90%)	2/2 (100%)	1/1 (100%)	0/0 (0%)
HCV RNA detectable at week 4	107/313 (34%)	213/330 (65%)*	218/329 (66%)*	97/268 (36%)	192/283 (68%)*	191/277 (69%)*	10/45 (22%)	21/47 (45%)*	27/52 (52%)*
HCV RNA ND at week 8	51/60 (85%)	184/208 (88%)	184/204 (90%)	48/56 (86%)	170/190 (89%)	166/182 (91%)	3/4 (75%)	14/18 (78%)	18/22 (82%)
HCV RNA detectable at week 8	81/271 (30%)	46/129 (36%)	52/131 (40%)	73/233 (31%)	38/104 (37%)	44/102 (43%)*	8/38 (21%)	8/25 (32%)	8/29 (28%)

PR48 = peginterferon/ribavirin × 48 weeks; PR4B24 = peginterferon/ribavirin × 4 weeks + peginterferon/ribavirin/boceprevir × 24 weeks; PR4B44 = peginterferon/ribavirin × 4 weeks + peginterferon/ribavirin/boceprevir × 44 weeks; ND = nondetectable.
*$P < 0.05$ when compared with PR48.

Treatment-Experienced Patients

An initial Phase I trial evaluated varying doses of boceprevir (100–400 mg daily) for 2 weeks in treat-

ment-experienced patients, which resulted in a mean 2.06-$\log_{10}$ reduction in HCV RNA for the highest dose of boceprevir.[17,35] Investigators evaluated the efficacy of boceprevir in a Phase Ib, randomized-to-sequence, open-label, 2-dose level, crossover study.[4,10,17,35,36,47–49] Twenty-six previous nonresponse patients, defined as $<$2-$\log_{10}$ reduction in HCV RNA after 12 weeks of peginterferon alfa-2b ± ribavirin, received boceprevir TID as monotherapy for 7 days, peginterferon alfa-2b 1.5 μg/kg once weekly as monotherapy for 14 days, and combination therapy for 14 days.[4,10,17,35,47] A 14-day washout period interrupted each treatment intervention to allow for HCV RNA to return to baseline values. Fourteen patients received boceprevir at 200 mg per dose and 12 patients received boceprevir at 400 mg per dose.[4,10,17,35,36,47–49]

Boceprevir was shown to have clinical activity as illustrated by a maximum mean 1.08-$\log_{10}$ decrease in HCV RNA after low-dose boceprevir monotherapy and a maximum mean 1.95-$\log_{10}$ and 2.28-$\log_{10}$ decrease in HCV RNA after combination therapy for 1 and 2 weeks, respectively (compared with a 1.08-$\log_{10}$ decrease with peginterferon alfa-2b monotherapy).[4,10,17,35,36,47–49] Boceprevir 400 mg TID resulted in a maximum mean 1.60-$\log_{10}$ decrease in HCV RNA after low-dose boceprevir monotherapy and a maximum mean 2.48-$\log_{10}$ and 2.68-$\log_{10}$ decrease in HCV RNA after combination therapy for 1 and 2 weeks, respectively (compared with a 1.26-$\log_{10}$ decrease with peginterferon alfa-2b monotherapy). HCV RNA became undetectable in 8 patients within the 2-week combination therapy period.[47]

The safety and efficacy of boceprevir was evaluated in a Phase III, multicenter, randomized, double-blinded, placebo-controlled trial: Retreatment with HCV Serine Protease Inhibitor Boceprevir and PegIntron/Rebetol 2 (RESPOND-2).[5,13,16,50] Patients had to have demonstrated responsiveness to interferon (minimum duration of therapy, 12 weeks); thus, null-response patients were not included.[5,7,10,13,24,41,43,45,46] Previous nonresponse was defined as ≥2-$\log_{10}$ decrease by week 12 but detectable HCV RNA throughout therapy.[4,7,13,42] Relapse was defined as undetectable HCV RNA at the end of treatment without attainment of SVR.[4,13] A total of 403 patients were randomized in a 1:2:2 ratio to the following treatment groups: PR48 (SOC: peginterferon alfa-2b 1.5 μg/kg weekly + ribavirin 800–1400 mg/d, dosed according to weight; for 48 weeks and matching placebo), PR4B32 (SOC lead-in; 4 weeks and SOC + boceprevir 800 mg TID; 32 additional weeks ± SOC/placebo; 12 additional weeks if HCV RNA detectable after treatment week 8), and PR4B44 (SOC lead-in; 4 weeks and SOC + boceprevir 800mg TID; 44 additional weeks).[4,5,7,10,13,16,38,41,43,45,50,51] In all 3 groups, treatment was stopped according to a standard futility rule, defined as detectable HCV RNA at week 12.[4,13,46] Patients were stratified according to previous response (nonresponse vs relapse) and genotype 1 subtype (1a vs 1b).[13] The majority of patients were previous relapse patients (64%).[13]

