GASTROENTEROLOGY & HEPATOLOGY™
The Independent Peer-Reviewed Journal

January 2012 | A SPECIAL MEETING REVIEW EDITION | Volume 8, Issue 1, Supplement 1

Highlights in the Treatment of Hepatitis C Virus Infection From AASLD 2011

The 62nd Annual Meeting of the American Association for the Study of Liver Diseases
November 4–8, 2011
San Francisco, California

With commentary by

John M. Vierling, MD, FACP
Professor of Medicine and Surgery
Chief of Hepatology
Baylor College of Medicine
Houston, Texas

Special Reporting on:

HCV RNA Quantification Cutoff Is Significant in Boceprevir-Based Treatment

Telaprevir-Based Regimens Provide Durable Sustained Virologic Response in Patients with Genotype 1 HCV Infection

Milk Thistle Extract Is Not Beneficial in Previously Treated Patients with HCV Infection

Boceprevir-Containing Regimens Are Effective in HCV/HIV-Coinfected Patients

PLUS Meeting Abstract Summaries

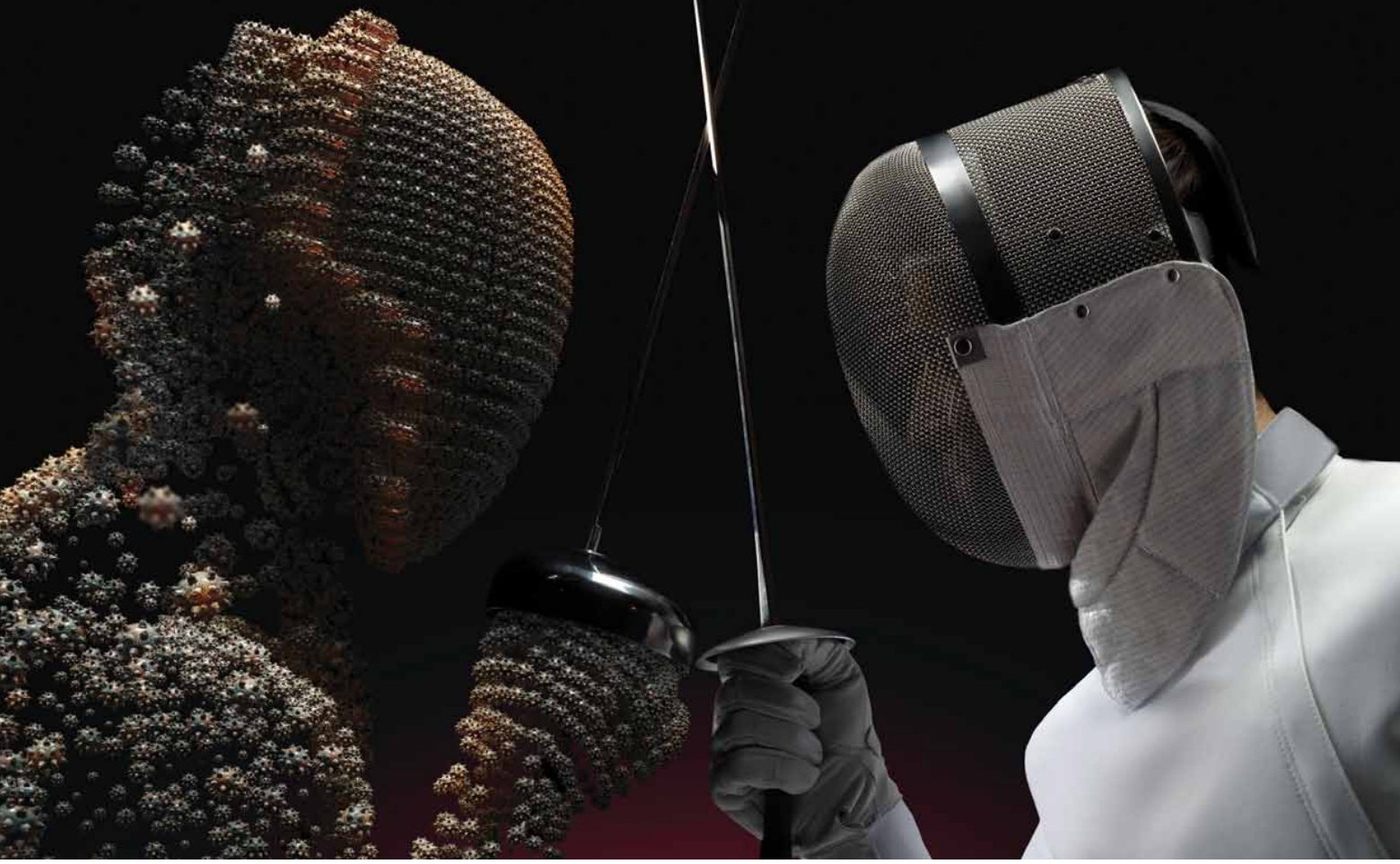
GASTROENTEROLOGY & HEPATOLOGY™
The Independent Peer-Reviewed Journal

Table of Contents

Indexed through the National Library of Medicine (PubMed/Medline), PubMed Central (PMC), and EMBASE

VICTRELIS 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:

