GASTROENTEROLOGY & HEPATOLOGY
The Independent Peer-Reviewed Journal

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A SPECIAL MEETING REVIEW EDITION

Advances in the Treatment of Hepatitis C Virus Infection From AASLD 2012

The 63rd Annual Meeting of the American Association for the Study of Liver Diseases

November 9–13, 2012 • Boston, Massachusetts

Special Reporting on:

- Timing and Magnitude of Ribavirin Dose Reduction Do Not Impact SVR Rates with Boceprevir Plus Peginterferon α and Ribavirin
- A 12-Week Interferon-Free Treatment Regimen with ABT-450/r, ABT-267, ABT-333, and Ribavirin Achieves High SVR_{12} Rates
- High Rate of SVR with the All-Oral Combination of Daclatasvir Plus Sofosbuvir with or without Ribavirin
- An Interferon-Free, Ribavirin-Free 12-Week Regimen of Daclatasvir, Asunaprevir, and BMS-791325 Achieved High SVR_4 Rates

PLUS Meeting Abstract Summaries

With Expert Commentary by:
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San Antonio, Texas

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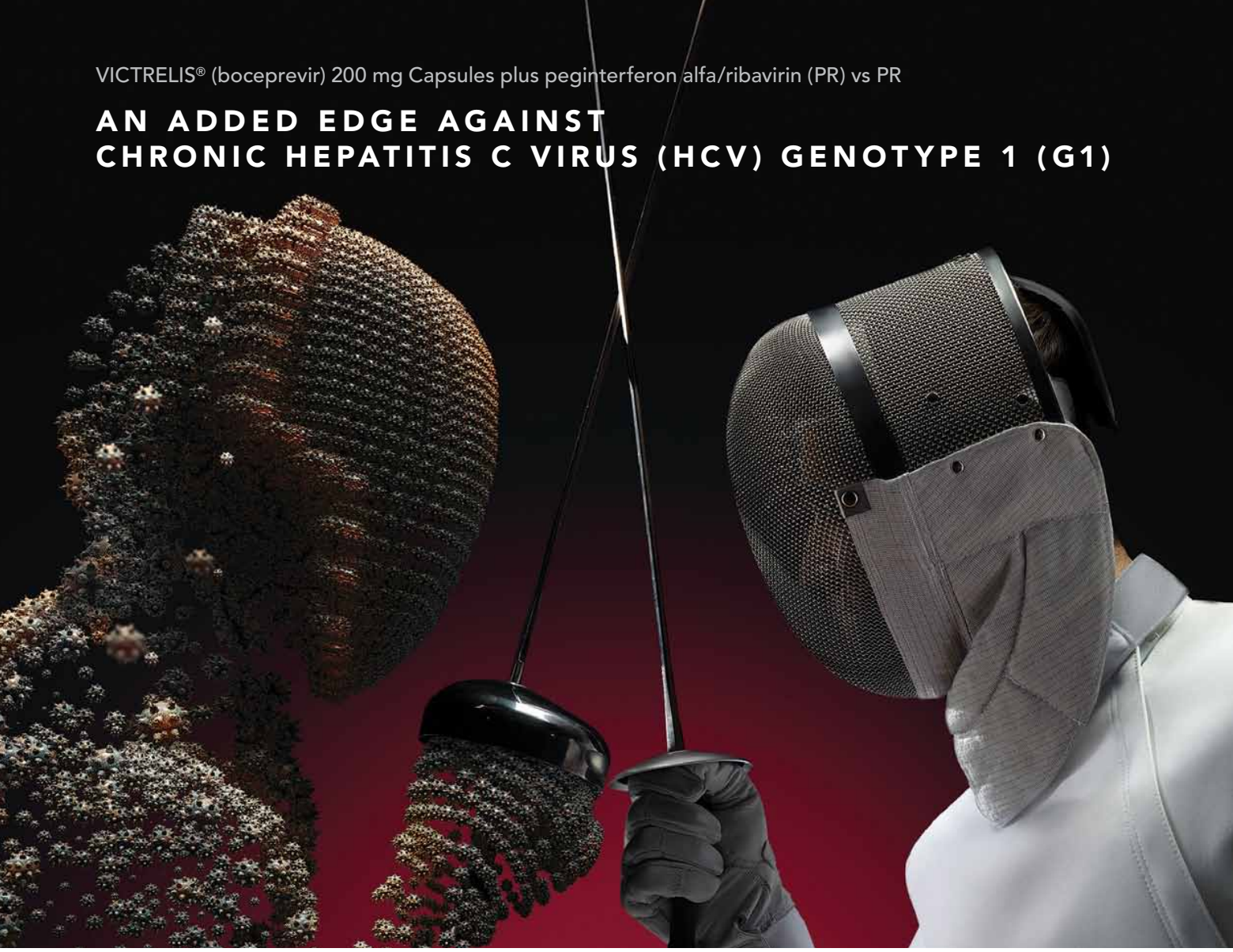
VICTRELIS® (boceprevir) 200 mg Capsules plus peginterferon alfa/ribavirin (PR) vs PR

AN ADDED EDGE AGAINST CHRONIC HEPATITIS C VIRUS (HCV) GENOTYPE 1 (G1)



INDICATIONS AND USAGE

VICTRELIS is indicated for the treatment of chronic HCV G1 infection, in combination with PR, in adult patients (18 years and older) with compensated liver disease, including cirrhosis, who are previously untreated or who have failed previous interferon and ribavirin therapy.

The following points should be considered when initiating VICTRELIS for treatment of chronic HCV infection:

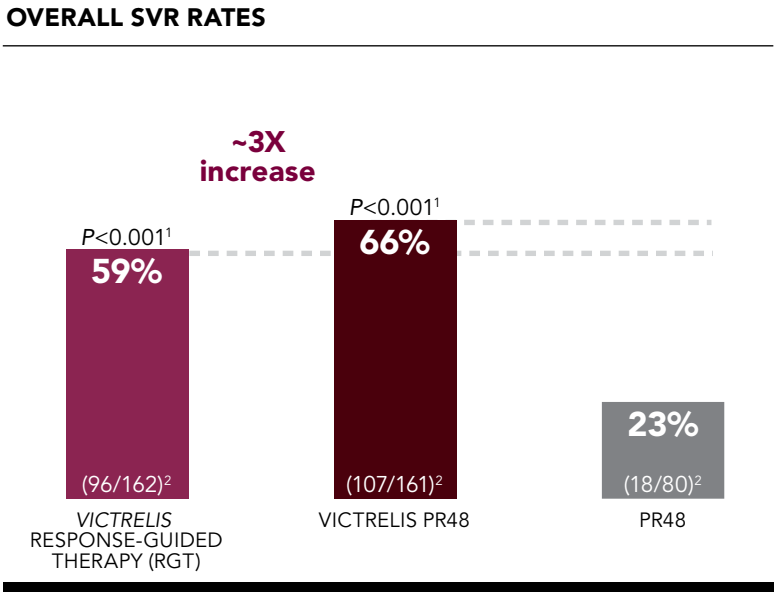
- VICTRELIS must not be used as monotherapy and should only be used in combination with PR.
- VICTRELIS efficacy has not been studied in patients who have previously failed therapy with a treatment regimen that includes VICTRELIS or other HCV NS3/4A protease inhibitors.
- VICTRELIS in combination with PR has not been studied in patients documented to be historical null responders (<2-$\log_{10}$ HCV-RNA decline by Treatment Week 12) during prior therapy with PR. The clinical studies included subjects who were poorly interferon responsive. Subjects with <0.5-$\log_{10}$ HCV-RNA decline in viral load at Treatment Week 4 with PR alone are predicted to have a null response (<2-$\log_{10}$ viral load decline at Treatment Week 12) to PR therapy.
- Poorly interferon responsive patients who were treated with VICTRELIS in combination with PR have a lower likelihood of achieving a sustained virologic response (SVR), and a higher rate of detection of resistance-associated substitutions upon treatment failure, compared to patients with a greater response to PR.

Visit **victrelis.com**
or scan this QR code to go there directly.

VICTRELIS® boceprevir 200 MG CAPSULES

VICTRELIS® (boceprevir) + PR vs PR: In adult patients with chronic HCV G1 infection with compensated liver disease who previously failed PR therapy

An added edge that nearly tripled virologic cure (SVR)[a] rates



- VICTRELIS, in combination with PR, has not been studied in patients documented to be historical null responders (<2-$\log_{10}$ HCV-RNA decline by Treatment Week 12) during prior therapy with PR.

RESPOND-2 Study Design. A randomized, parallel-group, double-blind, Phase 3 study in previously treated patients with chronic HCV G1 infection (N=403). Subjects had demonstrated interferon responsiveness (as defined historically by a decrease in HCV-RNA viral load ≥2-$\log_{10}$ by Treatment Week 12, but never achieved SVR [partial responders] or HCV-RNA not detected at end of prior treatment with a subsequent HCV-RNA detected in plasma [relapsers]). All subjects received a 4-week lead-in of PR (peginterferon alfa-2b 1.5 µg/kg/week subcutaneously plus weight-based ribavirin 600 to 1,400 mg/day orally BID), followed by either: a response-guided regimen that consisted of 32 weeks of triple therapy with PR + VICTRELIS 800 mg orally TID, followed by 12 additional weeks of PR if virus not cleared by Treatment Week 8 (VICTRELIS RGT); 44 weeks of triple therapy (VICTRELIS PR48); or 44 weeks of PR + placebo (PR48). Primary study end point was SVR.[1] All subjects with HCV-RNA detected in plasma at Treatment Week 12 were discontinued from treatment. SVR was defined as plasma HCV-RNA <25 IU/mL at Follow-up Week 24. Plasma HCV-RNA results at Follow-up Week 12 were used if plasma HCV-RNA results at Follow-up Week 24 were missing. Mean age of subjects randomized was 53 years. The racial distribution of subjects was 85% white, 12% black, and 3% others. The distribution by gender was 67% men and 33% women.

SELECTED SAFETY INFORMATION

- All contraindications to PR also apply since VICTRELIS must be administered with PR.
- Because ribavirin may cause birth defects and fetal death, VICTRELIS in combination with PR is contraindicated in pregnant women and in men whose female partners are pregnant. Avoid pregnancy in female patients and female partners of male patients. Patients must have a negative pregnancy test prior to therapy; have monthly pregnancy tests; and use 2 or more forms of effective contraception, including intrauterine devices and barrier methods, during treatment and for at least 6 months after treatment has concluded. Systemic hormonal contraceptives may not be as effective in women while taking VICTRELIS.
- VICTRELIS is contraindicated in coadministration with drugs that are highly dependent on CYP3A4/5 for clearance, and for which elevated plasma concentrations are associated with serious and/or life-threatening events. VICTRELIS is also contraindicated in coadministration with potent CYP3A4/5 inducers, where significantly reduced VICTRELIS plasma concentrations may be associated with reduced efficacy.

BID = 2 times a day; RESPOND-2 = Retreatment with HCV Serine Protease Inhibitor Boceprevir and PR-2; RNA = ribonucleic acid; TID = 3 times a day.

