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Boceprevir

Abstract

Boceprevir (SCH 503034; SCH-503034) is a peptidomimetic NS3/4A serine protease inhibitor, representing a new class of hepatitis C virus (HCV) inhibitors. It is being developed by Merck & Co. as part of a combination therapy regimen for the treatment of HCV infections. In two phase III trials, the HCV RESPOND-2 and HCV SPRINT-2 trials, the primary endpoints were met. Phase III development continues in the US, Europe, and Canada. This review looks at the key development milestones and therapeutic trials of this drug.

1. Introduction

Merck & Co. is developing boceprevir, an orally administered, selective inhibitor of hepatitis C protease non-structural protein 3, as part of a combination therapy regimen for the treatment of hepatitis C virus (HCV) infections. Phase III development is ongoing in the US.

Boceprevir is a ketoamide that reversibly binds the NS3 protease active site serine. This mechanism of action is distinct from existing therapies; the drug represents a new class of HCV inhibitors. The company is initially focusing on the treatment of patients with HCV genotype 1 who have not responded to combination therapy with pegylated interferon (peg-IFN) and ribavirin.

The compound was previously being developed by Schering-Plough; however, the company combined with Merck & Co. in November 2009 under the name Merck.[1]

1.1 Key Development Milestones

Both the phase III HCV RESPOND-2 and HCV SPRINT-2 trials met their primary endpoints of significantly more patients achieving sustained virologic response (SVR) with boceprevir plus standard of care (SOC) [peg-IFN alfa-2b plus ribavirin], compared with SOC alone. Based on these data, Merck plans to submit a rolling new drug application (NDA) for boceprevir in the treatment of chronic HCV genotype 1 infections sometime during 2010.[2] Boceprevir was granted fast-track status by the US FDA for the treatment of chronic hepatitis C in late January 2006.[3]

The HCV RESPOND-2 and HCV SPRINT-2 trials each evaluated two treatment strategies with boceprevir. Both evaluated 48 weeks' treatment for all patients with response guided therapy, in which patients with undetectable virus at week 8, and then again at later timepoints, were able to cease all treatment at 36 weeks and 28 weeks in the RESPOND-2 and SPRINT-2 studies, respectively. RESPOND-2 enrolled 403 patients whose prior therapy had failed, whereas SPRINT-2 enrolled 1097 treatment-naive patients; both trials were conducted in the US and globally and have now been completed.[2,4-6]

Schering-Plough is also conducting a phase III trial investigating the efficacy and tolerability of

boceprevir in combination with peg-IFN alfa-2a and ribavirin in 198 subjects with HCV genotype 1 infection that has failed prior peg-IFN/ribavirin therapy (NCT00845065). Study completion is expected in November 2010. Another phase III trial is evaluating the efficacy of boceprevir in combination with peg-IFN alfa-2b and ribavirin in treatment-naive patients with chronic hepatitis C (NCT01023035). The study enrolled 685 subjects and is expected to reach completion in November 2011. A 3-year follow-up study is being conducted in patients with chronic HCV infection who were previously treated with boceprevir plus peg-IFN alfa-2b with or without ribavirin (NCT00689390).

Final results from part I of the phase II HCV SPRINT-1 (HCV Serine Protease Inhibitor Therapy-1; NCT00423670) were reported in November 2008. This study evaluated boceprevir (800 mg three times daily) in combination with peg-IFN alfa-2b plus ribavirin in 595 patients in the US, Canada, and the EU. In part II of the study, boceprevir was administered in combination with low-dose ribavirin plus peg-IFN alfa-2b. Final results of part II were reported in April 2009.[6-8]

Following positive phase I results, a phase II trial was initiated in September 2005 to evaluate boceprevir (100–800 mg three times daily) in combination with peg-IFN alfa-2b, with and without added ribavirin (NCT00160251). The trial enrolled 357 patients with chronic hepatitis C (genotype 1) whose previous treatment with peg-IFN alfa plus ribavirin had failed. This trial took place in the US and Europe, and results have been reported.[9,10]