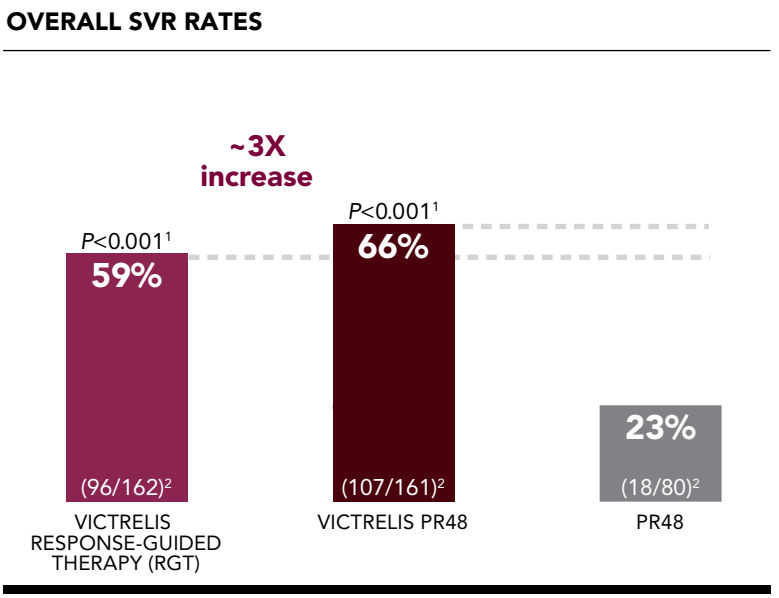
- VICTRELIS must not be used as monotherapy and should only be used in combination with PR
- VICTRELIS efficacy has not been studied in patients who have previously failed therapy with a treatment regimen that includes VICTRELIS or other HCV NS3/4A protease inhibitors
- VICTRELIS in combination with 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 **http://www.victrelis.com**
or scan this QR code to go there directly

VICTRELIS™
boceprevir

VICTRELIS + PR vs PR: In adult patients with chronic HCV G1 infection 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 undetectable HCV-RNA at end of prior treatment with a subsequent detectable HCV-RNA 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 1400 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 = SVR.[1] All subjects with detectable HCV-RNA in plasma at Treatment Week 12 were discontinued from treatment. SVR was defined as plasma HCV-RNA undetectable 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.

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 and concomitant ribavirin
- 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 = twice 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 undetectable HCV-RNA from serum by a sensitive polymerase chain reaction (PCR) assay 24 weeks following the discontinuation of therapy. 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 include: alfuzosin, carbamazepine, phenobarbital, phenytoin, rifampin, dihydroergotamine, ergonovine, ergotamine, methylergonovine, cisapride, St. John's Wort (hypericum perforatum), lovastatin, simvastatin, drosperinone, *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, 2011; Silver Spring, MD. Available at: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AntiviralDrugsAdvisoryCommittee/UCM254076.pdf. Accessed October 5, 2011. **3.** Ghany MG, Strader DB, Thomas DL, et al. AASLD practice guidelines. Diagnosis, management, and treatment of hepatitis C: an update. *Hepatology*. 2009;49(4):1335–1374. **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.

Visit **http://www.victrelis.com**
or scan this QR code to go there directly

VICTRELIS™
boceprevir

VICTRELIS™ (boceprevir)

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	Drosperinone	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/mL, and a limit of HCV-RNA detection of approximately 10-15 IU/mL. For the purposes of assessing Response-Guided Therapy milestones, a confirmed "detectable but below limit of quantification" HCV-RNA result should not be considered equivalent to an "undetectable" HCV-RNA result.

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 >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
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, flecainide, 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.
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 (maybe 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: ritonavir	↓ boceprevir* ↑ or ↓ HIV protease inhibitors	Boceprevir concentrations decreased with ritonavir; the effect of ritonavir-boosted HIV protease inhibitors on boceprevir exposure is unknown. The effect of VICTRELIS on HIV protease inhibitor concentrations is unknown.
HMG-CoA Reductase Inhibitors: atorvastatin	↑ atorvastatin	Titrate atorvastatin dose carefully and do not exceed maximum daily dose of 20 mg during coadministration with VICTRELIS
Immunosuppressants: cyclosporine, sirolimus, tacrolimus	↑ immunosuppressants	Plasma concentrations of cyclosporine, sirolimus and tacrolimus are expected to be increased significantly during coadministration with VICTRELIS. Close monitoring of immunosuppressant 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.

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.

VICTRELIS™
boceprevir

HCV RNA Quantification Cutoff Is Significant in Boceprevir-Based Treatment

The addition of the oral hepatitis C virus (HCV) NS3/4A protease inhibitor boceprevir to peginterferon and ribavirin is associated with significant improvements in sustained virologic response (SVR) rates, both in treatment-naïve patients (SPRINT-2 trial) and in previously treated patients (RESPOND-2 trial).[1,2] In both of these phase III trials, patients were randomly assigned to 1 of 3 treatment arms: a response-guided treatment regimen containing boceprevir, peginterferon, and ribavirin, in which treatment duration was based on HCV RNA levels at Weeks 8–24; a fixed-duration regimen containing boceprevir, peginterferon, and ribavirin, in which the treatment duration was 48 weeks for all patients; or a regimen containing peginterferon and ribavirin.

In these studies, HCV RNA levels were measured using the TaqMan v2 assay, which has a lower limit of quantification (LOQ) of 25 IU/mL and a lower limit of detection (LOD) of 9.3 IU/mL. In real-world practice, however, assays with differing cutoffs are used. To correlate these clinical trial findings with the assay cutoffs used in clinical practice, Eric J. Lawitz and colleagues analyzed how the response cutoff used affected SVR rates and relapse rates.[3] This analysis was presented at the 2011 Annual Meeting of the American Association for the Study of Liver Diseases (AASLD).