[a]Sustained virologic response (SVR) was defined as plasma HCV-RNA <25 IU/mL at Follow-up Week 24. This is generally considered a "virologic cure," as the rate of late relapse (beyond 24 weeks) is <1%.[3,4]

SELECTED SAFETY INFORMATION

- Drugs that are contraindicated with VICTRELIS® (boceprevir) include: alfuzosin, carbamazepine, phenobarbital, phenytoin, rifampin, dihydroergotamine, ergonovine, ergotamine, methylergonovine, cisapride, St. John's Wort (hypericum perforatum), lovastatin, simvastatin, drospirenone, *Revatio*® (sildenafil) or *Adcirca*® (tadalafil) (when used for the treatment of pulmonary arterial hypertension), pimozide, triazolam, and orally administered midazolam.
- Anemia and/or Neutropenia – The addition of VICTRELIS to PR is associated with an additional decrease in hemoglobin concentrations compared with PR alone and/or may result in worsening of neutropenia associated with PR therapy alone. Dose reduction or discontinuation of peginterferon alfa and/or ribavirin may be required. Dose reduction of VICTRELIS is not recommended. VICTRELIS must not be administered in the absence of PR.
- Complete blood count (with white blood cell differential counts) must be conducted in all patients prior to initiating combination therapy with VICTRELIS. Complete blood counts should be obtained at Treatment Weeks 4, 8, and 12, and should be monitored closely at other time points, as clinically appropriate.
- The most commonly reported adverse reactions (>35%) in clinical trials in adult patients receiving the combination of VICTRELIS with PR were: fatigue, anemia, nausea, headache, and dysgeusia. Of these commonly reported adverse reactions, fatigue, anemia, nausea, and dysgeusia occurred at rates ≥5% above the rates for PR alone in either clinical study. The incidence of these adverse reactions in previously untreated subjects that were treated with combination therapy with VICTRELIS compared with PR alone were: fatigue (58% vs 59%), anemia (50% vs 30%), nausea (46% vs 42%), and dysgeusia (35% vs 16%), respectively. The incidence of these adverse reactions in previous treatment failure patients that were treated with combination therapy with VICTRELIS compared with PR alone were: fatigue (55% vs 50%), anemia (45% vs 20%), nausea (43% vs 38%), and dysgeusia (44% vs 11%), respectively.
- VICTRELIS is a strong inhibitor of CYP3A4/5 and is partly metabolized by CYP3A4/5. The potential for drug-drug interactions must be considered prior to and during therapy.

Please see Brief Summary of Prescribing Information on the pages that follow.

References: 1. Bacon BR, Gordon SC, Lawitz E, et al; for HCV RESPOND-2 Investigators. Boceprevir for previously treated chronic HCV genotype 1 infection. *N Engl J Med.* 2011;364(13):1207–1217. **2.** Birnkrant D. Direct-acting antivirals: a new era for the treatment of chronic hepatitis C. Slide deck presented at: Antiviral Drugs Advisory Committee Meeting; April 27–28, 2011; Silver Spring, MD. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AntiviralDrugsAdvisoryCommittee/UCM254076.pdf. Accessed October 5, 2011. **3.** Ghany MG, Nelson DR, Strader DB, et al. An update on treatment of genotype 1 chronic hepatitis C virus infection: 2011 practice guideline by the American Association for the Study of Liver Diseases. *Hepatology.* 2011;54(4):1433–1444. **4.** Pearlman BL, Traub N. Sustained virologic response to antiviral therapy for chronic hepatitis C virus infection: a cure and so much more. *Clin Infect Dis.* 2011;52(7):889–900.

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VICTRELIS® boceprevir 200 MG CAPSULES

VICTRELIS® (boceprevir) 200 mg Capsules

CONTRAINDICATIONS

Contraindications to peginterferon alfa and ribavirin also apply to VICTRELIS combination treatment.

VICTRELIS combination treatment is contraindicated in:

- Pregnant women and men whose female partners are pregnant because of the risks for birth defects and fetal death associated with ribavirin.
- Coadministration with drugs that are highly dependent on CYP3A4/5 for clearance, and for which elevated plasma concentrations are associated with serious and/or life-threatening events, including those in Table 2.
- Coadministration with potent CYP3A4/5 inducers, where significantly reduced boceprevir plasma concentrations may be associated with reduced efficacy, including those in Table 2.

Table 2: Drugs that are contraindicated with VICTRELIS

Drug Class	Drugs Within Class that are Contraindicated With VICTRELIS	Clinical Comments
Alpha 1-Adrenoreceptor antagonist	Alfuzosin	Increased alfuzosin concentrations can result in hypotension.
Anticonvulsants	Carbamazepine, phenobarbital, phenytoin	May lead to loss of virologic response to VICTRELIS
Antimycobacterial	Rifampin	May lead to loss of virologic response to VICTRELIS.
Ergot Derivatives	Dihydroergotamine, ergonovine, ergotamine, methylergonovine	Potential for acute ergot toxicity characterized by peripheral vasospasm and ischemia of the extremities and other tissues.
GI Motility Agent	Cisapride	Potential for cardiac arrhythmias.
Herbal Products	St. John's Wort (hypericum perforatum)	May lead to loss of virologic response to VICTRELIS.
HMG-CoA Reductase Inhibitors	Lovastatin, simvastatin	Potential for myopathy, including rhabdomyolysis.
Oral Contraceptives	Drospirenone	Potential for hyperkalemia.
PDE5 enzyme Inhibitor	REVATIO® (sildenafil) or ADCIRCA® (tadalafil) when used for the treatment of pulmonary arterial hypertension*	Potential for PDE5 inhibitor-associated adverse events, including visual abnormalities, hypotension, prolonged erection, and syncope.
Neuroleptic	Pimozide	Potential for cardiac arrhythmias.
Sedative/Hypnotics	Triazolam; orally administered midazolam†	Prolonged or increased sedation or respiratory depression.

* See *Drug Interactions, Table 5* for coadministration of sildenafil and tadalafil when dosed for erectile dysfunction.

† See *Drug Interactions, Table 5* for parenterally administered midazolam.

WARNINGS AND PRECAUTIONS

Pregnancy (Use with Ribavirin and Peginterferon Alfa)

Ribavirin may cause birth defects and/or death of the exposed fetus. Extreme care must be taken to avoid pregnancy in female patients and in female partners of male patients. Ribavirin therapy should not be started unless a report of a negative pregnancy test has been obtained immediately prior to initiation of therapy. Women of childbearing potential and men must use at least two forms of effective contraception during treatment and for at least 6 months after treatment has concluded. Routine monthly pregnancy tests must be performed during this time. Systemic hormonal contraceptives may not be as effective in women while taking VICTRELIS. Two alternative effective methods of contraception, including intrauterine devices and barrier methods, should be used in women during treatment with VICTRELIS and concomitant ribavirin.

Anemia (Use with Ribavirin and Peginterferon Alfa)

Anemia has been reported with peginterferon alfa and ribavirin therapy. The addition of VICTRELIS to peginterferon alfa and ribavirin is associated with an additional decrease in hemoglobin concentrations. Complete blood counts should be obtained pretreatment, and at Treatment Weeks 4, 8, and 12, and should be monitored closely at other time points, as clinically appropriate. If hemoglobin is less than 10 g/dL, a decrease in dosage or interruption of ribavirin is recommended; and if hemoglobin is less than 8.5 g/dL, discontinuation of ribavirin is recommended.

Refer to the Package Insert for ribavirin for additional information regarding dosage reduction and/or interruption.

In clinical trials with VICTRELIS, the proportion of subjects who experienced hemoglobin values less than 10 g/dL and less than 8.5 g/dL was higher in subjects treated with the combination of VICTRELIS with PegIntron®/REBETOL® than in those treated with PegIntron/REBETOL alone (see Table 4). With the interventions used for anemia management in the clinical trials, the average additional decrease of hemoglobin was approximately 1 g/dL. Certain adverse reactions consistent with symptoms of anemia, such as dyspnea, exertional dyspnea, dizziness and syncope were reported more frequently in subjects who received the combination of VICTRELIS with PegIntron/REBETOL than in those treated with PegIntron/REBETOL alone.

In clinical trials with VICTRELIS, dose modifications (generally of PegIntron/REBETOL) due to anemia occurred twice as often in subjects treated with the combination of VICTRELIS with PegIntron/REBETOL (26%) compared to PegIntron/REBETOL (13%). The proportion of subjects who discontinued study drug due to anemia was 1% in subjects treated with the combination of VICTRELIS with PegIntron/REBETOL and 1% in subjects who received PegIntron/REBETOL. The use of erythropoiesis stimulating agents was permitted for management of anemia, at the investigator's discretion, with or without ribavirin dose reduction in the Phase 2 and 3 clinical trials. The proportion of subjects who received an erythropoiesis stimulating agent was 43% in the VICTRELIS-containing arms compared to 24% in the PegIntron/REBETOL arms. The proportion of subjects who received a transfusion for the management of anemia was 3% of subjects in the VICTRELIS-containing arms compared to less than 1% in subjects who received PegIntron/REBETOL alone.

Thromboembolic events have been associated with erythropoiesis stimulating agent use in other disease states; and have also been reported with peginterferon alfa use in hepatitis C patients. Thromboembolic events were reported in clinical trials with VICTRELIS among subjects receiving the combination of VICTRELIS with PegIntron/REBETOL, and among those receiving PegIntron/REBETOL alone, regardless of erythropoiesis stimulating agent use. No definite causality assessment or benefit risk assessment can be made for these events due to the presence of confounding factors and lack of randomization of erythropoiesis stimulating agent use.

Neutropenia (Use with Ribavirin and Peginterferon Alfa)

In Phase 2 and 3 clinical trials, seven percent of subjects receiving the combination of VICTRELIS with PegIntron/REBETOL had neutrophil counts of less than 0.5 x 10^9/L compared to 4% of subjects receiving PegIntron/REBETOL alone (see Table 4). Three subjects experienced severe or life-threatening infections associated with neutropenia, and two subjects experienced life-threatening neutropenia while receiving the combination of VICTRELIS with PegIntron/REBETOL. Complete blood count (with white blood cell differential counts) must be conducted in all patients prior to initiating VICTRELIS combination therapy. Complete blood counts should be obtained at Treatment Weeks 4, 8, and 12, and should be monitored closely at other time points, as clinically appropriate. Decreases in neutrophil counts may require dose reduction or discontinuation of peginterferon alfa and ribavirin.

Refer to Package Inserts for peginterferon alfa and ribavirin for additional information regarding dose reduction or discontinuation for peginterferon alfa and ribavirin.

Drug Interactions

See Table 2 for a listing of drugs that are contraindicated for use with VICTRELIS due to potentially life-threatening adverse events, significant drug interactions or loss of virologic activity. Please refer to Table 5 for established and other potentially significant drug interactions.

Laboratory Tests

HCV-RNA levels should be monitored at Treatment Weeks 4, 8, 12, and 24, at the end of treatment, during treatment follow-up, and for other time points as clinically indicated. Use of a sensitive real-time reverse-transcription polymerase chain reaction (RT-PCR) assay for monitoring HCV-RNA levels during treatment is recommended. The assay should have a lower limit of HCV-RNA quantification of equal to or less than 25 IU per mL, and a limit of HCV-RNA detection of approximately 10 to 15 IU per mL. For the purposes of assessing Response-Guided Therapy milestones, a confirmed "detectable but below limit of quantification" HCV-RNA result should not be considered equivalent to an "undetectable" HCV-RNA result (reported as "Target Not Detected" or "HCV-RNA Not Detected").