SVR was significantly higher with the addition of boceprevir (59%–66% vs 21% with SOC; $P < 0.001$).[4,5,7,10,13,16,24,37,42–44,46,50] This increase in SVR was largely fueled by the higher end of treatment responses rates (70%–77% with boceprevir vs 31% with SOC) coupled with lower rates of relapse (12%–25% vs 32%).[4,5,7,10,13,16,24,37,42–44,46,50] This benefit was seen in both previous nonresponse patients (SVR 40%–52% vs 7% with SOC), as well as previous relapse patients (69%–75% vs 29% with SOC).[4,5,7,13,41,45,46,51] Importantly, SVR could be attained with a shortened course of therapy in almost one half of all treated patients (46%).[46] An important exception was seen in treatment-experienced patients with cirrhosis who had a higher rate of SVR with an entire year of treatment (77% vs 35%).[13] In patients who were responsive to SOC lead-in, boceprevir conferred higher response rates (SVR, 73%–79%; SOC, 25%).[10,13,43,46] Even in the 25% of patients who were poorly responsive to SOC lead-in, boceprevir resulted in attainment of SVR in 33% to 34% of patients compared with 0% of patients treated with SOC.[10,13,20,45,46] Attainment of SVR was highly associated with undetectable HCV RNA at treatment week 8 (week 4 of boceprevir or matching placebo) (≥86%) regardless of treatment group.[4,13,45,50] However, a larger proportion of patients met these criteria if treated with boceprevir (46%–52% vs 9% in the SOC arm) .[4,13,45,50] **Table IV** summarizes the results of SVR from RESPOND-2.[13]

SPRINT-1, SPRINT-2, and RESPOND-2 excluded patients who had liver diseases from other causes, decompensated cirrhosis, HIV coinfection, hepatitis B virus coinfection, previous organ transplantation, renal insufficiency, pre-existing psychiatric disease, seizure disorder, cardiovascular disease, poorly controlled diabetes, pregnancy or breastfeeding, hemoglobinopathies, autoimmune disease, active substance abuse, and active cancer.[4,13,16,25,26] Future

studies in some of these populations will be critical to decision making in clinical practice. A Phase IIb study involving HIV/HCV coinfected, treatment-naive patients is currently evaluating the utility of boceprevir in this population.[4,20]

Adverse Events

A total of 2098 patients were exposed to at least 1 dose of boceprevir, ranging from a total daily dose of 300 to 2400 mg.[52] Most of these patients (91%) received the currently approved dose of boceprevir (2400 mg/d). The tolerability of boceprevir, in combination with peginterferon and ribavirin, was assessed in 2095 subjects between 1 Phase II trial and 2 Phase III trials, representing a median exposure of 201 days of boceprevir among subjects from these pooled data.[18,52] Because boceprevir was studied, and subsequently approved, in combination with peginterferon and ribavirin, it may be difficult to establish a definite causality relationship between this agent and a particular adverse event.

Adverse events occurred in almost 100% of all study patients.[25,51] Common adverse effects shared by all treatment groups, regardless of addition of boceprevir, include: fatigue (60% vs 53%–57% with boceprevir), headache (42% vs 46%), nausea (42% vs 43%–48%), pyrexia (33% vs 32%–33%), chills (28% vs 33%–36%), insomnia (32% vs 33%), anorexia (25%–26% vs 16%–24%), diarrhea (24%–25% vs 16%–22%), and alopecia (22%–27% vs 16%–27%).[4,5,13,18,25,26,37] Rash or other skin disorders were not associated with boceprevir.[4,26,43,50]

Overall, rates of discontinuation due to adverse drug reactions were higher among patients who received boceprevir (8%–19% vs 2%–16%; *P* values, 0.02–0.15).[4,25,26,36,45] Dose modifications of peginterferon or ribavirin due to adverse drug reactions also were more common among patients who received boceprevir (39% vs 24%).[18] Rates of serious adverse events were similar between SOC and boceprevir regimens (5%–12% vs 9%–14%, respectively; *P* values, 0.03–0.23).[13,24,25,37,43,45] Eight deaths were reported in the completed clinical trials; 2 of these deaths, both suicides, were possibly related to a study drug (most likely peginterferon), with 1 occurring in a patient who received boceprevir and 1 occurring in a patient who had not received boceprevir.[52]

Table IV. Retreatment with HCV Serine Protease Inhibitor Boceprevir and PegIntron/Rebetol 2: sustained virologic response rates (intention-to-treat).[13]

	Combined			Prior Nonresponse			Prior Relapse		
Variable	PR48	PR4B32	PR4B44	PR48	PR4B32	PR4B44	PR48	PR4B32	PR4B44
Overall	17/80 (21%)	95/162 (59%)*	107/161 (66%)*	2/29 (7%)	23/57 (40%)*	30/58 (52%)*	15/51 (29%)	72/105 (69%)*	77/103 (75%)*
HCV RNA ND at week 8	7/7 (100%)	64/74 (86%)	74/84 (88%)	–	–	–	–	–	–

PR48 = peginterferon/ribavirin × 48 weeks; PR4B32 = peginterferon/ribavirin × 4 weeks + peginterferon/ribavirin/boceprevir × 32 weeks; PR4B44 = peginterferon/ribavirin × 4 weeks + peginterferon/ribavirin/boceprevir × 44 weeks; ND = nondetectable.
*$P < 0.05$ when compared with PR48.