2. Scientific Summary

2.1 Pharmacokinetics

2.1.1 Clinical

In a trial among 54 volunteers, boceprevir (50–800 mg) was rapidly absorbed following oral administration with time to maximum concentration (t_{max}) values ranging from 1 to 2.25 hours across six dosing levels. Plasma concentrations of the drug declined in a biphasic manner with elimination half life ($t_{½}$) values ranging from 7 to 15 hours.[11]

In a clinical trial among 61 patients with HCV-1 infection whose prior peg-IFN alpha therapy had failed, boceprevir (100–400 mg twice daily, and 400 mg three times daily) was shown to be rapidly absorbed following oral administration, with a mean t_{max} value of 1–2 hours across the dose range.[12]

2.1.2 Preclinical

Boceprevir demonstrated oral bioavailabilities of 26% and 30% in rats and dogs, respectively.

Table I. Features and properties

Alternate names	SCH 503034; SCH-503034
Originator	Schering-Plough
Highest development phase	III (Canada, EU, US)
Active development-indications	Hepatitis C
Class	Imino acids, small molecules
Mechanism of action	Hepatitis C protease inhibitors, hepatitis C virus NS3 protein inhibitors
Chemical name	(1*R*,2*S*,5*S*)-*N*- [3-Amino-1-(cyclobutylmethyl)-2,3-dioxopropyl] -3- [(2*S*)-2- [[(1,1-dimethylethyl)carbamoyl] amino] -3,3-dimethylbutanoyl] -6,6-dimethyl-3-azabicyclo [3.1.0] hexane-2-carboxamide
Molecular formula	C_{27} H_{45} N_5 O_5
CAS registry number	394730-60-0
Route of administration	PO
Pharmacodynamics	Exhibits antiviral activity alone and in combination with interferon-alpha *in vitro* and *in vivo;* displays dose-related antiviral activity in patients with hepatitis C virus-1 infection; specific resistance mutations to boceprevir declined at different rates, this may reflect the relative fitness of the mutants
ATC Codes	
WHO ATC code	J05A-E (protease inhibitors)
EphMRA ATC code	J5B1 (viral hepatitis products)

The compound had a dissociation constant of 17 nmol/L and was highly selective for HCV.[13]

2.2 Adverse Events

2.2.1 Hepatitis C Virus (HCV) Infections

Phase III

***HCV RESPOND-2*:** The five most common treatment-emergent adverse events (TEAEs) in the boceprevir 48-week treatment group, boceprevir response-guided therapy group and control group, respectively, were fatigue (57%, 54%, and 50%), headache (40%, 43%, and 49%), nausea (42%, 44%, and 38%), anemia (47%, 43%, and 20%), and dysgeusia (45%, 43%, and 11%). Treatment discontinuations due to anemia were 3% and 0% in the two respective boceprevir groups, compared with 0% in the control group. Treatment discontinuations due to adverse events (AEs) overall were 12% and 8% for the respective boceprevir groups, compared with 3% in the control group. The HCV RESPOND-2 study was conducted in 403 patients with chronic HCV genotype 1 infections who had previous failed prior therapy with peg-IFN and ribavirin.[2]

***HCV SPRINT-2*:** In the boceprevir 48-week group, boceprevir response-guided therapy group and control group, respectively, the five most common TEAEs reported during the study were fatigue (57%, 53%, and 60%), headache (46%, 46%, and 42%), nausea (43%, 48%, and 42%), anemia (49%, 49%, and 29%), and pyrexia (32%, 33%, and 33%). Treatment discontinuations due to anemia were 2% for each of the boceprevir groups, compared with 1% in the control group. Treatment discontinuations due to AEs overall, were 16% and 12% for the respective boceprevir groups, compared with 16% in the control group. The HCV SPRINT-2 trial was conducted in 1097 treatment-naive patients with chronic genotype 1 HCV infections.[2]