Patients were categorized into 1 of 3 groups according to on-treatment response: those with HCV RNA levels that were undetectable (below the LOD of 9.3 IU/mL), those with HCV RNA levels that were detectable but below the LOQ (9.3–25 IU/mL), and those with HCV RNA levels that were quantifiable (>25 IU/mL). In a pooled analysis of patients from both the SPRINT-2 and RESPOND-2 trials, the proportion of

ABSTRACT SUMMARY Quad Regimen Containing VX-222 and Telaprevir for Treatment-Naïve Patients with HCV Genotype 1 Infection

The ZENITH trial is an ongoing, phase II study evaluating 12-week response-guided treatment with the HCV polymerase inhibitor VX-222 plus telaprevir, in combination with peginterferon and ribavirin, in treatment-naïve patients with genotype 1 HCV infection. A total of 106 patients were originally assigned to 1 of 2 treatment regimens: VX-222 plus telaprevir; or quad therapy with VX-222, telaprevir, peginterferon, and ribavirin. The dual therapy regimens were halted early due to viral breakthrough. The trial was continued using the 4-drug combination plus a newly added 3-drug regimen consisting of telaprevir, VX-222, and ribavirin.

At the 2011 AASLD Annual Meeting, David R. Nelson presented a Week 24 interim analysis of the ZENITH trial, focusing on the 59 patients who received the 4-drug regimen: VX-222 (100 mg [n=29] or 400 mg [n=30] twice daily), telaprevir (1,125 mg twice daily), peginterferon (180 µg/week), and ribavirin (1,000–1,200 mg/day) for 12 weeks.[1] In this response-guided approach, patients could stop all treatment at Week 12 if they had undetectable levels of HCV RNA at Weeks 2 and 8 (as measured using the Taqman v2 assay); patients whose HCV RNA levels were detectable at either Week 2 or Week 8 received a total of 24 weeks of peginterferon and ribavirin.

Among patients who received VX-222 at a dose of 400 mg, 15 of 30 patients (50%) were able to stop treatment at Week 12; SVR was achieved by 14 of 15 of those patients (93%). Of the 15 patients receiving the 400-mg dose of VX-222 who were assigned to 24 weeks of treatment, 13 patients (87%) had undetectable levels of HCV RNA at 12 weeks post-treatment.

Among patients receiving the 100-mg dose of VX-222, 11 of 29 patients (38%) were able to stop treatment at Week 12; 82% of those patients (9/11) attained SVR. Of the 18 patients in the 100-mg VX-222 arm who were assigned to 24 weeks of treatment, 15 patients (83%) had undetectable levels of HCV RNA at 12 weeks post-treatment.

In an intent-to-treat analysis of all patients, undetectable HCV RNA levels at Week 24 were observed in 90% of patients assigned to the 400-mg dose of VX-222 and in 83% of patients assigned to the 100-mg dose of VX-222. Relapses occurred in 3 patients: 2 in the 100-mg VX-222 arm and 1 in the 400-mg VX-222 arm.

In terms of safety, the most frequently reported adverse events included fatigue (56%), nausea (49%), diarrhea (48%), anemia (37%), pruritus (34%), and rash (31%). Severe adverse events occurring in more than 1 patient included neutropenia (5.1%), hypomagnesemia (3.4%), and anemia (3.4%).

Reference

1. Nelson DR, Gane EJ, Jacobson IM, et al. VX-222/telaprevir in combination with peginterferon-alfa-2a and ribavirin in treatment-naïve genotype 1 HCV patients treated for 12 weeks: ZENITH study, SVR12 interim analysis. Presented at the Annual Meeting of the American Association for the Study of Liver Diseases; November 4–8, 2011; San Francisco, California. Abstract LB-14.

patients who had an HCV RNA level that was detectable but below the LOQ at Week 8 was 14.5% in the response-guided treatment arm and 17.3% in the fixed-duration boceprevir-treatment arm. Interestingly, the proportion of patients whose responses fell into this intermediate category (detectable but below the LOQ) peaked at Week 8, which is the most critical time point for response-guided therapy. At the end of the follow-up period (24 weeks post-therapy), only 1 of 571 patients (0.2%) had an HCV RNA level that was detectable but below the LOQ.

The use of different cutoffs at Week 8 also appeared to affect SVR rates. SVR rates were 84–89% among patients with undetectable HCV RNA levels at Week 8, 63–75% in patients with HCV RNA levels that were detectable but below the LOQ at Week 8, and 13–24% in patients with detectable HCV RNA levels at Week 8. In a combined analysis of all treatment arms, SVR rates were 89% in patients with undetectable HCV RNA levels and 67% in patients with HCV RNA levels that were detectable but below the LOQ.

Lawitz also discussed how variability in the timing of the Week 8 blood draw could impact the observed HCV RNA levels, as the Week 8 sample could be collected any time between treatment Weeks 7 and 9. Although most patients submitted samples on Week 8, a minority of patients had blood collected earlier or later; therefore, changes in viral load between Weeks 7 and 9 could be relevant. Indeed, the investigators found that the proportion of patients attaining undetectable HCV RNA levels increased during this period, from 47% at Week 7 to 66% at Week 9, and the proportion of patients with quantifiable HCV RNA levels declined correspondingly, from 36% at Week 7 to 18% at Week 9. However, the proportion of patients in the intermediate group—those with detectable but not quantifiable HCV RNA levels—remained stable at 16–17% between Weeks 7 and 9.