Anemia

Anemia was the principal adverse drug effect associated with boceprevir.[24] In clinical trials, rates of anemia, defined as a hemoglobin (Hgb) level <10 g/dL, were higher in patients who received boceprevir (49%–55% vs 20%–34%; $P < 0.001$).[4,5,7,16,24–26,35,37,38,41,43–45,51,53] The majority of cases were classified as grade 1 or 2 anemia (97%).[10,25] Grade 3 or 4 anemia (ie, Hgb <8 g/dL), although rare, was higher in groups treated with boceprevir (22 of 734 vs 6 of 363).[13,25,26,45] The addition of boceprevir usually results in an additional 1-g/dL decrease in Hgb levels.[25,44]

Investigators were allowed to reduce the dose of ribavirin and/or use erythropoietin-stimulating agents (ESAs) at their discretion.[10,25,26] The dose of ribavirin was reduced in 13% to 21% of patients taking boceprevir.[5,25,45,50] These rates were similar to those of patients who were not taking boceprevir.[26] In patients who received boceprevir, there was also an increased utilization of these ESAs (41%–46% vs 21%–24%; $P < 0.001$).[4,5,7,24,25,43–45,50,53] In SPRINT-2, the mean duration of ESAs was 94 to 156 weeks in patients receiving boceprevir compared with 121 weeks in those treated with SOC.[53] Red blood cell transfusions, while rare, were higher among patients treated with boceprevir (20 of 734 vs 2 of 363).[25,41] These interventions ultimately resulted in low rates of discontinuation due to anemia (0%–3%).[7,10,13,24,37,38,45]

Interestingly, in some trials, patients who developed anemia also exhibited increased rates of SVR.[25,26,44–46] Patients with >3-g/dL decreases in Hgb were more likely to attain SVR (43% vs 30%; $P < 0.001$).[16] Anemia may potentially serve as a surrogate marker of increased ribavirin concentrations; hence, this clinical correlation.[10,16,26] If true, then administration of ESAs may be a preferred intervention in patients who have anemia.[10,26] However, this association elucidated by SPRINT-1 was not seen in SPRINT-2; SVR rates were similar, regardless of the anemia management strategy used.[26,44,54] Furthermore, ESAs are not without risk and are associated with an increased chance of thromboembolic events.[44,54] An ongoing study is evaluating ribavirin dose reduction versus ESA administration in boceprevir regimens.[37,44,46]

Other Boceprevir-Associated Adverse Drug Reactions

Dysgeusia was the second more frequent adverse drug effect associated with boceprevir.[24] Among healthy volunteers, the incidence of dysgeusia increased from <10% in those receiving boceprevir ≤1200 mg/d to >25% in those who received boceprevir 2400 to 3600 mg/d.[52] In clinical trials, rates of dysgeusia were higher in patients who received boceprevir (27%–49% vs 9%–29%; $P < 0.001$).[13,24–26] Dry skin was also reported more frequently in patients treated with boceprevir (21%–22% vs 8%; P values, 0.004–0.009).[4,13,25,45]

Incidences of grade 1 neutropenia and thrombocytopenia were also higher with boceprevir (85%–86% and 28%–33%, respectively) compared with placebo (77% and 13%, respectively).[25] Rates of grade 3 neutropenia (absolute neutrophil count, 500–750 cells/μL) was significantly higher in the boceprevir treatment groups compared with SOC (24%–25% vs 14%; $P < 0.001$).[25] Five cases of severe or life-threatening neutropenia were reported collectively from all clinical data, all occurring among patients who received boceprevir; in each case, neutropenia resolved with discontinuation of all study drugs.[52] Three cases of grade 4 thrombocytopenia (platelets <25,000/mL) occurred among patients receiving boceprevir compared with none among SOC. Nonetheless, these cases did not require additional intervention for management.

Resistance

The development of viral resistance is influenced by 3 major factors: the genetic barrier, or number of amino acid substitutions required, to resistance; the in vivo fitness of the viral variant, or how capable it is in filling the replication space left by the wild-type virus; and drug exposure relative to the inhibitory concentration for the viral variant.[40,55] Successful treatment is compromised by either incomplete viral suppression during therapy or pre-existing viral variants present before therapy.[56]

HCV has a high rate of replication (10^{12} virions daily).[5,9,11,15,23,55,57–59] This high rate, coupled with a lack of proofreading by the RNA-dependent-RNA-polymerase (NS5B), results in a high error rate during replication and, consequently, a variety of genetically distinct but closely related strains, known as quasispecies.[5,7,57–59,60,61] In genotype 1, the subtype 1a virus seems to have a lower genetic barrier to resistance for protease inhibitors compared with genotype 1b, resulting in greater rates of treatment failure.[7,20,40,45,55] This finding may be a significant area of consternation because replicon studies have been based on an HCV 1b sub-

type consensus strain.[39] The difference between the 2 subtypes can result in the development of different resistance profiles.[39,42,50,56] Two nucleotide mutations must occur at position R155K (CGG → AAG) for resistance to develop in genotype 1b, whereas only 1 mutation is required in genotype 1a (R155K [AGG → AAG]).[20,39,55,62] Hence, in vivo, genotype 1a resistance tends to be predominated with R155K/T, V36M, and T54A/S mutations; genotype 1b, on the other hand, most often reveals D168A/V, A156S, T54A/S, and I170A as common mutations.[42]