Complete blood count (with white blood cell differential counts) must be conducted in all patients prior to initiating VICTRELIS combination therapy. Complete blood counts should be obtained at Treatment Weeks 4, 8, and 12, and should be monitored closely at other time points, as clinically appropriate.

Refer to the Package Inserts for peginterferon alfa and ribavirin, including pregnancy testing requirements.

ADVERSE REACTIONS

See peginterferon alfa and ribavirin Package Inserts for description of adverse reactions associated with their use.

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of VICTRELIS cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The following serious and otherwise important adverse drug reactions (ADRs) are discussed in detail in another section of the labeling: Anemia and neutropenia.

The most commonly reported adverse reactions (>35% of subjects regardless of investigator's causality assessment) in adult subjects were fatigue, anemia, nausea, headache, and dysgeusia when VICTRELIS was used in combination with PegIntron and REBETOL.

The safety of the combination of VICTRELIS 800 mg three times daily with PegIntron/REBETOL was assessed in 2095 subjects with chronic hepatitis C in one Phase 2, open-label trial and two Phase 3, randomized, double-blind, placebo-controlled clinical trials.

SPRINT-1 (subjects who were previously untreated) evaluated the use of VICTRELIS in combination with PegIntron/REBETOL with or without a four-week lead-in period with PegIntron/REBETOL compared to PegIntron/REBETOL alone. SPRINT-2 (subjects who were previously untreated) and RESPOND-2 (subjects who had failed previous therapy) evaluated the use of VICTRELIS 800 mg three times daily in combination with PegIntron/REBETOL with a four-week lead-in period with PegIntron/REBETOL compared to PegIntron/REBETOL alone. The population studied had a mean age of 49 years (3% of subjects were older than 65 years of age), 39% were female, 82% were white and 15% were black.

During the four week lead-in period with PegIntron/REBETOL in the VICTRELIS-containing arms, 28/1263 (2%) subjects experienced adverse reactions leading to discontinuation of treatment. During the entire course of treatment, the proportion of subjects who discontinued treatment due to adverse reactions was 13% for subjects receiving the combination of VICTRELIS with PegIntron/REBETOL and 12% for subjects receiving PegIntron/REBETOL alone. Events resulting in discontinuation were similar to those seen in previous studies with PegIntron/REBETOL. Only anemia and fatigue were reported as events that led to discontinuation in >1% of subjects in any arm.

Adverse reactions that led to dose modifications of any drug (primarily PegIntron and REBETOL) occurred in 39% of subjects receiving the combination of VICTRELIS with PegIntron/REBETOL compared to 24% of subjects receiving PegIntron/REBETOL alone. The most common reason for dose reduction was anemia, which occurred more frequently in subjects receiving the combination of VICTRELIS with PegIntron/REBETOL than in subjects receiving PegIntron/REBETOL alone.

Serious adverse events were reported in 11% of subjects receiving the combination of VICTRELIS with PegIntron/REBETOL and in 8% of subjects receiving PegIntron/REBETOL.

Adverse events (regardless of investigator's causality assessment) reported in greater than or equal to 10% of subjects receiving the combination of VICTRELIS with PegIntron/REBETOL and reported at a rate of greater than or equal to 5% than PegIntron/REBETOL alone in SPRINT-1, SPRINT-2, and RESPOND-2 are presented in Table 3.

Table 3: Adverse Events Reported in ≥10% of Subjects Receiving the Combination of VICTRELIS with PegIntron/REBETOL and Reported at a Rate of ≥5% than PegIntron/REBETOL alone

Adverse Events	Previously Untreated (SPRINT-1 & SPRINT-2)		Previous Treatment Failures (RESPOND-2)	
	Percentage of Subjects Reporting Adverse Events		Percentage of Subjects Reporting Adverse Events	
Body System Organ Class	VICTRELIS + PegIntron + REBETOL (n=1225)	PegIntron + REBETOL (n=467)	VICTRELIS + PegIntron + REBETOL (n=323)	PegIntron + REBETOL (n=80)
Median Exposure (days)	**197**	**216**	**253**	**104**
Blood and Lymphatic System Disorders				
Anemia	50	30	45	20
Neutropenia	25	19	14	10
Gastrointestinal Disorders				
Nausea	46	42	43	38
Dysgeusia	35	16	44	11
Diarrhea	25	22	24	16
Vomiting	20	13	15	8
Dry Mouth	11	10	15	9
General Disorders and Administration Site Conditions				
Fatigue	58	59	55	50
Chills	34	29	33	30
Asthenia	15	18	21	16
Metabolism and Nutrition Disorders				
Decreased Appetite	25	24	26	16
Musculoskeletal and Connective Tissue Disorders				
Arthralgia	19	19	23	16
Nervous System Disorders				
Dizziness	19	16	16	10
Psychiatric Disorders				
Insomnia	34	34	30	24
Irritability	22	23	21	13
Respiratory, Thoracic, and Mediastinal Disorders				
Dyspnea Exertional	8	8	11	5
Skin and Subcutaneous Tissue Disorders				
Alopecia	27	27	22	16
Dry Skin	18	18	22	9
Rash	17	19	16	6

Other Important Adverse Reactions Reported in Clinical Trials

Among subjects (previously untreated subjects or those who failed previous therapy) who received VICTRELIS in combination with peginterferon alfa and ribavirin, the following adverse drug reactions were reported. These events are notable because of their seriousness, severity, or increased frequency in subjects who received VICTRELIS in combination with peginterferon alfa and ribavirin compared with subjects who received only peginterferon alfa and ribavirin.

Gastrointestinal Disorders

Dysgeusia (alteration of taste) was an adverse event reported at an increased frequency in subjects receiving VICTRELIS in combination with peginterferon alfa and ribavirin compared with subjects receiving peginterferon alfa and ribavirin alone (Table 3). Adverse events such as dry mouth, nausea, vomiting and diarrhea were also reported at an increased frequency in subjects receiving VICTRELIS in combination with peginterferon alfa and ribavirin.

Laboratory Values

Changes in selected hematological parameters during treatment of adult subjects with the combination of VICTRELIS with PegIntron and REBETOL are described in Table 4.

Hemoglobin

Decreases in hemoglobin may require a decrease in dosage/interruption or discontinuation of ribavirin.

Neutrophils and Platelets

The proportion of subjects with decreased neutrophil and platelet counts was higher in the VICTRELIS-containing arms compared to subjects receiving PegIntron/REBETOL alone. Three percent of subjects receiving the combination of VICTRELIS with PegIntron/REBETOL had platelet counts of less than 50 x 10^9/L compared to 1% of subjects receiving PegIntron/REBETOL alone. Decreases in neutrophils or platelets may require a decrease in dosage or interruption of peginterferon alfa, or discontinuation of therapy.

Table 4: Selected Hematological Parameters

	Previously Untreated (SPRINT-1 & SPRINT-2)		Previous Treatment Failures (RESPOND-2)	
	Percentage of Subjects Reporting Selected Hematological Parameters		Percentage of Subjects Reporting Selected Hematological Parameters	
Hematological Parameters	VICTRELIS + PegIntron + REBETOL (n=1225)	PegIntron + REBETOL (n=467)	VICTRELIS + PegIntron + REBETOL (n=323)	PegIntron + REBETOL (n=80)
Hemoglobin (g/dL)				
<10	49	29	49	25
<8.5	6	3	10	1
Neutrophils (x 10^9/L)				
<0.75	31	18	26	13
<0.5	8	4	7	4

Table 4: Selected Hematological Parameters *(continued)*

	Previously Untreated (SPRINT-1 & SPRINT-2)		Previous Treatment Failures (RESPOND-2)	
	Percentage of Subjects Reporting Selected Hematological Parameters		Percentage of Subjects Reporting Selected Hematological Parameters	
Hematological Parameters	**VICTRELIS + PegIntron + REBETOL (n=1225)**	**PegIntron + REBETOL (n=467)**	**VICTRELIS + PegIntron + REBETOL (n=323)**	**PegIntron + REBETOL (n=80)**
Platelets (x 10^9/L)				
<50	3	1	4	0
<25	<1	0	0	0

DRUG INTERACTIONS

See also *Contraindications and Warnings and Precautions.*

Potential for VICTRELIS to Affect Other Drugs

Boceprevir is a strong inhibitor of CYP3A4/5. Drugs metabolized primarily by CYP3A4/5 may have increased exposure when administered with VICTRELIS, which could increase or prolong their therapeutic and adverse effects. Boceprevir does not inhibit CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 or CYP2E1 *in vitro*. In addition, boceprevir does not induce CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 or CYP3A4/5 *in vitro*.

Boceprevir is a potential inhibitor of p-glycoprotein (P-gp) based on in vitro studies. The potential for a drug interaction with sensitive substrates of p-glycoprotein (e.g., digoxin) has not been evaluated in a clinical trial.

Potential for Other Drugs to Affect VICTRELIS

Boceprevir is primarily metabolized by aldo-ketoreductase (AKR). In drug interaction trials conducted with AKR inhibitors diflunisal and ibuprofen, boceprevir exposure did not increase to a clinically significant extent. VICTRELIS may be coadministered with AKR inhibitors. Boceprevir is partly metabolized by CYP3A4/5. It is also a substrate for p-glycoprotein. Coadministration of VICTRELIS with drugs that induce or inhibit CYP3A4/5 could decrease or increase exposure to boceprevir.

Established and Other Potential Significant Drug Interactions

Table 5 provides recommendations based on established or potentially clinically significant drug interactions. VICTRELIS is contraindicated with drugs that are potent inducers of CYP3A4/5 and drugs that are highly dependent on CYP3A4/5 for clearance, and for which elevated plasma concentrations are associated with serious and/or life-threatening events.