Overall, patients with undetectable HCV RNA levels had high SVR rates (87–89%) regardless of when HCV RNA undetectability was attained. In contrast, among patients in the intermediate response category (detectable but below the LOQ), those who attained HCV RNA undetectability later in the course of therapy had lower SVR rates. In a combined analysis, 67% of patients with HCV RNA levels that were detectable but below the LOQ at Week 8 attained SVR; among patients with HCV RNA levels that were detectable but below the LOQ at Week 20, the SVR rate decreased to 19%.

Similar trends were seen for relapse rates. Relapse rates remained low (6–8%) in patients who attained undetectable HCV RNA levels, regardless of when undetectability was attained. Conversely, the relapse rate among patients whose HCV RNA level was detectable but below the LOQ increased as therapy progressed, from a 15% relapse rate among patients whose HCV RNA level was detectable but below the LOQ at Week 8, to 50% of patients whose HCV RNA level was detectable but below the LOQ at Week 20. A genotype analysis showed no difference in the frequency or impact of SVR according to genotype (1a vs 1b).

Lawitz concluded that the earlier patients attain undetectable levels of HCV RNA, the higher the chances of achieving SVR. Conversely, the later patients attain HCV RNA levels below the LOD, the higher the relapse rate. Thus, more vigilant monitoring of HCV RNA levels in patients with detectable levels of HCV RNA at Week 8 could improve SVR rates. Finally, while SVR can be evaluated using the lower LOQ, decisions regarding the duration of response-guided therapy, which are made at Week 8, should be based on the lower LOD.

References

1. Poordad F, McCone J, Bacon BR, et al. Boceprevir for untreated chronic HCV genotype 1 infection. *N Engl J Med*. 2011;364:1195-1206.
2. Bacon BR, Gordon SC, Lawitz E, et al. Boceprevir for previously treated chronic HCV genotype 1 infection. *N Engl J Med*. 2011;364:1207-1217.
3. Lawitz E, Poordad F, Bronowicki J, et al. The effect of using lower limit of quantitation (LLQ) vs lower limit of detection (LLD) for the definition of undetectable HCV RNA: data from the RESPOND-2 and SPRINT-2 trials. Presented at the Annual Meeting of the American Association for the Study of Liver Diseases; November 4–8, 2011; San Francisco, California. Abstract 167.

Telaprevir-Based Regimens Provide Durable Sustained Virologic Response in Patients with Genotype 1 HCV Infection

Recently published, phase III trials have demonstrated high SVR rates in patients with genotype 1 chronic HCV infection who were treated with regimens containing the HCV NS3/4A protease inhibitor telaprevir; this finding has been observed both in previously untreated patients and in patients who were previously treated with peginterferon-α and ribavirin.[1-3] Although a high proportion of patients respond to telaprevir, HCV variants that confer a decreased sensitivity to this drug have been detected in patients who do not attain SVR with telaprevir-based regimens.

The EXTEND trial is a multinational, 3-year study of patients enrolled in phase II and phase III studies of telaprevir. This trial was designed to assess the durability of responses in patients who attained SVR, to examine changes in HCV variants over time in patients who do not attain SVR, and to examine long-term clinical outcomes. At the 2011 AASLD Annual Meeting, Kenneth E. Sherman presented the second set of interim results from this trial.[4]

This analysis included 408 patients, 55% of whom attained SVR. Of these 223 patients, 222 patients (>99%) maintained undetectable levels of HCV

RNA over a median follow-up period of 21 months after achieving SVR. The single relapse occurred in a patient who discontinued treatment after receiving only 10 weeks of therapy; this relapse occurred 48 weeks after stopping treatment.

A resistance analysis using population-based sequence analysis was conducted in 185 patients who did not attain SVR. Overall, resistance mutations were no longer detected in 85% of patients after a median follow-up period of 29 months; this rate was 95% among patients with genotype 1b HCV infection and 77% among patients with genotype 1a HCV infection. No severe liver-related clinical events occurred during the follow-up period among patients who attained SVR. In the non-SVR population, 4 of 185 patients (2.2%) developed liver-related events, including 2 cases of hepatocellular carcinoma leading to liver transplantation, 1 case of hepatic encephalopathy, and 1 case of ascites.

Overall, these results continue to show that SVR is durable among patients treated with telaprevir-based regimens; in addition, most patients with resistant variants subsequently revert to wild-type virus. Severe clinical events occurred in a small proportion of patients who did not attain SVR.

References

1. Sherman KE, Flamm SL, Afdhal NH, et al. Response-guided telaprevir combination treatment for hepatitis C virus infection. *N Engl J Med*. 2011;365:1014-1024.
2. Zeuzem S, Andreone P, Pol S, et al. Telaprevir for retreatment of HCV infection. *N Engl J Med*. 2011;364:2417-2428.
3. Jacobson IM, McHutchison JG, Dusheiko G, et al. Telaprevir for previously untreated chronic hepatitis C virus infection. *N Engl J Med*. 2011;364:2405-2416.
4. Sherman KE, Sulkowski MS, Zoulim F, et al. Follow-up of SVR durability and viral resistance in patients with chronic hepatitis C treated with telaprevir-based regimens: interim analysis of the EXTEND study. Presented at the Annual Meeting of the American Association for the Study of Liver Diseases; November 4–8, 2011; San Francisco, California. Abstract 248.