Phase II

Final results from the phase II trial (HCV SPRINT-1) have shown that boceprevir, with or without peg-IFN alfa-2b plus ribavirin, was generally well tolerated in 595 treatment-naive patients with chronic genotype 1 hepatitis C. The most common AEs reported in the boceprevir arms were fatigue, anaemia, nausea, and headache. No increase in skin AEs (rash or pruritus) was reported in the boceprevir-treatment arms compared with the peg-IFN alfa-2b plus ribavirin control arm. Treatment discontinuations due to AEs ranged from 9% to 19% in the boceprevir arms, compared to 8% in the peg-IFN alfa-2b plus ribavirin control arm. These results were consistent with interim results, which showed that treatment discontinuations due to AEs were 8–15% for boceprevir treatment arms and 8% for the control arm. The most common AEs leading to discontinuation in the boceprevir arms were fatigue (2%), nausea (2%), depression, neutropenia, and anemia (<1% each). Incidence of rash-related AEs was similar between the boceprevir and control groups. Treatment-related anemia appeared to be associated with higher SVR rates.[7-9,14]

In a clinical trial among 61 patients with HCV-1 infection whose prior peg-IFN alpha therapy had failed, boceprevir (100–400 mg twice daily, and 400 mg three times daily) was shown to be well tolerated at all dose levels. AEs were mild or moderate and the safety profiles of patients who received boceprevir and placebo were similar. The most frequently reported AE was headache (12% and 29% for boceprevir and placebo, respectively).[12]

2.2.2 Healthy Volunteers

A phase I trial in 54 volunteers showed that the safety profiles of boceprevir (n = 36) and placebo (n = 18) were similar.[11]

2.3 Pharmacodynamics

2.3.1 Viral Infections

Clinical

Specific resistance mutations to boceprevir declined at different rates in data from an analysis of results from two phase II studies in patients with HCV. Samples from 604 patients (treatment-naive or peg-IFN alfa-2b plus ribavirin failures) who received boceprevir plus peg-IFN with/without ribavirin were evaluated in the analysis. No late relapse was confirmed in the 290 patients who had previously obtained SVR. A further 172 patients who had not achieved SVR

were followed-up for ≥2 years – these patients were from a trial in treatment-naive patients (38/373; 16%) and a trial in patients whose previous treatment had failed (134 of 226; 59%); none of these patients had received the current regimen. A total of 18 boceprevir resistant mutations were observed in the following proportions: R115K 64%; T54S 54%; V36M 54%; T54A 22%; other identified mutations were reported at rates of <9% each. The rate of return to wild-type NS3 1-81 sequence was higher for patients with V36M mutations compared with those who had T54S or R155K mutations. This variation in the rate of mutational decline may reflect the relative fitness of the mutants.[15]

Patients displayed resistant variants of the NS3 protease gene following boceprevir monotherapy, which was mimicked during re-treatment in combination with peg-IFN alfa-2b. This clonal analysis was performed on samples obtained from patients involved in a single-arm study comparing boceprevir alone or in combination with peg-IFN alfa-2b. Mutations in the NS3 protease were detected following boceprevir treatment and remained detectable in some patients following therapy with peg-IFN alfa-2b (alone or in combination).[16]

In patients with chronic hepatitis C genotype 1 treated with boceprevir monotherapy or in combination with peg-IFN, follow-up data for up to 4 years revealed long-term persistence of resistance mutations within the NS3 protease. After 1-year follow-up, high frequencies of resistant variants were detected in two patients.[17]

In a clinical trial among 61 patients with HCV-1 infection whose prior peg-IFN alpha therapy had failed, boceprevir (100–400 mg twice daily, and 400 mg three times daily) showed dose-related antiviral activity that was first detectable at 24 hours post-dose.[12]

An open-label study in patients with HCV-1 infection and prior peg-IFN alfa failure demonstrated that boceprevir in combination with peg-IFN alpha substantially reduced HCV RNA.[18]

Preclinical

Cell culture replicon studies demonstrated that the combination of boceprevir and valopicitabine showed dose-dependent enhancement of replicon inhibition, compared with the effect of each inhibitor used alone. In cross-resistance studies, boceprevir showed similar antiviral activity (50% effective dose [EC_{50}] 1.5–2 μmol/L) against wild-type and boceprevir-resistant replicons. Boceprevir showed similar activity (EC_{50} 0.3–0.4 μmol/L) against wild-type and valopicitabine-resistant replicons. When tested against known resistance mutations, each compound showed a 5- to 125-fold loss in susceptibility. In selection experiments, the combination of boceprevir and valopicitabine significantly reduced the frequency of resistant colonies in a dose-dependent manner, compared with each inhibitor used alone. No cytotoxicity was observed.[19]