Table 5: Established and Other Potentially Significant Drug Interactions

Concomitant Drug Class: Drug Name	Effect on Concentration of Boceprevir or Concomitant Drug	Recommendations
Antiarrhythmics: amiodarone, bepridil, propafenone, quinidine	↑ antiarrhythmics	Coadministration with VICTRELIS has the potential to produce serious and/or life-threatening adverse events and has not been studied. Caution is warranted and therapeutic concentration monitoring of these drugs is recommended if they are used concomitantly with VICTRELIS.
digoxin	↑ digoxin	Digoxin concentrations may be increased with VICTRELIS. Use the lowest dose initially with careful titration and monitoring of serum digoxin concentrations.
Anticoagulant: warfarin	↑ or ↓ warfarin	Concentrations of warfarin may be altered when coadministered with VICTRELIS. Monitor INR closely.
Antidepressants: trazadone, desipramine	↑ trazadone ↑ desipramine	Plasma concentrations of trazadone and desipramine may increase when administered with VICTRELIS, resulting in adverse events such as dizziness, hypotension and syncope. Use with caution and consider a lower dose of trazadone or desipramine.
escitalopram*	↓ escitalopram	Exposure of escitalopram was slightly decreased when coadministered with VICTRELIS. Selective serotonin reuptake inhibitors such as escitalopram have a wide therapeutic index, but doses may need to be adjusted when combined with VICTRELIS.
Antifungals: ketoconazole*, itraconazole, posaconazole, voriconazole	↑ boceprevir ↑ itraconazole ↑ ketoconazole ↑ posaconazole ↑ voriconazole	Plasma concentrations of ketoconazole, itraconazole, voriconazole or posaconazole may be increased with VICTRELIS. When coadministration is required, doses of ketoconazole and itraconazole should not exceed 200 mg/day.
Anti-gout: colchicine	↑ colchicine	Significant increases in colchicine levels are expected; fatal colchicine toxicity has been reported with other strong CYP3A4 inhibitors. Patients with renal or hepatic impairment should not be given colchicine with VICTRELIS. Treatment of gout flares (during treatment with VICTRELIS): 0.6 mg (1 tablet) x 1 dose, followed by 0.3 mg (half tablet) 1 hour later. Dose to be repeated no earlier than 3 days. Prophylaxis of gout flares (during treatment with VICTRELIS): If the original regimen was 0.6 mg twice a day, reduce dose to 0.3 mg once a day. If the original regimen was 0.6 mg once a day, reduce the dose to 0.3 mg once every other day. Treatment of familial Mediterranean fever (FMF) (during treatment with VICTRELIS): Maximum daily dose of 0.6 mg (may be given as 0.3 mg twice a day).
Anti-infective: clarithromycin	↑ clarithromycin	Concentrations of clarithromycin may be increased with VICTRELIS; however, no dosage adjustment is necessary for patients with normal renal function.
Antimycobacterial: rifabutin	↓ boceprevir ↑ rifabutin	Increases in rifabutin exposure are anticipated, while exposure of boceprevir may be decreased. Doses have not been established for the 2 drugs when used in combination. Concomitant use is not recommended.
Calcium Channel Blockers, dihydropyridine: felodipine, nifedipine, nicardipine	↑ dihydropyridine calcium channel blockers	Plasma concentrations of dihydropyridine calcium channel blockers may increase when administered with VICTRELIS. Caution is warranted and clinical monitoring is recommended.
Corticosteroid, systemic: dexamethasone	↓ boceprevir	Coadministration of VICTRELIS with CYP3A4/5 inducers may decrease plasma concentrations of boceprevir, which may result in loss of therapeutic effect. Therefore, this combination should be avoided if possible and used with caution if necessary.
Corticosteroid, inhaled: budesonide, fluticasone	↑ budesonide ↑ fluticasone	Concomitant use of inhaled budesonide or fluticasone with VICTRELIS may result in increased plasma concentrations of budesonide or fluticasone, resulting in significantly reduced serum cortisol concentrations. Avoid coadministration if possible, particularly for extended durations.
Endothelin Receptor Antagonist: bosentan	↑ bosentan	Concentrations of bosentan may be increased when coadministered with VICTRELIS. Use with caution and monitor closely.
HIV Non-Nucleoside Reverse Transcriptase Inhibitors: efavirenz*	↓ boceprevir	Plasma trough concentrations of boceprevir were decreased when VICTRELIS was coadministered with efavirenz, which may result in loss of therapeutic effect. Avoid combination.
HIV Protease Inhibitors: atazanavir/ritonavir*	↓ atazanavir ↓ ritonavir	Concomitant administration of boceprevir and atazanavir/ritonavir resulted in reduced steady-state exposures to atazanavir and ritonavir. Coadministration of atazanavir/ritonavir and boceprevir is not recommended.
darunavir/ritonavir*	↓ darunavir ↓ ritonavir ↓ boceprevir	Concomitant administration of boceprevir and darunavir/ritonavir resulted in reduced steady-state exposures to boceprevir, darunavir and ritonavir. Coadministration of darunavir/ritonavir and boceprevir is not recommended.
lopinavir/ritonavir*	↓ lopinavir ↓ ritonavir ↓ boceprevir	Concomitant administration of boceprevir and lopinavir/ritonavir resulted in reduced steady-state exposures to boceprevir, lopinavir and ritonavir. Coadministration of lopinavir/ritonavir and boceprevir is not recommended.
ritonavir*	↓ boceprevir	When boceprevir is administered with ritonavir alone, boceprevir concentrations are decreased.

Table 5: Established and Other Potentially Significant Drug Interactions *(continued)*

Concomitant Drug Class: Drug Name	Effect on Concentration of Boceprevir or Concomitant Drug	Recommendations
HMG-CoA Reductase Inhibitors: atorvastatin*	↑ atorvastatin	Exposure to atorvastatin was increased when administered with VICTRELIS. Use the lowest effective dose of atorvastatin, but do not exceed a daily dose of 40 mg when coadministered with VICTRELIS.
pravastatin*	↑ pravastatin	Concomitant administration of pravastatin with VICTRELIS increased exposure to pravastatin. Treatment with pravastatin can be initiated at the recommended dose when coadministered with VICTRELIS. Close clinical monitoring is warranted.
Immunosuppressants: cyclosporine*, tacrolimus*, sirolimus	↑ cyclosporine	Dose adjustments of cyclosporine should be anticipated when administered with VICTRELIS and should be guided by close monitoring of cyclosporine blood concentrations, and frequent assessments of renal function and cyclosporine-related side effects.
	↑ tacrolimus	Concomitant administration of VICTRELIS with tacrolimus requires significant dose reduction and prolongation of the dosing interval for tacrolimus, with close monitoring of tacrolimus blood concentrations and frequent assessments of renal function and tacrolimus-related side effects.
	↑ sirolimus	Blood concentrations of sirolimus are expected to increase significantly when administered with VICTRELIS. Close monitoring of sirolimus blood levels is recommended.
Inhaled beta-agonist: salmeterol	↑ salmeterol	Concurrent use of inhaled salmeterol and VICTRELIS is not recommended due to the risk of cardiovascular events associated with salmeterol.
Narcotic Analgesic/ Opioid Dependence: methadone, buprenorphine	↑ or ↓ methadone ↑ or ↓ buprenorphine	Plasma concentrations of methadone or buprenorphine may increase or decrease when coadministered with VICTRELIS. However, the combination has not been studied. Clinical monitoring is recommended as the dose of methadone or buprenorphine may need to be altered during concomitant treatment with VICTRELIS.
Oral hormonal contraceptives: drospirenone/ethinyl estradiol*	↑ drospirenone ↓ ethinyl estradiol	The effect of boceprevir on other progestins is unknown; however, increases in exposure are anticipated. Concentrations of ethinyl estradiol decreased in the presence of boceprevir. Systemic hormonal contraceptives should not be relied upon as an effective method of contraception in women during treatment with VICTRELIS. Two alternative effective methods of contraception should be used during combination treatment with ribavirin, and may include intrauterine devices and barrier methods.
PDE5 inhibitors: sildenafil, tadalafil, vardenafil	↑ sildenafil ↑ tadalafil ↑ vardenafil	Increases in PDE5 inhibitor concentrations are expected, and may result in an increase in adverse events, including hypotension, syncope, visual disturbances, and priapism. Use of REVATIO® (sildenafil) or ADCIRCA® (tadalafil) for the treatment of pulmonary arterial hypertension (PAH) is contraindicated with VICTRELIS. Use of PDE5 inhibitors for erectile dysfunction: Use with caution in combination with VICTRELIS with increased monitoring for PDE5 inhibitor-associated adverse events. Do not exceed the following doses: Sildenafil: 25 mg every 48 hours Tadalafil: 10 mg every 72 hours Vardenafil: 2.5 mg every 24 hours
Sedative/hypnotics: alprazolam; IV midazolam	↑ midazolam ↑ alprazolam	Close clinical monitoring for respiratory depression and/or prolonged sedation should be exercised during coadministration of VICTRELIS. A lower dose of IV midazolam or alprazolam should be considered.

* These combinations have been studied.

USE IN SPECIFIC POPULATIONS

Pregnancy

VICTRELIS must be administered in combination with peginterferon alfa and ribavirin.

Pregnancy Category X: Use with Ribavirin and Peginterferon Alfa

Significant teratogenic and/or embryocidal effects have been demonstrated in all animal species exposed to ribavirin; and therefore ribavirin is contraindicated in women who are pregnant and in the male partners of women who are pregnant. Interferons have abortifacient effects in animals and should be assumed to have abortifacient potential in humans.

Extreme caution must be taken to avoid pregnancy in female patients and female partners of male patients while taking this combination. Women of childbearing potential and their male partners should not receive ribavirin unless they are using effective contraception (two reliable forms) during treatment with ribavirin and for 6 months after treatment. Systemic hormonal contraceptives may not be as effective in women while taking VICTRELIS. Therefore, two alternative effective methods of contraception, including intrauterine devices and barrier methods, should be used in women during treatment with VICTRELIS and concomitant ribavirin.

In case of exposure during pregnancy, a Ribavirin Pregnancy Registry has been established to monitor maternal-fetal outcomes of pregnancies in female patients and female partners of male patients exposed to ribavirin during treatment and for 6 months following cessation of treatment. Physicians and patients are encouraged to report such cases by calling 1-800-593-2214.

Pregnancy Category B: VICTRELIS

VICTRELIS must not be used as a monotherapy. There are no adequate and well-controlled studies with VICTRELIS in pregnant women. No effects on fetal development have been observed in rats and rabbits at boceprevir AUC exposures approximately 11.8- and 2.0-fold higher, respectively, than those in humans at the recommended dose of 800 mg three times daily.

Nursing Mothers

It is not known whether VICTRELIS is excreted into human breast milk. Levels of boceprevir and/or metabolites in the milk of lactating rats were slightly higher than levels observed in maternal blood. Peak blood concentrations of boceprevir and/or metabolites in nursing pups were less than 1% of those of maternal blood concentrations. Because of the potential for adverse reactions from the drug in nursing infants, a decision must be made whether to discontinue nursing or discontinue treatment with VICTRELIS, taking into account the importance of the therapy to the mother.

Pediatric Use

The safety, efficacy, and pharmacokinetic profile of VICTRELIS in pediatric patients have not been studied.

Geriatric Use

Clinical studies of VICTRELIS did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, caution should be exercised in the administration and monitoring of VICTRELIS in geriatric patients due to the greater frequency of decreased hepatic function, concomitant diseases and other drug therapy.

Renal Impairment

No dosage adjustment of VICTRELIS is required for patients with any degree of renal impairment.

Hepatic Impairment

No dose adjustment of VICTRELIS is required for patients with mild, moderate or severe hepatic impairment. Safety and efficacy of VICTRELIS have not been studied in patients with decompensated cirrhosis. See Package Inserts for peginterferon alfa for contraindication in hepatic decompensation.

Human Immunodeficiency Virus (HIV) Co-Infection

The safety and efficacy of VICTRELIS alone or in combination with peginterferon alfa and ribavirin for the treatment of chronic hepatitis C genotype 1 infection have not been established in patients co-infected with HIV and HCV.

Hepatitis B Virus (HBV) Co-Infection

The safety and efficacy of VICTRELIS alone or in combination with peginterferon alfa and ribavirin for the treatment of chronic hepatitis C genotype 1 infection in patients co-infected with HBV and HCV have not been studied. For data regarding drug-drug interactions with antiretroviral agents in healthy subjects, see Established and Other Potential Significant Drug Interactions.

Organ Transplantation

The safety and efficacy of VICTRELIS alone or in combination with peginterferon alfa and ribavirin for the treatment of chronic hepatitis C genotype 1 infection in liver or other organ transplant recipients have not been studied. For data regarding drug-drug interactions with immunosuppressants, see Established and Other Potential Significant Drug Interactions.