ABSTRACT SUMMARY Boceprevir-Based Therapy Effective in Some Prior Null Responders

The PROVIDE study is an ongoing, multicenter, single-arm rollover study evaluating the efficacy of boceprevir, peginterferon, and ribavirin in patients who previously failed to respond to peginterferon and ribavirin. The PROVIDE study enrolled 168 patients who were previously assigned to the control arm of 1 of 4 boceprevir studies: SPRINT-1, SPRINT-2, RESPOND-2, or PEG 2a/BOC. Patients were required to have received at least 12 weeks of peginterferon and ribavirin. Failure to achieve SVR could have been due to 1 of 3 reasons: 1) futility, defined as a detectable level of HCV RNA at Week 12 in treatment-experienced patients or at Week 24 in previously untreated patients; 2) virologic breakthrough; or 3) relapse after attaining an end-of-treatment response. The PROVIDE treatment regimen consisted of boceprevir (800 mg 3 times daily), peginterferon α-2b (1.5 µg/kg weekly), and weight-based ribavirin (600–1,400 mg/day in 2 divided doses).

At the 2011 AASLD Annual Meeting, John M. Vierling and colleagues presented results of a subset analysis from the PROVIDE study in which the efficacy of boceprevir, peginterfon, and ribavirin was evaluated in 48 patients classified as prior null responders.[1] A null response was defined as a reduction in HCV RNA level less than 2 $\log_{10}$ from baseline to Week 12 while receiving peginterferon and ribavirin treatment in the prior study. All patients in this subanalysis received 4 weeks of peginterferon and ribavirin, followed by boceprevir plus peginterferon and ribavirin for up to 44 weeks.

Of the 48 patients in the analysis, 3 patients discontinued therapy during the 4-week lead-in period, 45 patients received at least 1 dose of boceprevir, and 19 patients completed treatment. Patients' mean age was 51 years; 65% of patients were male; 69% were white; 88% had a baseline viral load above 800,000 IU/mL; and 4% had evidence of cirrhosis. The primary study endpoint was SVR, which was defined as an undetectable HCV RNA level at 24 weeks post-therapy; SVR was attained in 16 of 42 evaluable patients (38%). End-of-treatment responses were attained in 20 of 43 patients (47%), and relapses following end-of-treatment response were detected in 3 of 19 patients (16%).

The investigators noted an association between declines in HCV RNA level after the 4-week lead-in period and the likelihood of subsequent SVR. Fifty percent of patients with a decline in HCV RNA level of at least 1 $\log_{10}$ at Week 4 achieved SVR, compared to an SVR rate of 34% among patients whose HCV RNA decline at Week 4 was less than 1 $\log_{10}$. Moreover, responses to peginterferon and ribavirin during the prior trial appeared to predict responses during the lead-in period of the PROVIDE study: 32 of the 42 patients (76%) who failed to attain a 2 $\log_{10}$ decline in HCV RNA levels at Week 12 in the SPRINT-2 or RESPOND-2 study also failed to attain a 1 $\log_{10}$ decline after the 4-week lead-in period in the PROVIDE study.

Due to the small number of patients in this analysis, the investigators were unable to evaluate baseline characteristics associated with SVR. Nonetheless, these results suggest that a treatment regimen consisting of boceprevir, peginterferon, and ribavirin can be effective in a group of well-documented prior null responders.

Reference

1. Vierling J, Flamm S, Gordon S, et al. Efficacy of boceprevir in prior null responders to peginterferon/ribavirin: the PROVIDE study. Presented at the Annual Meeting of the American Association for the Study of Liver Diseases; November 4–8, 2011; San Francisco, California. Abstract 931.

Milk Thistle Extract Is Not Beneficial in Previously Treated Patients with HCV Infection

Silymarin, an extract from the seeds of the milk thistle plant *Silybum marianum*, contains the major flavonolignans silybin A and silybin B and has been used for centuries as a treatment for patients with liver disorders. The compound has demonstrated anti-inflammatory, immunomodulatory, and antiviral activity in vitro.[1,2] However, clinical studies of silymarin in patients with hepatitis have yielded inconclusive results.

At the 2011 AASLD Annual Meeting, Michael W. Fried presented final results of the randomized, double-blind, placebo-controlled SyNCH trial, which was designed to evaluate the efficacy and safety of silymarin as a treatment for chronic HCV infection.[3] Conducted at 4 centers in the United States, this trial enrolled patients who were at least 18 years of age, had quantifiable levels of HCV RNA, and had not attained SVR following treatment with a prior

ABSTRACT SUMMARY Concomitant Use of Boceprevir and CYP3A4/5-Interacting Drugs in Patients with Genotype 1 HCV Infection

Boceprevir is metabolized primarily by aldo-ketoreductase and, to a lesser extent, by CYP3A4/5. Boceprevir also inhibits CYP3A4/5; therefore, coadministration of boceprevir may affect levels of drugs metabolized by CYP3A4/5. In a study presented at the 2011 Annual Meeting of the AASLD, Fred Poordad and colleagues evaluated the pharmacokinetic effects of coadministering boceprevir with other drugs; this study also analyzed adverse events and SVR rates in patients receiving concomitant medications.[1]

This analysis included patients from 3 boceprevir studies: SPRINT-1, SPRINT-2, and RESPOND-2. A total of 1,548 patients received boceprevir, peginterferon, and ribavirin; 547 patients received peginterferon and ribavirin alone. The most commonly used concomitant medications were antidepressants (used by 42% of patients), followed by benzodiazepines (31%) and steroids (20%). Less commonly used medications included calcium channel blockers (6%) and oral contraceptives (6%). Use of methadone was reported in only 1% of patients in SPRINT-2 and RESPOND-2.