Some of these mutations affect the active site of boceprevir, rendering the drug ineffective, without necessarily affecting viral substrate binding.[5,58,60,63,64] Boceprevir protrudes extensively from substrate envelope regions that correlate with known sites of resistance mutations.[61] Many of the primary drug resistance mutations can be explained by disruption of atomic interactions at the catalytic triad site.[40,61] In addition, mutations outside of the substrate envelope may also affect the inhibitor's affinity without altering the biological function of the enzyme.[61] Among the host of DAAs being developed, the NS3 protease inhibitors and the NS5A inhibitors seem to have low genetic barriers to resistance; single amino acid substitutions result in compromised binding ability of these compounds.[20,40,62] At present, it is unclear the extent to which mutations within the NS4A cofactor sites may also contribute to resistance.[39] Combination therapy with peginterferon greatly reduces the potential for the emergence of resistance, as many resistant variants remain sensitive to peginterferon.[4,7,41,57,65] Mathematical modeling indicates that at least triple DAA therapy, with nonoverlapping resistance profiles, will be required to prevent resistance emergence.[20,42,55,62–64,66]

Resistance to boceprevir is rare in treatment-naive patients.[4,39,56] The effect of IL28 genotype on resistance development has yet to be analyzed.[35] Naturally occurring resistance is reported to range anywhere from <1% to 10%.[37,55,56,67] For example, there is report of a treatment-naive, genotype 1a patient with A156T present with a 0.78% frequency.[59,60] Nonetheless, this small percentage actually equates to a large number of RNA molecules, $\sim 10^6$ to 10^7 RNA molecules per gram of liver carrying this mutation.[59] The low incidence of resistance may be related to the replicative fitness of these variants.[9,40,56,58,61,64] Nonetheless, it has been seen that some treatment-naive patients are host to a variety of mutations at baseline; for example, 1 patient was found to have V36A, A156V, and R155S at baseline, whereas another patient in the same study had V36A, A156T, and T54A at baseline.[68] Of greater concern, mutants resistant to NS3 protease and NS5B nonnucleoside inhibitors have been detected as the pre-existing dominant strain in a small percentage of patients (0.2%–2.8%), which may have significant implications in the future of HCV treatment.[55–58]

Viral resistance develops rapidly with NS3 protease inhibitor monotherapy, even within the first days of treatment.[5,42,55,57] The initial drop in HCV RNA is attributable to inhibition of wild-type virus, which leads to the uncovering of pre-existing resistant variants that cause treatment failure with subsequent cross-resistance.[37,39,40,56,60,67] Single mutations may be selected initially and then replaced by more fit combination mutants.[60] Mutations conferring resistance to NS3 protease inhibitors have been selected in vitro, with these same mutations observed in clinical trial patients as well.[58,65] A156T confers the highest level of resistance to boceprevir.[35,39,58,59,65,69] However, replicons carrying the A156T mutation were significantly less fit than replicons with other mutations.[5,65,70] Overall, there is an inverse correlation between resistance potential and variant fitness (ie, the 156 mutation had the lowest relative fitness).[39,55,64] In vitro replicon fitness of various mutants follows this order: A156T < R155K = V36M ≤ T54A.[58] However, some mutations, such as Q41R, significantly increase replicon fitness. All of the following mutations confer low to medium levels of resistance to boceprevir: V36M/A, T54A/S, V55A, R155G/K/L/T, A156S, and V170A/T.[35,36,39,45,55,58,59,63,64,69] However, some variants that show low resistance in vitro may be more damaging in vivo.[40] Novel mutations with unknown clinical significance at present have also been isolated at V48I, V55A, T72I, and I153V.[39]

Overall, with boceprevir monotherapy, mutations have been detected at the following positions: 7, 8, 14, 18, 33, 36, 46, 48, 49, 54, 55, 61, 71, 72, 80, 86, 87, 91, 117, 119, 122, 127, 131, 146, 147, 153, 155, 156, 170, 174, and 179.[39,45,63–65] In a previous nonresponse patient treated in a Phase Ib trial, the following mutations were detected after collecting ~90 clones: V36I, Q41R, F43S/C, T54A, V170A (before treatment with boceprevir), and A156S (and the end of follow-up).[56] Major mutations observed in Phase II trials included R155K (64%), T54S (54%), and V36M

(54%).[4,10,26,50] Mutations observed in <25% of the obtained samples included T54A, V55A, R155T, A156S, V158I, and V170A.[10,26] In clinical trials, resistant variants were found in 28% to 47% in patients who had a <1-$\log_{10}$ decrease in HCV RNA after SOC lead-in, compared with only 4% to 8% in patients who had a ≥1-$\log_{10}$ decrease in HCV RNA.[7,10,13,24,45] Nearly 100% (107 of 109) of patients who developed variants with reduced susceptibility to boceprevir experienced nonresponse, relapse, or breakthrough.[27]