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Timing and Magnitude of Ribavirin Dose Reduction Do Not Impact SVR Rates with Boceprevir Plus Peginterferon α and Ribavirin

The current standard-of-care therapy for patients with genotype 1 chronic hepatitis C virus (HCV) infection is triple therapy consisting of a protease inhibitor (boceprevir or telaprevir) plus peginterferon α and ribavirin. Patients on triple therapy may experience moderate-to-severe treatment-related anemia, which is often managed with ribavirin dose reduction and/or administration of the growth factor erythropoietin. To determine whether these interventions affect the efficacy of HCV therapy, Fred Poordad and colleagues investigated whether the timing and magnitude of ribavirin dose reduction alter sustained virologic response (SVR) rates in patients who are receiving boceprevir plus peginterferon and ribavirin.[1] Poordad presented the results of this study at the 63rd Annual Meeting of the American Association for the Study of Liver Diseases (AASLD), which was held November 9–13, 2012, in Boston, Massachusetts.

The Anemia Management Study was a randomized, multicenter, open-label study that assessed ribavirin dose reduction versus erythropoietin for management of anemia. This study enrolled 687 treatment-naïve patients with genotype 1 HCV infection who were at least 18 years of age. Baseline hemoglobin levels were 12–15 g/dL for women and 13–15 g/dL for men, and patients had baseline platelet counts above 100,000 cells/mm^3. Liver biopsies were performed to confirm the presence of chronic HCV infection. Patients with compensated cirrhosis were allowed to enroll in this study, but patients with other liver diseases were excluded. Patients who were coinfected with HIV and/or hepatitis B virus (HBV) were also excluded from the study.

The treatment regimen included a 4-week lead-in period during which patients received peginterferon (1.5 µg/kg/week) and weight-based ribavirin (600–1,400 mg/day); patients then received triple therapy with boceprevir (800 mg three times daily) plus peginterferon and ribavirin. The majority of patients received boceprevir plus peginterferon and ribavirin for 25–44 weeks; however, 26% of patients received boceprevir plus peginterferon and ribavirin for a period of 24 weeks or less as part of the study's response-guided therapy regimen. Hemoglobin levels were measured every 2 weeks for the first 12 weeks of the study, after which they were measured at 24, 28, 34, 40, and 48 weeks. If a patient's hemoglobin level fell to 10 g/dL or lower, he or she was randomized to receive ribavirin dose reduction (n=249) or erythropoietin (n=251); 187 patients in the study were treated with triple therapy but maintained acceptable hemoglobin levels and did not receive either anemia intervention. Ribavirin was dose-reduced in 3 steps of 200–400 mg/day; erythropoietin was administered at 40,000 units per week, with the dose modified to 20,000 units/week or 60,000 units/week at the physician's discretion. Patients with hemoglobin levels at or below 8.5 g/dL received a secondary anemia intervention (whichever treatment was not used as the primary intervention), and HCV therapy was discontinued if hemoglobin levels fell to 7.5 g/dL or lower. The primary endpoint of the study was SVR 24 weeks after the end of treatment (SVR_{24}).

As was previously reported at the 2012 meeting of the European Association for the Study of the Liver, SVR was achieved in 71% of patients on triple therapy, regardless of the anemia management strategy that was employed. In addition, the number of patients who relapsed was the same in the ribavirin dose-reduction group (10%; 19/196 patients) and the erythropoietin group (10%; 19/197 patients). Patients with undetectable levels of HCV RNA at the time of ribavirin dose reduction or erythropoietin administration had higher SVR rates compared to patients who had detectable levels of HCV RNA at the time of their anemia intervention (86% vs 56%). Which primary anemia management strategy was employed did not alter this result: Among patients with undetectable HCV RNA levels, SVR rates were 86% for the ribavirin dose-reduction group (111/129 patients) versus 86% for the erythropoietin group (107/124 patients); among patients with detectable HCV RNA levels, SVR rates were 56% (67/120 patients) versus 56% (71/127 patients), respectively.

The timing of the first ribavirin dose reduction did not significantly alter SVR rates: <4 weeks, 70%; >4–8 weeks, 64%; >8–12 weeks, 79%; >12–16 weeks, 82%; >16 weeks, 71%. In addition, SVR rates were similar for patients in the ribavirin dose-reduction arm who received 1–7 steps of ribavirin dose reduction, with SVR rates of 64–83%. When SVR rates were analyzed according to the average daily dose of ribavirin, the data showed that patients who received less than 10 mg/kg/day of ribavirin had an SVR rate of 76% (84/110 patients). Similarly, SVR rates were 69% (36/52 patients) for patients who received a ribavirin dose of 10–11 mg/kg/day, 74% (29/39 patients) for patients who received 11–12 mg/kg/day, 65% (20/31 patients) for patients who received 12–13 mg/kg/day, and 53% (9/17 patients) for patients who received more than 13 mg/kg/day. There was no significant difference in SVR rates between patients whose lowest ribavirin dose was less than 10

mg/kg/day for a minimum of 7 days and those whose lowest ribavirin dose was greater than 10 mg/kg/day (74% vs 68%). However, patients who received less than 50% of the assigned dose of ribavirin over the entire treatment period had significantly lower SVR rates compared to patients who received at least 50% of their assigned dose (18% vs 74–92%).

Since variants in the inosine triphosphatase (ITPA) gene have been shown to protect against ribavirin-induced anemia, this study also assessed anemia rates and SVR rates by *ITPA* activity and genotype. Low *ITPA* activity was associated with an anemia rate of 50% (90/180 patients) and an SVR rate of 69% (125/180 patients). Patients with normal *ITPA* activity had an anemia rate of 70% (264/379 patients) and an SVR rate of 62% (234/379 patients). Patients with *ITPA* genotype C/C had the lowest rate of anemia (44%) compared to patients with the A/A or A/C genotypes (68% and 57%, respectively); patients with the C/C genotype also had the lowest SVR rate (C/C: 59%; A/A: 63%; A/C: 69%). In addition, the risk of developing anemia was increased in patients with normal *ITPA* activity (odds ratio [OR], 1.96; 95% confidence interval [CI], 1.28–3.00; *P*<.0019), age greater than 40 years (OR, 1.98; 95% CI, 1.19–3.28; *P*=.0084), and/or grade 3/4 fibrosis (OR, 2.02; 95% CI, 1.03–3.98; *P*=.0421).

Poordad concluded by stating that the timing of ribavirin dose reduction, the average daily ribavirin dose, and the lowest ribavirin dose received did not significantly affect SVR rates in treatment-naïve patients who received triple therapy with boceprevir, peginterferon, and ribavirin. While the SVR rate was significantly affected by whether HCV RNA levels were detectable at the time of anemia intervention, the strategy that was employed to manage anemia (ribavirin dose reduction vs erythropoietin) did not affect the SVR rate. However, SVR rates were lower if patients received less than 50% of their assigned dose of ribavirin.

Reference

1. Poordad F, Lawitz E, Reddy K, et al. Timing and magnitude of ribavirin dose reduction (RBV DR) do not impact sustained virologic response (SVR) rates with boceprevir (BOC) + peginterferon alfa-2b / ribavirin (P/RBV) in the Anemia Management Study in chronic HCV genotype 1 patients. Presented at the 63rd Annual Meeting of the American Association for the Study of Liver Diseases; November 9–13, 2012; Boston, Massachusetts. Abstract #154.

ABSTRACT SUMMARY A Clinical Decision Tool for Predicting Treatment Response and SVR in Patients Treated with Boceprevir Plus Peginterferon and Ribavirin

Triple therapy comprised of boceprevir plus peginterferon and ribavirin is an efficacious treatment option for many patients with HCV infection. However, a number of factors can influence patient response. To further explore these factors and their impact on HCV therapy, Scott Devine and colleagues sought to develop clinical decision tools for predicting HCV undetectability at treatment Week 8 and SVR. An accurate predictive model could inform clinical decision-making about duration and success of treatment. The results of this study were presented as a poster at the 2012 AASLD meeting.[1]

Devine and coauthors built logistic regression models to predict HCV undetectability at treatment Week 8 and SVR. The analysis used data from 1,227 patients in the SPRINT-2, RESPOND-2, and PROVIDE studies of boceprevir. The factors used in these models included prior treatment with peginterferon and ribavirin, *interleukin (IL)-28B* genotype, HCV genotype 1 subtype, initial ribavirin dose, age, race, sex, HCV RNA level after 4 weeks of peginterferon and ribavirin therapy, $\log_{10}$ reduction in HCV RNA level from baseline to treatment Week 4, and baseline characteristics (weight, body mass index [BMI], hemoglobin level, fibrosis score, the ratio between alanine aminotransferase [ALT] level and the upper limit of normal, platelet count, statin use, steatosis score, and HCV RNA level).

Nomograms were not developed for the baseline-only prediction models because of their poor ability to predict treatment Week 8 response and SVR (C-statistics, 0.76 and 0.69, respectively). Instead, final models that included baseline variables plus HCV RNA level at treatment Week 4 were developed to predict response at treatment Week 8 (n=856 patients) and SVR (n=522 patients). Both models included treatment-naïve patients, relapsers, and partial and prior nonresponders. *IL-28B* genotype was not included in the analysis.

A step-down approach was used to reduce the final number of predictors. In the model to predict treatment Week 8 response, the final variables were race, initial ribavirin dose, platelet count, $\log_{10}$ reduction in HCV RNA level from baseline to treatment Week 4, and HCV RNA level at treatment Week 4. In the SVR model, the final factors were sex, BMI, ribavirin use, platelet count, HCV genotype 1 subtype, and HCV RNA level at treatment Week 4. The final model calibration curves were presented and had good discrimination abilities for both the treatment Week 8 response model and the SVR model (C-statistics, 0.89 and 0.83, respectively). In addition to successfully predicting treatment Week 8 response and SVR without invasive testing, these nomograms could also be useful for clinical decision-making about the initiation and maintenance of therapy.

Reference

1. Devine S, Kattan M, Muir A, et al. Clinical decision tool for predicting treatment week eight response and sustained virologic response in patients treated with boceprevir (BOC) plus peginterferon alfa and ribavirin (PR). Presented at the 63rd Annual Meeting of the American Association for the Study of Liver Diseases; November 9–13, 2012; Boston, Massachusetts. Abstract #1842.

A 12-Week Interferon-Free Treatment Regimen with ABT-450/r, ABT-267, ABT-333, and Ribavirin Achieves High SVR_{12} Rates

The HCV NS3/4A protease inhibitor ABT-450 has been identified as a potentially efficacious treatment option for HCV infection when it is administered in conjunction with 100 mg of ritonavir (ABT-450/r). In prior exploratory studies, patients with genotype 1 HCV infection achieved high SVR rates (>90%) when they were treated with an interferon-free regimen containing ABT-450/r. At the 2012 AASLD meeting, Kris V. Kowdley presented the results of an ongoing study that is evaluating the safety and efficacy of regimens containing ABT-450/r, ribavirin, and 1 or 2 other direct-acting antiviral agents: ABT-267, an NS5A inhibitor, and/or ABT-333, a non-nucleoside polymerase inhibitor.[1] This study enrolled noncirrhotic, treatment-naïve patients and prior null responders, and its goal was to determine which combination of these direct-acting antiviral agents was optimal for the treatment of genotype 1 HCV infection.