Coadministration of other drugs had no clinically concerning effect on exposure to boceprevir, as assessed by the area under the concentration-time curve (AUC). In terms of boceprevir's effects on coadministered drugs, boceprevir did increase exposure to midazolam, which is a CYP3A4 substrate. The mean AUC(τ) ratio for the drug alone versus with boceprevir was 5.30, indicating that boceprevir is an inhibitor of CYP3A4.

Boceprevir did not affect the metabolism of drugs that are not primarily metabolized by CYP3A4. However, exposure to the contraceptive drospirenone/ethinyl estradiol was increased by boceprevir (mean AUC(τ) ratio, 1.99), although CYP3A metabolism of drospirenone is thought to be modest. There were no clinically concerning interactions between boceprevir and the HIV drugs ritonavir, efavirenz (EFV), and tenofovir.

A toxicity analysis showed that boceprevir can be safely coadministered with many commonly prescribed drugs, including antidepressants and methadone. Adverse event rates were similar in the subgroup of boceprevir-treated patients receiving antidepressants compared to the overall population. Likewise, adverse event rates did not appear to be affected by various CYP3A4/5 substrates, including statins, phosphodiesterase-5 inhibitors, benzodiazepines, calcium channel blockers, methadone, oral contraceptives, pioglitazone, or steroids.

Among patients taking boceprevir plus a CYP3A4/5 substrate and/or inhibitor, several adverse events occurred more often in patients taking specific concomitant medications. Compared to patients who were not taking concomitant medications, patients taking macrolide antibiotics were more likely to experience anemia (49% vs 68%) and gastrointestinal effects (82% vs 100%), patients taking azole antifungals were more likely to experience dysgeusia (37% vs 43%) and paresthesia (4% vs 13%), women taking oral contraceptives were more likely to experience gastroesophageal reflux disease (6% vs 12%), patients receiving statins were more likely to experience rash (17% vs 27%), and patients receiving calcium channel blockers were more likely to experience gastrointestinal effects (9% vs 15%). SVR rates were not affected by use of concomitant medications.

The investigators caution that the number of patients in each category was small, so these results should not be considered conclusive. Other drug-drug interaction studies are ongoing, including a study investigating potential interactions in HIV-infected patients receiving protease inhibitors.

Reference

1. Poordad F, Lawitz E, Gordon SC, et al. Concomitant medication use in patients with hepatitis C genotype 1 treated with boceprevir (BOC) combination therapy. Presented at the Annual Meeting of the American Association for the Study of Liver Diseases; November 4–8, 2011; San Francisco, California. Abstract 937.

interferon-based regimen. Patients also were required to have an alanine aminotransferase (ALT) level of at least 65 IU/L. Exclusion criteria included evidence of decompensated cirrhosis, moderate or severe steatosis or steatohepatitis, co-infection with HIV or hepatitis B virus, use of milk thistle within 30 days of study entry, and lactose intolerance (due to the composition of the placebo capsules).

A total of 154 patients were randomly assigned to 1 of 3 groups: silymarin at a dose of 420 mg 3 times daily, silymarin at a dose of 700 mg 3 times per day, or placebo. All treatments were given for 24 weeks. The silymarin preparation used in the study was a standardized 140-mg capsule that is approved in some countries in Europe and Asia. The doses used in this trial were 3–5-fold higher than the customary oral dose of 140 mg 3 times per day; these doses were selected based on findings from a phase I dose-escalation study.[4] In this phase I study, silybin A and silybin B had low bioavailability at a dose of 140 mg 3 times daily, but these compounds exhibited nonlinear pharmacokinetics, suggesting that doses above 700 mg would improve bioavailability.

The median age of patients enrolled in the SyNCH trial was 54 years; the median ALT level was 106 IU/L; 71% of patients were male; 10–15% of patients reported a history of diabetes; and 21–35% of patients showed evidence of cirrhosis. Most patients were white, and the placebo group had a somewhat larger proportion of whites than the treatment groups. Approximately half of patients had used milk thistle prior to the study.

Overall, 138 patients completed the 24-week evaluation period, including 44 patients in the 420-mg silymarin group, 44 patients in the 700-mg silymarin group, and 50 patients in the placebo group. To meet the primary endpoint of the study, patients had to meet 1 of the following criteria: either an ALT level less than 45 IU/L; or an ALT level less than 65 IU/L, provided this was at least a 50% decline from baseline. The investigators found no significant difference between groups for this endpoint, with a total of 6 patients (2 in each of the 3 arms) achieving either of these criteria.

The SyNCH study also found no significant differences in terms of secondary endpoints, including change in serum ALT levels, change in serum HCV RNA levels, or differences in quality of life. Subset analyses also did not reveal any differences in ALT outcomes between groups; these analyses looked at the subset of patients with a complete ALT data set and the subset of patients with greater-than-80% adherence.