The fold increase in resistance with double mutations was approximately equal to the multiplicative product of individual mutations.[58,65] However, the replicon fitness of these mutants was typically lower than those of single mutants (ie, V36M + A156T).[58] Nonetheless, double mutations observed after Phase Ib trials with boceprevir included T54S + R155K and V36M + R155K.[57] These double mutations, and others seen in vitro (A156T + P89Q, A156T + Q86P), may be the evolution of resistant variants coupled with compensatory mutations to confer higher replicative fitness and thus result in long-term persistence at higher frequencies.[40,55–57,59] It is possible that the R155K substitution present in conjunction with other substitutions may allow improved fitness.[39,56] A second mutation would improve relative fitness (V36A + R155K).[39]

In patients failing to improve with triple therapy, the dominant viral population at time of breakthrough or relapse was resistant to the protease inhibitor, with subsequent disappearance of this variant as it was replaced by the wild-type virus over time without drug selection pressure.[4,5,24,40,50,57,60,63] This finding reinforces the importance of adhering to treatment futility recommendations for DAAs in patients who have inadequate viral responses as the development of treatment-emergent resistance is expected if therapy were to continue. Triple HCV therapy with boceprevir should be discontinued in all patients with either HCV RNA levels ≥100 IU/mL at treatment week 12 or detectable HCV RNA levels at treatment week 24.[18] Similarly for telaprevir, HCV therapy should be discontinued in all patients with either HCV RNA levels >1000 IU/mL at treatment week 4 or week 12 or detectable HCV RNA levels at treatment week 24.[19] Without the drug selection pressure, the reversion to wild-type virus took place within a few weeks to months, depending on the type of mutation; however, some variants may persist for even longer.[4,5,24,37,50] For example, the median time for reversion for V36M was 0.5 year, the median time for R155K was 1.19 years, and the median time for T54S was 1.43 years.[4,5,24,50] It is likely that these variants remain at low levels, beyond the limit of detection, potentially limiting future treatment options.[5,24] However, to date, none of these patients has been rechallenged with an alternative NS3 protease inhibitor.[50] Interestingly, the mutational pattern at long-term follow-up was not easily predicted from end-of-treatment analyses, as mentioned earlier.[56,57] Because HCV is a RNA virus reproducing entirely in the cytoplasm, no true archiving takes place, as with retrovirus HIV, so it may be possible that resistant variants are completely cleared due to competition with more fit, drug-sensitive viruses.[40]

Key mutations in boceprevir exhibit cross-resistance with other agents.[5,39,40,49] The most frequent telaprevir substitution is R155K.[35,62,70] Other mutations that have been seen in clinical trials include V36A/M, R155K, T54A, A156S/T/V, and V36M + R155K.[50,56] Similar to boceprevir, A156T/V or double mutations at position 36 + 155 or 36+ 156 confer high-level resistance to telaprevir, and V36A/M, T54A, R155K, and A156S confer low-level resistance to telaprevir.[7,39,56,58,69] However, Q41R, F43C/S, and V170A affect boceprevir more than telaprevir.[39,58] These differences are probably due to the structural differences between the 2 agents, affecting van der Waals interactions differently with the enzyme.[58] This is important as the development of other DAAs continue. A156T also confers a high level of resistance to SCH 900518 (narlaprevir), with additional resistance noted with the rather benign (to boceprevir) mutations R155K and A156S/T.[35,65] Although boceprevir remained fully active against mutations at D168, the mutations D168V and D168I led to significant decreases in the activity (~2000-fold) of TMC 435 (medivir), BI 201335, and ITMN 191 (danoprevir).[40,56,63,69,70] Reduced susceptibility was seen in MK 7009 (vaniprevir) with the following mutations: F43S, Q41R, R155K, A156T, and D168Y.[56,63,69] HCV nucleoside inhibitors, which seem to possess a higher genetic barrier to resistance, show less cross-reactivity with NS3 protease inhibitors.[66] NM 107 had unaltered activity against HCV replicons carrying boceprevir resistance (A156T/S, V170A, and T54A), and boceprevir had unaltered activity against HCV replicons carrying nucleoside resistance (S282T).[66] However, resistance to MK 5172 has been noted at position 156.[40] Currently, resistance

testing at baseline is not recommended in clinical practice because there are insufficient data to determine the cost-effectiveness of such measures.[55,63] With future combination regimens with DAAs, this standard of practice may change.