The key eligibility criteria for this study were age 18–70 years, chronic genotype 1 HCV infection, no cirrhosis, HCV RNA level greater than 50,000 IU/mL, and no HIV or HBV coinfection. Null responders had received at least 12 weeks of peginterferon and ribavirin therapy but did not achieve a 2 $\log_{10}$ IU/mL decrease in HCV RNA levels. Patients were treated with various combinations of ABT-450/r (100–200 mg/100 mg daily), ABT-267 (25 mg daily), ABT-333 (400 mg twice daily), and/or weight-based ribavirin; treatment was administered for 8, 12, or 24 weeks. The primary efficacy endpoint of

ABSTRACT SUMMARY Assessment of Boceprevir Pharmacokinetic/Pharmacodynamic Relationships for SVR and Anemia in HCV/HIV Coinfected and HCV Monoinfected Patients

Administration of ritonavir-boosted HIV protease inhibitors reduces boceprevir concentrations in healthy volunteers. To further explore this interaction, Larissa A. Wenning and colleagues conducted a study that assessed boceprevir pharmacokinetics in HCV/HIV coinfected patients.[1] In addition, this study evaluated the relationships among boceprevir pharmacokinetics/pharmacodynamics, SVR, and anemia. These data were presented in a poster at the 2012 AASLD meeting.

This study included data from 3 clinical trials: a phase II HCV/HIV coinfection study, the phase III SPRINT-2 study, and the phase III RESPOND-2 study. Boceprevir-related pharmacokinetic data were available for 51 patients in the coinfection study, 105 patients in SPRINT-2, and 84 patients in RESPOND-2. A population pharmacokinetic model was used to estimate pharmacokinetic parameters. For the study arms that contained boceprevir, the OR was estimated using a linear regression model for SVR or anemia in which boceprevir pharmacokinetics (area under the curve from 0–8 hours [$AUC_{0\text{-}8hr}$] or concentration at 8 hours [C_{8hr}]) were used as predictors.

The cross-study comparison of boceprevir pharmacokinetics found that the boceprevir $AUC_{0\text{-}8hr}$ was approximately 20% lower in the HCV/HIV coinfection study than in the studies of HCV monoinfected patients. In addition, the C_{8hr} was approximately 27% lower in the coinfection study compared to the monoinfection studies. The SVR and anemia pharmacokinetic/pharmacodynamic results were similar for both boceprevir $AUC_{0\text{-}8hr}$ and C_{8hr}. Thus, Wenning and coauthors were unable to determine whether $AUC_{0\text{-}8hr}$ or C_{8hr} was a better predictor of efficacy or safety. In addition, the study found no significant relationship between boceprevir pharmacokinetics and SVR rates. However, there was a lower probability of anemia (hemoglobin level of 8.5–10 g/dL) with decreasing boceprevir pharmacokinetics, although this result was not significant for the coinfection study data alone.

The investigators concluded that overall boceprevir exposure was reduced in HCV/HIV coinfected patients compared to HCV monoinfected patients. However, reduced boceprevir exposure is unlikely to adversely influence the efficacy of treatment, given that the relationship between boceprevir pharmacokinetics and SVR rates was not significant. While reduced boceprevir exposure was associated with a reduced probability of anemia, ribavirin pharmacokinetic data were not collected in the coinfection study; for this reason, ribavirin cannot be eliminated as a confounding factor in the analysis. However, the coinfection study showed no relationship between boceprevir pharmacokinetics and ribavirin dose.

Reference

1. Wenning LA, Flexner C, Liu R, et al. Assessment of boceprevir (VICTRELIS™) pharmacokinetic/pharmacodynamic relationships for sustained viral response (SVR) and occurrence of anemia: results in HCV/HIV co-infected patients and in combined mono- and co-infected patients. Presented at the 63rd Annual Meeting of the American Association for the Study of Liver Diseases; November 9–13, 2012; Boston, Massachusetts. Abstract #770.

this study is SVR_{24}; however, the data presented at the 2012 AASLD meeting were from an interim analysis, so only SVR_{12} rates were available at this time, and only patients receiving 8 or 12 weeks of treatment were assessed for the interim analysis.

A total of 571 patients (438 treatment-naïve patients and 133 prior null responders) received at least 1 dose of study medication. In the 8-week and 12-week treatment groups, the majority of patients were white, 44% of patients were women, the mean age was 50 years, the mean BMI was 27.1 kg/m^2, and one third of patients had genotype 1a HCV infection. The mean baseline HCV RNA level was approximately 6.6 log_{10} IU/mL.

The highest SVR_{12} rates were achieved in patients who were treated with all 3 direct-acting antiviral agents plus ribavirin for 12 weeks. In this treatment arm, SVR_{12} rates were 97.5% (77/79 patients) in treatment-naïve patients and 93.3% (42/45 patients) in prior null responders. In all other treatment regimens, SVR_{12} rates were 85.4–89.9%. When the data were analyzed according to HCV subtype, the SVR_{12} rate for patients with genotype 1b HCV infection who received all 3 direct-acting antiviral agents plus ribavirin was 100% for both treatment-naïve patients and null responders. Patients with genotype 1a HCV infection who were treated with this regimen had slightly lower SVR_{12} rates (96% in treatment-naïve patients and 89% in null responders). In an analysis of *IL-28B* genotypes, treatment with all 3 direct-acting antiviral agents plus ribavirin again resulted in the highest SVR_{12} rates for both treatment-naïve patients and null responders (treatment-naïve patients: 100% for *IL-28B* genotype CC vs 97% for *IL-28B* genotype non-CC; null responders: 100% for *IL-28B* genotype CC vs 93% for *IL-28B* genotype non-CC).

ABSTRACT SUMMARY The Second-Generation HCV NS3/4a Protease Inhibitor MK5172 Retains Potent In Vitro Activity Against Boceprevir-Resistant Genotype 1 HCV Isolates

The second-generation HCV NS3/4A protease inhibitor MK5172 has demonstrated activity against multiple HCV genotypes and has been shown to significantly reduce HCV viral load in patients with genotype 1 HCV infection. At the 2012 AASLD meeting, a poster by Robert A. Ogert and coauthors presented data from a study that sought to confirm the activity of MK5172 against HCV isolates from patients who were clinically resistant to boceprevir.[1] In this study, investigators amplified the NS3 gene of 13 different clinical isolates from patients who failed therapy with boceprevir plus peginterferon and ribavirin. The amplified NS3 genes were then tested against MK5172 using an in vitro, replicon-based, phenotypic assay. The resistant isolates were also tested against boceprevir, telaprevir, and simeprevir.

Six genotype 1a isolates and 8 genotype 1b isolates with boceprevir resistance-associated variants were grouped according to virologic response; there were 8 isolates from patients with incomplete virologic response (3 genotype1a, 5 genotype 1b), 4 isolates from patients who experienced virologic breakthrough (1 genotype 1a, 3 genotype 1b), 1 relapser (genotype 1a), and 1 nonresponder (genotype 1a). Viral load plots that indicated the presence of resistance-associated variants were presented based on these groupings.

Among patients with incomplete virologic response, the resistance-associated variants in genotype 1a isolates were V36M, T54S, R155K, R155K/T, and A156S, while the variants in genotype 1b isolates were T54A/S, T54A, V170A, T54S, and R155K. Among patients who experienced virologic breakthrough, the resistance-associated variant in the genotype 1a isolate was R155T, and the resistance-associated variants in the genotype 1b isolates were V55A, T54A, V170A, and M175L. The variants present in the genotype 1a patient who relapsed were T54S and R155K, while the patient who was a nonresponder had V36M and R155K variants.

The isolates from genotype 1a patients who failed boceprevir-based therapy were resistant to boceprevir, telaprevir, and simeprevir in vitro. As compared to baseline isolates, there was an 8–13-fold (boceprevir), 18–36-fold (telaprevir), and greater than 10-fold (simeprevir) shift in IC_{50} from baseline. However, the boceprevir failure genotype 1a isolates that were resistant to boceprevir, telaprevir, and simeprevir were responsive to MK5172 (IC_{50}, 0.6 nM–4.4 nM).

The isolates from genotype 1b patients who failed boceprevir were resistant to boceprevir (2.7-fold shift in IC_{50}) and telaprevir (2.8-fold shift in IC_{50}) compared to baseline isolates. In contrast to the boceprevir failure genotype 1a isolates, the majority of genotype 1b isolates remained sensitive to simeprevir. Similar to the boceprevir failure genotype 1a isolates, the boceprevir failure genotype 1b isolates were sensitive to MK5172 (IC_{50}, 0.04 nM–0.25 nM) and had a greater than 2-fold shift in IC_{50} from baseline. The investigators noted that further studies are under way, including a clonal sequence analysis and deep sequencing of select patient samples.

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ABSTRACT SUMMARY OPTIMIZE Trial Shows Noninferiority of Twice-Daily Telaprevir Compared to 3-Times-Daily Administration

At the 2012 AASLD meeting, Maria Buti and associates presented the results of the OPTIMIZE trial, the first phase III clinical trial comparing twice-daily administration of telaprevir versus administration every 8 hours.[1] The primary endpoint of the study was noninferiority in SVR_{12} rates for twice-daily versus every-8-hour dosing of telaprevir in combination with peginterferon and ribavirin.

A total of 740 treatment-naïve patients with genotype 1 HCV infection were randomized to receive 12 weeks of peginterferon (180 µg/week) and ribavirin (1,000–1,200 mg/day) plus telaprevir at 1 of 2 doses: either 750 mg every 8 hours or 1,125 mg every 12 hours. All patients then received peginterferon and ribavirin without telaprevir for an additional 12 or 36 weeks; the total treatment duration was 24 or 48 weeks. Administration of telaprevir was halted if HCV RNA levels were greater than 1,000 IU/mL at Week 4 or if HCV RNA levels were at or above 25 IU/mL at Weeks 12, 24, 32, or 40. Patients were followed until Week 72.

In terms of efficacy, twice-daily telaprevir was found to be noninferior to telaprevir administered every 8 hours (SVR_{12}, 74% vs 73%, respectively; 95% CI, –4.9 to 12). A subgroup analysis according to liver fibrosis status and *IL-28B* genotype also demonstrated similar SVR_{12} rates for both dosing regimens. Among cirrhotic patients, SVR_{12} rates were 54% for patients who received telaprevir at a dose of 1,125 mg twice daily versus 49% for those who received telaprevir at a dose of 750 mg every 8 hours. In noncirrhotic patients, SVR_{12} rates were 78% and 77% for twice-daily versus every-8-hour dosing of telaprevir, respectively. In addition, rapid virologic response (RVR) rates were similar for both dosing regimens (69% and 67%, respectively). In patients who achieved RVR, SVR rates were 86% and 85% for twice-daily versus every-8-hour dosing of telaprevir; in patients who did not achieve RVR, the SVR rate was 47% with either dosing regimen. Relapse rates were 8% for patients who received 1,125 mg of telaprevir twice daily and 7% for patients who received 750 mg of telaprevir every 8 hours. Both dosing regimens had an on-treatment virologic failure rate of 10%.