Adherence to the prescribed medication, which was assessed using returned dose cups, was found to be excellent; more than 90% of patients maintained greater-than-80% adherence. Silymarin was also well tolerated,

ABSTRACT SUMMARY Efficacy and Safety of Boceprevir-Based Regimens in Treatment-Naïve Black Patients

Because black patients typically show lower response rates to therapy, the SPRINT-2 study enrolled and analyzed black patients separately from nonblack patients. At the 2011 AASLD Annual Meeting, Jonathan McCone, Jr., and colleagues presented data on the efficacy and safety of boceprevir-based therapy in black patients enrolled in the SPRINT-2 trial.[1]

Of the 159 treatment-naïve black patients who were enrolled in this study, 52 patients were assigned to receive peginterferon and ribavirin for 48 weeks; 52 patients were assigned to receive response-guided therapy with boceprevir, peginterferon, and ribavirin; and 55 patients were assigned to receive boceprevir, peginterferon, and ribavirin for 48 weeks. Patients in all treatment groups received peginterferon and ribavirin alone for 4 weeks before the addition of boceprevir or placebo.

The addition of boceprevir to peginterferon and ribavirin was associated with a significant improvement in SVR rates. Among the 154 patients without cirrhosis, SVR rates were 54% for patients treated with boceprevir plus peginterferon and ribavirin for 48 weeks, 50% for patients treated with response-guided boceprevir plus peginterferon and ribavirin, and 26% for patients treated with peginterferon and ribavirin alone. In patients without cirrhosis who had an undetectable HCV RNA level at Weeks 8–24, boceprevir-containing treatment regimens yielded SVR rates of 92–95%. Among patients without cirrhosis who were late responders—defined as having an HCV RNA level that was detectable at Week 8 but undetectable at Week 24—SVR rates were 58–86%. Due to small patient numbers, the authors were unable to draw conclusions about the efficacy of boceprevir-containing therapy in the subset of patients with cirrhosis. However, the authors recommended that these patients be given boceprevir plus peginterferon and ribavirin for 48 weeks.

In terms of adverse events, patients who received 48 weeks of boceprevir-based treatment or response-guided boceprevir-based treatment had higher rates of anemia than patients in the control group (71%, 63%, and 31%, respectively) and a higher requirement for erythropoietin (mean days of use: 148, 82, and 93 days, respectively). Dysgeusia was also more common among patients who received boceprevir-containing regimens: 40% among patients who received the 48-week boceprevir-based regimen, 29% among patients who received the response-guided boceprevir-based regimen, and 12% in the control group. Rates of neutropenia were similar across all 3 arms (31%, 35%, and 35%, respectively).

Reference

1. McCone J, Jacobson IM, Bacon BR, et al. Treatment-naive black patients treated with boceprevir combined with peginterferon alfa-2b + ribavirin. Results from HCV SPRINT-2. Presented at the Annual Meeting of the American Association for the Study of Liver Diseases; November 4–8, 2011; San Francisco, California. Abstract 981.

with the most common adverse events being mild or moderate gastrointestinal effects. There was no significant difference in the incidence of serious adverse events, which were reported in 5–6 patients in the silymarin arms and 1 patient in the control group. One patient in the low-dose silymarin group committed suicide 12 weeks after discontinuing the drug.

A pharmacokinetic analysis yielded results similar to the results of the phase I study, with random plasma concentrations of silybin A varying from 2 ng/mL to 2,000 ng/mL. The median and highest steady-state silybin A concentrations were increased 2-fold in the higher-dose versus the lower-dose group.

Based on the results of this well-controlled study, the investigators concluded that silymarin did not appear to significantly affect biochemical or virologic outcomes in a select group of previously treated patients with chronic HCV infection.

References

1. Morishima C, Shuhart MC, Wang CC, et al. Silymarin inhibits in vitro T-cell proliferation and cytokine production in hepatitis C virus infection. *Gastroenterology*. 2010;138:671-681.
2. Wagoner J, Negash A, Kane OJ, et al. Multiple effects of silymarin on the hepatitis C virus lifecycle. *Hepatology*. 2010;51:1912-1921.
3. Fried MW, Navarro VJ, Afdhal NH, et al. A randomized, placebo-controlled trial of oral silymarin (milk thistle) for chronic hepatitis C: final results of the SYNCH multicenter study. Presented at the Annual Meeting of the American Association for the Study of Liver Diseases; November 4–8, 2011; San Francisco, California. Abstract 228.
4. Hawke RL, Schrieber SJ, Soule TA, et al. Silymarin ascending multiple oral dosing phase I study in noncirrhotic patients with chronic hepatitis C. *J Clin Pharmacol*. 2010;50:434-449.

ABSTRACT SUMMARY Efficacy of Telaprevir-Based Regimens in HCV/HIV–Co-infected Patients

In a late-breaking abstract at the 2011 AASLD Annual Meeting, Kenneth E. Sherman and colleagues presented interim results of a phase II study evaluating telaprevir, peginterferon α-2a, and ribavirin in genotype 1 HCV treatment-naïve patients who were co-infected with HIV.[1]

The study was divided into 2 parts; in both parts, patients were randomly assigned to 1 of 2 antiviral treatment regimens: telaprevir (750 mg every 8 hours), peginterferon α-2a (180 µg/week), and ribavirin (800 mg/day) for 12 weeks, followed by 36 weeks of peginterferon and ribavirin; or 48 weeks of placebo plus peginterferon and ribavirin. In Part A, patients received no concurrent antiretroviral therapy (ART). In Part B, patients received their assigned antiviral therapy plus a stable, predefined ART: either an EFV-based regimen or an atazanavir/ritonavir (ATV/r)-based regimen. Patients assigned to telaprevir and an EFV-based regimen received telaprevir at a dose of 1,125 mg every 8 hours.