Boceprevir showed time-dependent inhibition of single chain NS3 *in vitro*, with a binding constant of approximately 14 nmol/L. The compound suppressed HCV replicon synthesis following 72 hour exposure, with 50% and 90% inhibitory dose values of 200 nmol/L and 400 nmol/L, respectively. Boceprevir also showed antiviral activity when administered in combination with IFN alpha in the HCV replicon assay.[20]

2.4 Therapeutic Trials

2.4.1 Viral Infections

Phase III

***HCV RESPOND-2*:** Significantly more patients treated with boceprevir plus standard therapy (peg-IFN alfa-2b and ribavirin) achieved SVR than those treated with standard therapy alone, in the phase III RESPOND-2 study in patients with chronic HCV genotype 1 infections whose prior therapy had failed. In this study, patients (n = 403) were randomized into three groups (48 weeks control, 48 weeks control plus boceprevir, control plus boceprevir using response-guided therapy) in a 1 : 1 : 1 ratio. The 48-week treatment period consisted of a 4-week lead-in with 1.5 μg/kg/week of peg-IFN alfa-2b and ribavirin 600–1400 mg/day, followed by the addition of boceprevir 800 mg three times a day for 44 weeks. In the response-guided therapy group, patients with undetectable virus at week 8 and again at certain points later in the studies were able to stop

all treatment at 36 weeks. Patients who did not meet these criteria continued treatment with standard therapy alone for a total treatment duration of 48 weeks. Control group recipients received standard therapy at the doses described above plus placebo for 48 weeks. In the boceprevir 48-week and response-guided therapy groups, 66% and 59% of patients achieved SVR, respectively, compared with 21% of patients in the control group ($p < 0.0001$ for both, intent-to-treat [ITT] analysis).[2]

***HCV SPRINT-2*:** Significantly more patients treated with boceprevir plus standard therapy (peg-IFN alfa-2b and ribavirin) achieved SVR than those treated with standard therapy alone, in the phase III SPRINT-2 study in treatment-naive patients with chronic HCV genotype 1 infections. In this study, patients ($n = 1097$) were enrolled into two cohorts, one consisting of 938 non-African American patients, and the other with 159 African American patients. Patients were then randomized into three treatment groups (48 weeks control, 48 weeks control plus boceprevir, control plus boceprevir using response-guided therapy) at a 1 : 2 : 2 ratio. The 48-week treatment period consisted of a 4-week lead-in with 1.5 μg/kg/week of peg-IFN alfa-2b and ribavirin 600–1400 mg/day, followed by the addition of boceprevir 800 mg three times a day for 44 weeks. In the response-guided therapy group, patients with undetectable virus at week 8 and again at certain points later in the studies were able to stop all treatment at 28 weeks. Patients who did not meet these criteria continued treatment with standard therapy alone for a total treatment duration of 48 weeks. Control group recipients received standard therapy at the doses described here plus placebo for 48 weeks. Overall, 66% and 63% of patients in the boceprevir 48-week and response-guided therapy groups achieved SVR, respectively, compared with 38% of patients in the control group ($p < 0.0001$ for both, ITT analysis). Results for the non-Africa American and African American cohorts were analyzed separately. In the non-African American cohort, 69% and 67% of patients in the boceprevir 48-week and response-guided therapy groups achieved SVR, respectively, compared with 40% in the control group ($p < 0.0001$ for both, ITT analysis). In the African American cohort, 53% and 42% of patients in the boceprevir 48-week and response-guided therapy groups achieved SVR, respectively, compared with 23% in the control group ($p = 0.004$ and $p = 0.044$, respectively; ITT analysis).[2]

Phase II

Long-term outcomes were assessed in an analysis of results from two phase II trials of boceprevir plus peg-IFN with/without ribavirin in patients with HCV infections; SVR following boceprevir combination therapy was shown to be durable. Samples from 604 patients (treatment-naive or peg-IFN alfa-2a plus ribavirin failures) who received boceprevir plus peg-IFN with/without ribavirin were evaluated. No late relapse was confirmed in the 290 patients who had previously obtained SVR.[15]