Drug Interactions

Boceprevir is metabolized via CYP3A4/5 and the aldo-keto reductase pathway, specifically AKR1C2 and AKR1C3.[6,20,34,44] Boceprevir is also a substrate of p-glycoprotein.[6,53] A brief summary of potential drug interactions with boceprevir is provided in Table V.[6]

In vitro studies with known CYP3A4/5 inhibitors, such as ketoconazole, described the decreased formation of boceprevir metabolites by 36% to 68%.[4,34] In vitro studies exhibited 100% inhibition of boceprevir with ritonavir, with a small increase in boceprevir plasma trough concentrations (4%); however, overall boceprevir drug exposure was decreased by 19%.[6,34,71] Likewise, potent inducers of CYP3A4/5, such as St. John's wort or rifampin, should also be avoided to reduce the potential of decreased boceprevir levels and subsequent treatment failure.[6,50] The coadministration of boceprevir and efavirenz resulted in decreased boceprevir plasma trough concentrations by 44% and decreased drug exposure by 19%, hence precluding this combination in HCV/HIV coinfected patients at present.[6,50,65,71]

Table V. Potential drug interactions with boceprevir.[6]

Contraindicated
Anticonvulsants (carbamazepine, phenobarbital, phenytoin)
Antimycobacterials (rifampin, rifabutin)
β-receptor agonists (salmeterol)
HMG-CoA reductase inhibitors (simvastatin, lovastatin)
PDE-5 inhibitors, in pulmonary hypertension (sildenafil, tadalafil)
Caution
Antiarrhythmics (amiodarone, flecainide)
Antidepressants (trazodone)
Antifungals (ketoconazole, itraconazole, posaconazole, voriconazole)
Anxiolytics (alprazolam)
Corticosteroids, inhaled (budesonide, fluticasone)
Dihydropyridine calcium channel blockers (nifedipine, felodipine, nicardipine)
HMG-CoA reductase inhibitors (atorvastatin)
Immunosuppressants (cyclosporine, tacrolimus)
Opioids (methadone, buprenorphine)
PDE-5 inhibitors, in erectile dysfunction (sildenafil, tadalafil, vardenafil)
Warfarin

HMG-CoA = 3-hydroxy-3-methylglutaryl coenzyme A; PDE-5 = phosphodiesterase type 5.

Boceprevir additionally acts as a strong, reversible inhibitor of CYP3A4 and p-glycoprotein.[4,6,44,50] Hence, current recommendations contraindicate the coadministration of boceprevir with drugs, such as simvastatin or certain immunosuppressive agents, that are highly dependent on CYP3A4/5 for clearance and in which high levels are associated with serious or life-threatening effects.[6,50,72]

Because biotransformation is conducted via 2 different major enzyme pathways, boceprevir may be less affected by CYP3A4 interactions.[34] In studies conducted with aldo-keto reductase inhibitors, such as ibuprofen, boceprevir exposure was not significant despite the inhibition of metabolites by 55% to 91%.[6,34] This finding may possibly be related to the fact that various isoforms of aldo-keto reductase are present in multiple tissues, resulting in decreased saturation.[6]

Aside from pharmacokinetic interactions, certain pharmacodynamic interactions must be considered as well. Zidovudine should be avoided due to an increased potential for anemia.[6,73] Certainly, because boceprevir is currently indicated to be given with peginterferon and ribavirin, this remains a strong consideration. Medications such as efavirenz, which might have cumulative psychiatric effects with peginterferon, may be an additional area of pharmacodynamic concern.[73]

Dosage and Administration

Boceprevir is available as 200-mg capsules.[18] The recommended dosage of boceprevir is 4 capsules (800 mg) taken TID (every 7–9 hours). The dose of boceprevir should not be adjusted to manage adverse drug reactions.[18,44] In clinical trials, depending on the severity of adverse event, investigators were able to adjust the dose of peginterferon alfa-2b (hold for up to

2 weeks or 2-step reduction to 1 and 0.5 μg/kg) or ribavirin (step-wise 200 mg reductions).[13,26] Patients with contraindications to or toxicity associated with peginterferon or ribavirin should not receive boceprevir as monotherapy.[44,74] Each dose of boceprevir should be taken with food because of an increased AUC by up to 65%.[18] Adherence to time interval is especially important in treatment-experienced patients, in whom <60% adherence to time intervals resulted in decreased rates of SVR.[75]

The clinical trials with boceprevir included a 4-week lead-in period with peginterferon alfa-2b and ribavirin.[26] There is a recently completed trial using boceprevir with peginterferon alfa-2a, the results of which are expected to be similar.[4,24] The theory behind this choice was to allow both backbone components to reach optimum steady-state concentrations, resulting in a significant HCV viral load reduction, with the intention of therefore reducing the likelihood of the emergence of drug-resistant mutations.[7,10,26,35,36,38,45,67] However, the true benefit of this lead-in strategy may be its utility as an early on-treatment predictor of response to guide consideration for the addition of DAAs.[7,10,20,24,25,44] Moreover, this lead-in period can provide some indication of patient tolerability and adherence.[16,25]

The results of SPRINT-2 suggest that non-black patients with RVR can be treated with peginterferon alfa-2b and ribavirin without compromising chances of SVR (albeit, at the cost of a longer course of treatment but with the potential benefit of decreased adverse effects and health care costs).[16,46] Data from previous work also suggest that treatment-naive patients with IL28B C/C genotype, indicating favorable response to SOC, could potentially be treated similarly by using dual therapy.[16]