The safety and tolerability of telaprevir were similar for patients dosed at 1,125 mg twice daily versus 750 mg every 8 hours. The most common adverse events in both groups were fatigue, pruritus, anemia, nausea, rash, and headache. Serious adverse events occurred in 8–9% of patients. Treatment discontinuation due to adverse events occurred in 15% of patients who received 1,125 mg of telaprevir twice daily and 19% of patients who received 750 mg of telaprevir every 8 hours. Since the safety profiles and SVR rates were similar for both treatment arms, Buti and colleagues concluded that telaprevir dosed at 1,125 mg twice daily plus peginterferon and ribavirin could offer a safe, effective, and simplified treatment option for patients with genotype 1 HCV infection.

Reference

1. Buti M, Agarwal K, Horsmans Y, et al. OPTIMIZE trial: noninferiority of twice daily telaprevir versus administration every 8 hours in treatment-naïve, genotype-1 HCV-infected patients. Presented at the 63rd Annual Meeting of the American Association for the Study of Liver Diseases; November 9–13, 2012; Boston, Massachusetts. Abstract #LB-8.

Among patients who were treated for 8 or 12 weeks with all 3 direct-acting antiviral agents plus ribavirin, viral breakthrough was not observed in any of the treatment-naïve patients, but breakthrough did occur in 3 null responders. Among patients who were treated with all 3 direct-acting antiviral agents plus ribavirin, relapse occurred in 9 treatment-naïve patients in the 8-week treatment group, 1 treatment-naïve patient in the 12-week treatment group, and 0 of the null responders. Among the patients in the 8-week treatment arm who relapsed, treatment-emergent resistance variants were detected in 3 of 9 patients. In the 12-week treatment groups, samples from patients with viral breakthrough or relapse showed the presence of resistance variants known to be selected by ABT-450, ABT-267, or ABT-333.

In terms of safety, Kowdley noted that all 8-week and 12-week treatment regimens were well tolerated. Overall, only 2 of 448 patients discontinued treatment due to adverse events. In addition, there were 5 serious adverse events (1%), 1 of which (arthralgia) occurred in the 24-week treatment group and may have been related to the study drugs. The most common grade 3/4 laboratory anomaly was an elevated level of indirect bilirubin (≥2× the upper limit of normal), which occurred in 24 treatment-naïve patients (6.7%) and 11 null responders (2.2%); when such elevations occurred, they were transient and asymptomatic. The most common adverse events included fatigue, headache, insomnia, and nausea. Kowdley noted that the investigators did not detect any new safety issues when patients received combination therapy with 2 or 3 of the direct-acting antiviral agents evaluated in this study.

As has been observed with ribavirin monotherapy, the ribavirin-containing treatment regimens in this study were associated with declines in hemoglobin levels. Patients who received 3 direct-acting antiviral agents without ribavirin had a lower incidence of hemoglobin levels below

ABSTRACT SUMMARY Treatment of Genotype 1 HCV–Infected Patients with Severe Fibrosis or Compensated Cirrhosis: The International Telaprevir Early Access Program

HEP3002 is an ongoing, international, early-access program for genotype 1 HCV–infected patients with severe fibrosis or compensated cirrhosis. At the 2012 AASLD meeting, Massimo Colombo and coworkers presented a poster with interim results from this study.[1] Overall, the study has enrolled more than 1,900 telaprevir-treated patients from 16 countries; the first 609 patients were included in this interim analysis.

Enrollment criteria included genotype 1 HCV infection, severe fibrosis or compensated cirrhosis (Metavir score of F3 or F4), and a platelet count over 90,000 cells/mm^3. The mean age of the patients was 53.5 years, 66.5% of the patients were male, and 97.7% were white. In addition, 66% of patients had HCV RNA levels of at least 800,000 IU/mL, 45% of patients had severe fibrosis, 55% had cirrhosis, and 28% had genotype 1a HCV infection. At baseline, 20% of patients were treatment-naïve, 28% were prior relapsers, 15% were partial prior responders, 29% were prior null responders, 3% were nonresponders for unspecified reasons, and 5% had prior viral breakthrough.

Patients were treated with telaprevir (750 mg every 8 hours) plus peginterferon and ribavirin for 12 weeks. Peginterferon and ribavirin were then administered for an additional 12–36 weeks using a response-guided treatment paradigm. At Week 4, 54% of patients had undetectable HCV RNA levels. By Week 12, 79% of patients had undetectable HCV RNA levels. The percentage of patients who showed an HCV RNA response at Week 12 was lower for prior null responders (73%) than for prior relapsers or treatment-naïve patients (85% for both groups).

Grade 1–4 anemia developed in 59% of patients (n=359), with 31% of patients experiencing severe anemia. Grade 1–4 rash developed in 42% of patients, with severe rash occurring in 4% of patients. Discontinuation due to adverse events occurred in 14% of patients (11.7% of patients with F3 fibrosis and 15.8% of patients with F4 fibrosis). Reasons for discontinuation included rash (4.9%), anemia (3.1%), asthenia (1.1%), abdominal pain (1.0%), nausea (1%), pruritus (1%), and vomiting (1%). The investigators noted that the rates of discontinuation for rash and anemia were similar to those observed in the phase III registration trials for telaprevir. Three cirrhotic patients (0.5%) died during the peginterferon and ribavirin phase of therapy due to hepatic failure/ischemic colitis and multiorgan failure; 1 of these deaths was deemed to be treatment-related, and 1 death was possibly treatment-related.

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1. Colombo M, Fernandez I, Abdurakhmanov D, et al. Treatment of hepatitis C genotype 1 patients with severe fibrosis or compensated cirrhosis: the international telaprevir early access program. Presented at the 63rd Annual Meeting of the American Association for the Study of Liver Diseases; November 9–13, 2012; Boston, Massachusetts. Abstract #LB-15.

10 g/dL. There was also a trend toward fewer events of anemia, insomnia, nausea, and cough in patients whose treatment did not include ribavirin. Kowdley indicated that these data provide some justification for further evaluation of ribavirin-sparing regimens in future studies.

The study investigators concluded that treatment with ABT-450/r, ABT-267, and ABT-333 plus ribavirin for 12 weeks was well tolerated. In addition, both treatment-naïve patients and null responders in this treatment arm achieved high SVR_{12} rates. Importantly, SVR was achieved even in patients who had predictors of poor response (genotype 1a infection, non-CC *IL-28B* genotype, and/or prior null response). Given these promising results, the combination of ABT-450/r, ABT-267, and ABT-333—with or without ribavirin—will be studied in planned phase III trials.

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High Rate of SVR with the All-Oral Combination of Daclatasvir Plus Sofosbuvir with or without Ribavirin

The introduction of oral agents that can effectively treat HCV infection will offer new treatment options for patients. The first-in-class NS5A replication complex inhibitor daclatasvir and the nucleotide analogue NS5B inhibitor sofosbuvir are direct-acting antiviral agents that can be administered orally.[1-4] Previous studies have shown that administration of daclatasvir and sofosbuvir in combination with peginterferon and ribavirin can achieve high SVR rates in treatment-naïve patients with genotype 1 HCV infection.[5,6] In a late-breaking abstract presented at the 2012 AASLD meeting, Mark S. Sulkowski presented the results of a parallel-group, open-label study that investigated interferon-free regimens consisting of daclatasvir plus sofosbuvir with and without ribavirin in treatment-naïve patients with chronic HCV infection.[7]

This study enrolled a total of 88 HCV-infected patients without cirrhosis: 44 patients were infected with genotype 1 HCV (73% genotype 1a), and 44 patients were infected with genotype 2 or 3 HCV (52% genotype 2 and 41% genotype 3). The mean HCV RNA level was at least 6.2 $\log_{10}$ IU/mL in all treatment groups. Patients' mean age was 50–56 years, 54% of patients were male, 32% had *IL-28B* genotype CC, and 65% had a Metavir score of F2 or greater.

Patients were randomized 1:1:1 to receive 1 of 3 regimens: (1) sofosbuvir for 7 days, followed by daclatasvir and sofosbuvir for 23 weeks; (2) daclatasvir and sofosbuvir for 24 weeks; or (3) daclatasvir and sofosbuvir plus ribavirin for 24 weeks. During the study, the protocol was amended to include an additional 82 patients with genotype 1 HCV infection who received daclatasvir and sofosbuvir with or without ribavirin for 12 weeks. Daclatasvir (60 mg) and sofosbuvir (400 mg) were administered orally. Patients with genotype 1 HCV infection received 1,000–1,200 mg/day of ribavirin, while patients with genotype 2 or 3 HCV infection received 800 mg/day of ribavirin. The primary endpoint of the study was SVR_{12}, which was defined as an HCV RNA level less than 25 IU/mL 12 weeks after the end of treatment. SVR_4 rates were also assessed.

Plasma HCV RNA levels were measured using the Roche COBAS TaqMan Version 2.0, which has a lower limit of quantitation of 25 IU/mL and a limit of detection less than 10 IU/mL. Population sequencing was used to evaluate resistance-associated variants. Viral breakthrough was confirmed by an HCV RNA increase of at least 1 $\log_{10}$ IU/mL from nadir or an HCV RNA level at or above the lower limit of quantitation at Week 8.

Analysis of patients with genotype 2 or 3 HCV infection showed that both SVR_4 and SVR_{12} were achieved by 91% of patients (40/44). Among the 4 patients infected with genotype 2 or 3 HCV who did not achieve SVR_{12}, 1 patient relapsed at post-treatment Week 4 due to a pre-existing NS5A-A30K polymorphism, 2 patients were lost to follow-up, and 1 patient added peginterferon and ribavirin according to the protocol.

Among the 82 patients with genotype 1 HCV infection who were treated with daclatasvir and sofosbuvir with or without ribavirin for 12 weeks, 95–98% had confirmed undetectable levels of HCV RNA. At the time of this AASLD presentation, 68 of the 82 patients had reached post-treatment Week 12, and all had achieved SVR_{12}. There were no confirmed virologic relapses in the 12-week treatment arm at either post-treatment Week 4 or post-treatment Week 12.

Among patients with genotype 1 HCV infection who were in the 24-week treatment arms, all 44 patients had undetectable HCV RNA levels at the end of treatment (100% SVR_4 and 100% SVR_{12}). Forty-three of these 44 patients (93%) achieved SVR_{24}. One patient who had a history of injection drug use developed viremia at SVR_{24}, but further analysis of the patient's clinical history and physical examination and a comparison of viral sequences between baseline and post-treatment Week 24 suggested that this viremia was due to reinfection rather than a viral relapse. Almost all of the patients who reached post-treatment Week 24 achieved SVR_{24} (39/40 of genotype 1 patients and 41/43 of genotype 2 or 3 patients). The investigators did not detect a difference in response due to genotype 1 HCV subtype, *IL-28B* genotype, or the presence/absence of ribavirin in the treatment regimen.