Final results from part I of the phase II HCV SPRINT-1 study in 595 evaluable, treatment-naive patients with hepatitis C (genotype 1) showed that in a 48-week treatment regimen, the SVR rate was 75% at 24 weeks after the end of treatment in patients who received 4 weeks of peg-IFN alfa-2b and ribavirin prior to the addition of boceprevir 800 mg three times daily (peg-IFN alfa-2a plus ribavirin lead-in) to the combination for 44 weeks (48 total weeks of treatment). In comparison, an SVR rate of 38% was achieved in patients in the control group who received peg-IFN alfa-2b and ribavirin only for 48 weeks. In a 28-week boceprevir and peg-IFN alfa-2a plus ribavirin lead-in regimen (4 weeks of peg-IFN alfa-2b and ribavirin prior to addition of boceprevir for 24 weeks), the SVR rate at 24 weeks after the end of treatment was 56%. Additionally, in patients who received boceprevir and peg-IFN alfa-2a plus ribavirin lead-in, SVR rates of 82% in the 28-week regimen, and 94% in the 48-week regimen were achieved in patients who had rapid virologic response (RVR). RVR was defined as undetectable virus in plasma after 4 weeks of boceprevir treatment.

In part II of the HCV SPRINT-1 study, boceprevir was administered in combination with peg-IFN alfa-2b and either low-dose ($n = 59$) or standard-dose ($n = 16$) ribavirin. At 48 weeks, the SVR rate was markedly lower in the low-dose

Table II. History

Date	Comment
10 August 2010	inThought analysis for hepatitis C updated
5 August 2010	Efficacy and adverse event data from the phase III HCV RESPOND-2 and SPRINT-2 trials released by Merck[2]
5 August 2010	Merck completes the phase III RESPOND-2 and SPRINT-2 trials in hepatitis C in the US, EU, and Canada
18 April 2010	Interim efficacy and pharmacodynamic data from a combined analysis of two phase II trials in hepatitis C virus infections presented at the 45th Annual Meeting of the European Association for the Study of the Liver (EASL-2010)[15]
4 November 2009	Schering-Plough has combined with Merck & Co. under the name Merck
3 November 2009	Pharmacodynamics data from a clinical trial in hepatitis C presented at the 60th Annual Meeting of the American Association for the Study of Liver Diseases (AASLD-2009)[16]
2 November 2009	Schering-Plough completes enrollment in the HCV SPRINT-2 and HCV RESPOND-2 trials for hepatitis C in Canada, Europe, and the US
1 November 2009	Efficacy data from the phase II HCV SPRINT-1 trial in hepatitis C presented at the 60th Annual Meeting of the American Association for the Study of Liver Diseases (AASLD-2009)[23]
26 April 2009	Pharmacodynamics data from a long-term, follow-up, clinical trial in patients with chronic hepatitis C presented at the 44th Annual Meeting of the European Association for the Study of the Liver (EASL-2009)[17]
23 April 2009	Final efficacy and tolerability data from the phase II HCV SPRINT-1 trial in hepatitis C presented at the 44th Annual Meeting of the European Association for the Study of the Liver (EASL-2009)[7]
27 January 2009	Schering-Plough completes enrollment in the phase III HCV SPRINT-2 trial for treatment-naive hepatitis C; enrollment is now complete in boceprevir registration studies
14 December 2008	New score for hepatitis C (PO)
24 November 2008	Final efficacy and adverse events data from a phase II trial (HCV SPRINT-1) in hepatitis C (genotype 1) released by Schering-Plough[6]
24 November 2008	Schering-Plough completes a phase II trial (HCV SPRINT-1) in chronic hepatitis C (genotype 1) in the US, Canada, and the EU
31 August 2008	Phase III clinical trials in hepatitis C (treatment-experienced patients, combination therapy) in Canada (PO)
31 August 2008	Phase III clinical trials in hepatitis C (treatment-experienced patients, combination therapy) in the EU (PO)
31 August 2008	Phase III clinical trials in hepatitis C (treatment-experienced patients, combination therapy) in the US (PO)
31 August 2008	Phase III clinical trials in hepatitis C (treatment-naive patients, combination therapy) in Canada (PO)
31 August 2008	Phase III clinical trials in hepatitis C (treatment-naive patients, combination therapy) in the EU (PO)
31 August 2008	Phase III clinical trials in hepatitis C (treatment-naive patients, combination therapy) in the US (PO)
6 August 2008	Top-line interim efficacy data from a phase II (HCV SPRINT-1) trial in hepatitis C released by Schering-Plough[8]
27 April 2008	Interim adverse events data from the phase II HCV SPRINT-1 trial in hepatitis C presented at the 43rd Annual Meeting of the European Association for the Study of the Liver (EASL-2008)[14,22]
6 November 2007	Pharmacodynamics data from *in vitro* cell culture replicon studies presented at the 58th Annual Meeting of the American Association for the Study of Liver Diseases (AASLD-2007)[19]
18 October 2007	Results from two phase II clinical trials in patients with hepatitis C added to the adverse events and viral infections therapeutic trials sections[9]
16 April 2007	Phase II clinical trials in hepatitis C in Canada (PO)
16 April 2007	Phase II clinical trials in hepatitis C in Europe (PO)
27 April 2006	Schering-Plough has completed enrollment in the original protocol dose groups of a phase II trial for hepatitis C in the US, and has expanded the trial to include an additional dose group
30 January 2006	Boceprevir has received fast-track status for treatment of chronic hepatitis C in the US (PO, capsule)
12 December 2005	Data presented at the 56th Annual Meeting and Postgraduate Course of the American Association for the Study of Liver Diseases (AASLD-2005) have been added to the adverse events, pharmacokinetics and viral infections pharmacodynamics sections[11,12,18,20]
29 September 2005	Data presented at the at the 230th American Chemical Society National Meeting (230th-ACS-2005) have been added to the pharmacokinetics section[13]
22 September 2005	Phase II clinical trials in hepatitis C in the US (PO)
22 September 2005	Profile created from data presented at the 230th American Chemical Society National Meeting (230th-ACS-2005)