However, the new treatment paradigm for chronic HCV genotype 1 infection is RGT. RGT is based on the lower limit of detection, not the lower limit of quantitation; the 2 terms are not synonymous, and further analysis suggests that differences between the measures are clinically relevant.[76] In treatment-naive patients without cirrhosis, HCV RNA undetectable at weeks 8 and 24 results in 28 weeks of therapy (24 weeks of triple therapy).[10,16,24,25,44,50,53] For treatment-naive patients whose levels remain detectable at week 8 but are undetectable at week 24, triple therapy continues until week 36 (32 weeks of triple therapy), followed by SOC through week 48 (12 additional weeks of peginterferon and ribavirin).[10,25,44,50,53] **Table VI** provides an algorithm summarizing RGT.[18]

In treatment-experienced patients (previous partial response or previous relapse), patients receive 36 weeks of treatment (32 weeks of triple therapy) if HCV RNA are undetectable at weeks 8 and 24.[10,13,16,24,50,53] Similarly, for treatment-experienced patients whose levels remain detectable at week 8 but are undetectable at week 24, triple therapy continues until week 36 (32 weeks of triple therapy), followed by SOC through week 48

Table VI. Response-guided therapy treatment algorithm.[18]

Patient Group	Treatment Response (HCV RNA)			Treatment Duration*
	Week 8	Week 12	Week 24	
Treatment-naive	ND	ND	ND	28 weeks†
	Detectable	≤100 IU/mL	ND	48 weeks†
Prior partial response/prior relapse	ND	ND	ND	36 weeks*
	Detectable	≤100 IU/mL	ND	48 weeks†
Compensated cirrhosis				48 weeks†‡

HCV = hepatitis C virus; ND = nondetectable.

*All treatment regimens begin with a 4-week lead-in period with peginterferon and ribavirin, without boceprevir. Peginterferon and ribavirin are continued, with boceprevir, for the remaining duration of treatment. Boceprevir is stopped at week 36 if treatment duration is 48 weeks.

†If HCV RNA >100 IU/mL at week 12, triple therapy should be discontinued. If HCV RNA detectable at week 24, triple therapy should be discontinued.

‡Boceprevir is continued for 44 weeks after the 4-week lead-in period with peginterferon and ribavirin.

(12 additional weeks of peginterferon and ribavirin).[10,13,24,50,53] All patients with compensated cirrhosis are treated for 48 weeks (44 weeks of triple therapy).[13] Discontinuation of boceprevir is recommended in all patients with HCV RNA ≥100 IU/mL at treatment week 12 or detectable HCV RNA at week 24.[13,18,25]

Further information regarding dosing in the following populations is necessary: HIV coinfection, pre- and post-transplant patients, low platelets, decompensated liver disease/cirrhosis, renal failure, and pediatrics.[16,18,43,74]

Pharmacoeconomic Considerations

The pharmacoeconomics of boceprevir therapy have been examined in the published literature.[53,77,78] Cammà et al[77] created a Markov decision model to assess the cost-effectiveness of triple therapy for HCV (peginterferon-alfa, ribavirin, and boceprevir or telaprevir) versus SOC (peginterferon, ribavirin) dual therapy in treatment-naive patients with genotype 1 viruses. Their model consisted of treatment-naive white patients aged 50 years, weighing 70 kg, with genotype 1 HCV, and a Metavir score of F2 for liver fibrosis over a time horizon of 20 years. The Markov decision model used 5 competing strategies: (1) boceprevir RGT; (2) boceprevir IL28B genotype–guided therapy; (3) boceprevir RVR-guided therapy; (4) telaprevir RGT; and (5) telaprevir IL28B genotype–guided therapy, whereby the IL28B genotype was a predictor of virologic response to therapy. Outcomes analyzed included life-years gained (LYG), costs (in 2011 euros), and incremental cost-effectiveness ratio. According to Cammà et al, the most effective and cost-effective strategies were boceprevir RVR-guided therapy and telaprevir IL28B genotype–guided therapy, which resulted in 4.04 and 4.42 LYG and incremental cost-effectiveness ratios of €8.304 per LYG and €11.455 per LYG, respectively. This model was highly sensitive to IL28B genotype, likelihood of RVR and SVR, and prices of boceprevir/telaprevir. Cammà et al concluded that triple therapy was cost-effective when compared with dual therapy.

The discount rate is the pharmacoeconomic method used to convert future clinical benefits into present value. Because the clinical benefit of HCV treatment may take place years after therapy, another study[78] examined the long-term benefits of dual therapy (SVR set at 40%) compared with triple therapy (SVR set at 70%) in simulation models with a choice of different values for yearly discount rates. Messori el al[78] accomplished this by measuring the long-term benefits under different conditions based on their standard model and used quality-adjusted life-years (QALYs) to quantify the benefits. The gain they saw with triple versus dual therapy decreased from 0.45 QALYs with a 0% discount rate to 0.22 QALYs with a 6% discount rate. As expected, Messori et al found that varying the discount rate affected the magnitude of estimated benefit and therefore should be analyzed closely when determining the value-based price for the newer HCV treatments.