The most common adverse events observed in this study were fatigue (range, 29–50%), headache (range, 16–38%), and nausea (range, 16–32%). Grade 3/4 adverse events occurred in 0% of patients in the group treated with a sofosbuvir lead-in followed by 23 weeks of daclatasvir and sofosbuvir, 14% of patients treated for 24 weeks with daclatasvir and sofosbuvir, 7% of patients treated for 24 weeks with daclatasvir and sofosbuvir plus ribavirin, 2% of patients treated for 12 weeks with daclatasvir and sofosbuvir, and 2% of patients treated for 12 weeks with daclatasvir and sofosbuvir plus ribavirin. Anemia was the most common grade 3/4 laboratory anomaly, but it only occurred in patients treated with ribavirin (n=6 patients [21%] in the 24-week daclatasvir and sofosbuvir plus ribavirin group; n=5 patients [12%] in the 12-week daclatasvir and sofosbuvir plus ribavirin group). One patient in the 24-week daclatasvir and sofosbuvir group and 1 patient in the 24-week daclatasvir and sofosbuvir plus ribavirin group discontinued treatment due to adverse events.

In summary, patients treated with daclatasvir and sofosbuvir achieved high SVR rates regardless of HCV genotype or whether ribavirin was included in the treatment regimen. Genotype 1 HCV–infected patients treated for 12 weeks achieved an SVR_4 rate of 96%, and genotype 1 HCV–infected patients treated for 24 weeks achieved an SVR_{24} rate of 98%. Patients infected with genotype 2 or 3 HCV achieved an SVR_{24} rate of 93%. Patient responses did not change with genotype 1 HCV subtype, *IL-28B* genotype, or the addition of ribavirin. Overall, this treatment regimen was well tolerated, with low hemoglobin levels observed only in patients who were treated with ribavirin.

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An Interferon-Free, Ribavirin-Free 12-Week Regimen of Daclatasvir, Asunaprevir, and BMS-791325 Achieved High SVR_4 Rates

Previous preliminary studies revealed that 24 weeks of treatment with daclatasvir (an NS5A replication complex inhibitor) and asunaprevir (an NS3 protease inhibitor) is an effective treatment option for prior null responders who are infected with genotype 1b HCV but not for those infected with genotype 1a HCV.[1,2] In an effort to enhance virologic response, improve efficacy in difficult-to-treat patient populations, and shorten treatment durations, Gregory T. Everson and colleagues assessed a peginterferon-free, ribavirin-free regimen of 3 direct-acting antiviral agents with different mechanisms of action: daclatasvir, asunaprevir, and BMS-791325 (a selective nonnucleoside NS5B polymerase inhibitor).[3]

This phase IIa, open-label study enrolled noncirrhotic treatment-naïve patients who were infected with genotype 1 HCV and had baseline HCV RNA levels above 105 IU/mL. In part 1 of the study, 32 patients were randomized 1:1 to receive asunaprevir (200 mg twice daily), daclatasvir (60 mg once daily), and BMS-791325 (75 mg twice daily) for either 24 weeks (group 1) or 12 weeks (group 2). In part 2 of the study, patients were randomized to the same treatment regimens but received a higher dose of BMS-791325 (150 mg twice daily). Part 1 and part 2 of the study were sequentially enrolled, with enrollment in part 2 being delayed until data were collected from part 1 of the study. The primary endpoint of the study was an undetectable level of HCV RNA (below the lower limit of quantitation of 25 IU/mL) at post-treatment Week 12.

At the 2012 AASLD meeting, Everson presented interim data from part 1 of this study; endpoints for this interim analysis were SVR_4 rates for patients who received 24 weeks of treatment and SVR_{12} rates for those who received 12 weeks of treatment.[4] Baseline patient characteristics were similar for patients in the 12-week and 24-week treatment arms in part 1 of the study. The median age of the 32 patients in part 1 of the study was 48 years, 53% of patients were male, 75% were white, and the mean baseline HCV RNA level was 6.26 $\log_{10}$ IU/mL. By study design, 75% of these patients were infected with genotype 1a HCV. The majority of patients (72%) had a non-CC *IL-28B* genotype. Half the patients in this group had a Metavir fibrosis score of F0/F1, 44% had a score of F2/F3, and 6% had a score above F3; patients in the latter group were found to be noncirrhotic by liver biopsy.

In terms of viral kinetics, all patients in the 24-week treatment group showed a rapid decline in HCV viral load. By Week 4 of treatment, all patients (32/32) had HCV RNA levels below the lower limit of quantitation. HCV RNA levels remained undetectable through post-treatment Week 4. Similarly, patients in the 12-week treatment arm experienced a sharp decline in HCV RNA levels, and all patients in this group had viral loads below the limit of detection at post-treatment Week 12.

At treatment Week 12, 94% of patients in the 24-week treatment arm and 88% of patients in the 12-week treatment arm had undetectable HCV RNA levels. At the end of therapy, these rates were 94% and 100%, respectively. The SVR_4 rate was 94% for both the 24-week and 12-week treatment arms. The SVR_{12} rate in the 12-week treatment arm was also 94%. In a subgroup analysis of patients with genotype 1a HCV infection, 92% of patients in the 24-week treatment arm and 100% of

patients in the 12-week treatment arm achieved SVR_4. Everson highlighted the fact that a high SVR rate was achieved even though many of the patients in this study had a non-CC *IL-28B* genotype and/or a high viral load.

Overall, treatment with daclatasvir, asunaprevir, and BMS-791325 was well tolerated. No patients discontinued treatment due to adverse events. The most common adverse events were headache (31%), diarrhea (25%), and asthenia (16%). There was 1 serious adverse event (renal calculus), but it was found to be unrelated to the treatment regimen. One patient in the 12-week treatment group experienced a grade 3/4 headache, which resolved, and 1 patient had grade 3/4 lymphopenia at a single study visit, which occurred at a time when the patient had influenza. There were no grade 3/4 elevations in ALT, aspartate aminotransferase, or bilirubin levels.

Based on the interim data presented at the 2012 AASLD meeting, Everson and associates concluded that 12 weeks of therapy with the direct-acting antiviral agents daclatasvir, asunaprevir, and BMS-791325 was well tolerated. In addition, both 12 weeks and 24 weeks of treatment resulted in high SVR rates for patients infected with genotype 1 HCV, including patients with high viral loads and/or non-CC *IL-28B* genotypes. Everson noted that this treatment is promising and will continue to be evaluated in the future. This trial is currently being expanded to include null responders, treatment-experienced patients, and patients with advanced fibrosis.

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Commentary

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Several presentations at the 2012 meeting of the American Association for the Study of Liver Diseases (AASLD) focused on the management of hepatitis C virus (HCV) infection. Multiple treatment options are coming to the forefront.

Poordad, et al presented results from the Anemia Management Study, which examined whether sustained virologic response (SVR) rates are affected by the timing and magnitude of ribavirin dose reduction in HCV patients receiving boceprevir plus peginterferon and ribavirin.[1] Management of anemia was attempted through ribavirin dose reduction or erythropoietin (EPO). The importance of this study is that it is the only prospective randomized trial to assess the effect of EPO on SVR using a protease inhibitor. It conclusively showed that there was no benefit to using EPO over ribavirin dose reduction as the initial management strategy. Moreover, it suggested that there are potential safety signals, with 11 thromboembolic events in the EPO arm compared to 1 event in the ribavirin dose-reduction arm. This study also highlights the fact that when patients are anemic, ribavirin can be dose-adjusted to whatever degree is necessary, as long as there is maintenance of at least 50% of the overall dose throughout the duration of treatment in order to not impact SVR.

One of the most important abstracts at this year's AASLD meeting has set a new bar for expectations in treating null responders. Kowdley, et al reported results from a 12-week trial of different combinations of 4 drugs: ritonavir-boosted ABT-450, a protease inhibitor; ABT-267, an NS5A inhibitor; ABT-333, a non-nucleoside polymerase inhibitor; and ribavirin.[2] In only 12 weeks, the various combinations of these agents achieved an SVR of up to 98% in treatment-naïve patients and of 93% in a null responder population. This SVR rate is the highest achieved in a null responder population using an all-oral regimen, and it has established the expectation that it is possible to achieve greater than 90% SVR rates in both treatment-naïve and treatment-experienced patients using an all-oral regimen. The limitation to this finding is that there were no cirrhotic patients in this study, and therefore their response to these regimens is unknown.

Sulkowski, et al presented results from a trial that examined daclatasvir, a first-in-class NS5A replication complex inhibitor, combined with the nucleotide analogue NS5B inhibitor sofosbuvir.[3] Both the 12-week and 24-week regimens of this combination achieved very high SVR rates in patients with HCV genotypes 1, 2, or 3. Although development of the daclatasvir/sofosbuvir combination will likely not proceed due to industry complications, this study provides a good proof of principle that the combination of a nucleoside analogue with an NS5A inhibitor can led to very high sustained response rates in a multigenotypic patient population. In so doing, this study sets the stage for the development of combinations

using other drugs from these classes, such as GS-5885.

The combination of daclatasvir; asunaprevir, an NS3 protease inhibitor; and the relative newcomer BMS-791325, a selective non-nucleoside NS5B inhibitor in patients infected with genotype 1 HCV, was examined in a phase IIa study reported by Everson, et al.[4] The combination was well tolerated and resulted in high SVR rates after 12 weeks and 24 weeks of treatment. This trial provided perhaps the most surprising data that emerged from the AASLD meeting because non-nucleoside agents are conventionally thought to have weak antiviral activity and yet BMS-791325 boosted sustained response rates up to 94%.

Poster presentations on HCV reported some interesting data. Wenning, et al presented results of a study that assessed boceprevir pharmacokinetics in patients coinfected with HCV and human immunodeficiency virus (HIV). Boceprevir exposure was reduced in patients with HCV and HIV compared to patients with HCV alone.[5] The OPTIMIZE trial showed that twice-daily administration of telaprevir was as effective as administration 3 times daily among treatment-naïve patients with genotype 1 HCV infection.[6]

The Future of Hepatitis C Therapy

These trials give clinicians a snapshot of the future landscape, when there will be multiple all-oral regimens available with very high response rates that will allow treatment of a larger volume and breadth of patients. Patients who have failed interferon-based therapies or who are reluctant to receive them may now have other alternatives. These studies have the potential to broaden the range of patient types that can be treated in the future. In addition, phase III trials are examining regimens such as sofosbuvir and GS-5885 with or without ribavirin[7] and ABT-450 with ritonavir, ABT-267, ABT-333, and ribavirin.[8] Two new protease inhibitors, simeprevir and faldaprevir, are nearing the completion of phase III trials and will be coming to market in 2014.[9,10] Clinicians may choose to delay initiation of treatment in certain patients as they anticipate the arrival of future therapies.

It should be noted, however, that research in this field is still early. Some of these regimens have not been tested in large enough numbers, and toxicities may derail some of the development programs. We need to be cautiously optimistic, but not declare that the game is over until it is truly over. Future research to improve the understanding of HCV therapy should focus on the response of the cirrhotic patient. A larger percentage of our population is developing advanced cirrhosis. We need to understand how drugs perform in these patients and determine whether different toxicities or increased resistance may arise. Research should also focus on patients who are considered nonresponsive to interferon, in order to ensure that we understand why it is that some regimens are apparently more effective than others.

The future of hepatitis C therapy is very bright, with multiple treatment options coming to the forefront. These choices will add to the complexity of selecting the best course of management for these patients. Every 6 months, there seems to be a substantial amount of new information that changes our understanding of hepatitis C therapy and propels treatment forward. Clinicians should keep an eye toward the future and the next major international meeting, where our focus may be somewhat readjusted as we fine-tune our understanding of this therapeutic area.

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