Table III. Forecasts

InThought Probability of Approval[a]											
Indication				Approval Date Estimate			inThought Approvability Index				Last Update
Hepatitis C				15 Aug 2012			80% (A)				10 Aug 2010
InThought Worldwide Revenue[b]											
Indication	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	Last Update
Hepatitis C	0	0	0	221	443	566	631	620	669	674	27 Apr 2010

a The Wolters Kluwer Health Approvability Index is a dynamic tool that assesses the progress of a drug candidate through clinical development, evaluating strength of clinical data and trial design, benchmarked against historical parameters and likelihood to maintain forward momentum. Points are assigned for specific line items relating to safety, efficacy, and other factors in each phase of clinical development. Possible points total 100 upon drug approval, and are allocated in each phase according to the historical approval rate of similar drugs, such that the current points of a drug relate to its probability of approval. In addition, a letter grade is assigned and reflects the momentum of a drug candidate in its current phase, with 'A' indicating significantly above average/likely to progress, 'C' indicating average, and 'F' indicating significantly below average/unlikely to progress. 'NYR' stands for 'Not Yet Rated,' indicating that the probability of approval is based on historical approval rates for similar drugs according to indication, molecule type, novelty, and phase, but without analyses of clinical data, trial design, and other factors specific to the individual agent.

b All numbers in $US millions.

than the high-dose group (36% vs 50%). Furthermore, compared with outcomes observed with boceprevir plus peg-IFN alfa-2b plus standard-dose ribavirin in part I of the study, SVR rates were lower and relapse rates higher in the low-dose ribavirin group.[6-8,14,21,22]

In analysis of results from the phase II HCV SPRINT-1 study, overall 38% of patients who had a null response to peg-IFN and ribavirin therapy after the 4-week lead-in, achieved SVR. Broken down into the two treatment arms, 25% and 55% of patients achieved SVR who received 24 and 48 weeks of boceprevir treatment, respectively.[4,23]

In a phase II study in 357 patients chronically infected with HCV genotype 1 who were non-responders to previous peg-IFN and ribavirin combination therapy, 7–14% of patients in the boceprevir crossover arms achieved a SVR compared with 2% in the control arm. Results from the study also showed that viral loads in some patients decreased but then rebounded to baseline levels while still receiving therapy. Also, some patients relapsed following the end of treatment. Several resistant variants were seen in these patients.[9]

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