Tungol et al[53] identified factors that decision makers and payers should consider before making a formulary choice of which protease inhibitor to include. In addition to SVR rates compared with SOC, decision makers should consider increased treatment costs, patient management and adherence, comparative safety and efficacy, and appropriate utilization of management controls.[53]

Currently, there are 2 protease inhibitors available as part of a triple-therapy regimen for patients with genotype 1 chronic HCV infections: boceprevir and telaprevir.[18,19] The 2011 average wholesale prices (in US $) for a course of each agent are listed in **Table VII**.[79] The cost for a course of boceprevir therapy varies based on length

Table VII. Average wholesale price (AWP) of boceprevir and telaprevir treatment courses.[79]

Generic (Brand) Name	Regimen	Acquisition Cost (AWP, 2011 US $)
Boceprevir*	800 mg PO q8h × 24 weeks	31,671.36
Boceprevir	800 mg PO q8h × 32 weeks	42,228.48
Boceprevir	800 mg PO q8h × 44 weeks	58,064.16
Telaprevir†	750 mg PO q8h × 12 weeks	59,038.56

*Trademark: Victrelis® (Merck & Co, Inc, Whitehouse Station, New Jersey).
†Trademark: Incivek® (Vertex Pharmaceuticals Inc, Cambridge, Massachusetts).

of therapy according to RGT (range, $31,671.36–$58,064.16). A full course of therapy for telaprevir is always 12 weeks ($59,038.56). To date, there are no head-to-head comparisons of the 2 available agents. As described in the previous pharmacoeconomic studies,[53,77,78] in addition to drug costs, multiple other factors must be considered to justify the cost-effectiveness of therapy. For example, patient adherence (a difficult measure even in clinical trials) is a crucial factor to consider because nonadherence to these agents will lead to treatment failure and resistance development. It will be prudent to believe that successfully treating eligible patients with these new DAAs will not only result in clinical benefits but cost savings from reduced morbidity as well. At this time, additional pharmacoeconomic studies are necessary to examine this further.

DISCUSSION

A paradigm shift in the management of chronic HCV infection occurred with the introduction of compounds that were specifically targeted as antiviral therapy for hepatitis C.[6,20–22] Since 2001, the SOC with peginterferon and ribavirin only offered low cure rates (SVR range, 30%–50%) for patients infected with genotype 1 HCV, the predominant genotype seen in the United States.[4–7,13,15] With the addition of boceprevir to the HCV armamentarium, the SVR rates have been increased to ~70% for treatment-naive and treatment-experienced patients.[13,25] With >50 DAAs at varying stages of development, boceprevir offers a glimpse of hope for what the next few years may offer in HCV management.[20] Boceprevir is a potent inhibitor (K_i of 14 nM[18,27,28]) of NS3 protease indicated for the treatment of chronic HCV genotype 1 infection in combination with peginterferon and ribavirin for treatment-naive patients and patients who failed to improve with previous interferon and ribavirin treatment.[18]

Results of Phase III clinical trials allowed for important insights in the utilization of boceprevir. In addition to higher SVR rates with boceprevir triple therapy, SPRINT-2[1] and RESPOND-2[2] used a 4-week lead-in phase with peginterferon and ribavirin. The lead-in phase is crucial in decreasing viral relapse, decreasing emergence of resistance, predicting patients' likelihood of SVR, weighing the risks and benefits of continuing therapy, and addressing adherence.[7,10,20,26,35,67] With the exception of compensated cirrhotic patients (44 weeks of triple therapy after a 4-week lead-in), RGT is indicated for most patients eligible for boceprevir therapy, allowing for a chance of shorter therapy duration.[13,18] Treatment futility rules at weeks 12 and 24 are important to follow to avoid unnecessary drug exposure and adverse events.

Boceprevir was well tolerated in clinical trials; however, rates of anemia (defined as Hgb <10 g/dL) and dysgeusia were higher in patients who received boceprevir (49%–55% vs 20%–34% [$P < 0.001$]; 27%–49% vs 9%–29% [$P < 0.001$]).[13,24–26]

Boceprevir should not be used in nongenotype 1 HCV infections or in patients with contraindications to peginterferon or ribavirin therapy. Further information regarding dosing in the following populations is necessary: HIV coinfection, pre- and posttransplant patients, low platelets, decompensated liver disease/cirrhosis, renal failure, and pediatrics.

Precautions for drug interactions will continue to grow as new studies are available because boceprevir is metabolized via CYP3A4/5 and the aldo-keto reductase pathway and is also a substrate of p-glycoprotein.[6,20,34,44,53] Drug–drug interactions with boceprevir and many other drugs have not yet been fully elucidated. Practitioners should continue to seek out additional information as more data become available. The close management of adherence, adverse drug events, and drug interactions will become increasingly important as complexities arise, clearing an excellent niche for specialists with expertise in the management of HCV.

CONCLUSIONS

Boceprevir is a covalent reversible inhibitor of the HCV NS3 serine protease indicated for the treatment of chronic HCV genotype 1 infection in combination with peginterferon and ribavirin. After almost a decade of no new HCV drugs since the introduction of pegylated interferon in 2001, boceprevir is a welcome addition in our battle against HCV eradication. It is currently 1 of only 2 FDA-approved DAAs available to treat adult (age ≥18 years) patients with compensated liver diseases who are either treatment naive or previously failed to improve with interferon and ribavirin therapy.

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CONFLICTS OF INTEREST

The authors have indicated that they have no conflicts of interest regarding the content of this article.

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