The investigators assessed virologic responses during therapy using the TaqMan v2 assay, which has a lower LOQ of 25 IU/mL and a LOD below 10–15 IU/mL. Of the 62 randomized patients, 60 received at least 1 dose of study medication, including 13 patients in Part A (no ART) and 47 patients in Part B (with ART). The mean age of enrolled patients was 46 years; 88% were male; 27% were black; 68% had genotype 1a HCV infection; and 3.3% had cirrhosis. HCV RNA levels at or above 800,000 IU/mL were observed in 92% of patients in Part A and 81% of patients in Part B. Mean CD4+ T-cell counts were 690 cells/mm^3 for patients in Part A and 562 cells/mm^3 for patients in Part B.

On-treatment virologic responses were higher among patients receiving the telaprevir-based antiviral regimen than among patients receiving peginterferon and ribavirin alone. Early virologic response, defined as an undetectable level of HCV RNA at Weeks 4 and 12, was observed in 63% of patients receiving the telaprevir-based regimen compared to 4.5% of patients receiving peginterferon and ribavirin alone. Of the 60 patients evaluable at Week 24, undetectable HCV RNA levels were observed in 74% of telaprevir-treated patients and 55% of patients who received peginterferon and ribavirin.

Two HCV breakthroughs were detected in patients receiving telaprevir-based therapy and ART, including 1 patient receiving an EFV-based regimen and 1 patient receiving an ATV/r-based regimen. No HIV viral breakthroughs were detected. The absolute number of CD4+ T cells declined while patients were on therapy, although the relative proportion of CD4+ T cells remained stable.

In regard to toxicity, the safety profile of telaprevir in this study was similar to that seen in HCV monoinfected patients. Adverse events that occurred more often (≥10% higher) in the telaprevir-treated group versus the control group were abdominal pain, vomiting, nausea, pyrexia, dizziness, depression, and pruritis. No severe rashes were noted.

Comparing the 2 ART regimens, the incidence of bilirubin adverse events was higher among patients who received the ATV/r regimen than among patients who received the EFV regimen (27% vs 0%); the incidence of indirect hyperbilirubinemia was also higher in patients who received the ATV/r regimen. Among patients who received ART and telaprevir, 3 patients discontinued at least 1 study drug due to an adverse event. The adverse events that prompted discontinuation included cholelithiasis, jaundice, and hemolytic anemia.

Finally, the ART regimen did not appear to affect the pharmacokinetics of telaprevir. The effects of telaprevir on ART pharmacokinetics were consistent with previous reports in healthy individuals.

Reference

1. Sherman KE, Rockstroh JK, Dieterich DT, et al. Telaprevir combination with peginterferon alfa-2a/ribavirin in HCV/HIV coinfected patients: 24-week treatment interim analysis. Presented at the Annual Meeting of the American Association for the Study of Liver Diseases; November 4–8, 2011; San Francisco, California. Abstract LB-8.

Wako Wako Diagnostics

The Only DCP* (PIVKA-II) Test Cleared by the FDA

Wako's AFP-L3% and DCP have received 510(k) clearance from the FDA as risk assessment tests for the development of HCC. For additional information, please visit our website: www.wakodiagnostics.com/gh.
Contact Wako Diagnostics: USA: 877-714-1924, or liver@wakousa.com.

Assessing Patients for HCC Risk?

Ask for the DCP test trusted by doctors

- Qualified for routine clinical use- ARUP laboratories [1]
- Biomarker for HCC surveillance-recommended by UCLA study [2]
- DCP differentiates early HCC from cirrhosis: 92% sensitivity, 93% specificity [3]
- DCP identifies HCC not detected by AFP; complements AFP and AFP-L3 [3-5]

To order, use the test codes below.

	ARUP	LabCorp	Quest	Mayo
DCP*	0081312	141325	19982	NA
AFP-L3%	0081208	141300	19529	88878
HCC Risk Panel	0081326	140002	16222	NA

* Des-gamma-carboxy prothrombin

References:
1. Owen WE, Roberts WL, Performance characteristics of the LiBASys® des-gamma-carboxy prothrombin assay, Clin Chim Acta. 2008 Mar;389(1-2):183-5. 2. Durazo FA, Blatt LM, Corey WG, Lin JH, Han S, Saab S, Busuttil RW, Tong MJ, Des-γ-carboxyprothrombin, α-fetoprotein and AFP-L3 in patients with chronic hepatitis, cirrhosis and hepatocellular carcinoma, J Gastroenterol Hepatol, 2008;23(10):1541-1548. 3. Volk ML, Hernandez JC, Su GL, Lok AS, Marrero JA, Risk factors for hepatocellular carcinoma may impair the performance of biomarkers: A comparison of AFP, DCP, and AFP-L3, Cancer Biomarkers, 2007;3:79-87. 4. Carr BI, Kanke F, Wise M, Satomura S, Clinical Evaluation of Lens culinaris Agglutinin-Reactive α-Fetoprotein and Des-γ-Carboxy Prothrombin in Histologically Proven Hepatocellular Carcinoma in the United States, Dig Dis Sci. 2007;52:776-782. 5. Toyoda H, Kumada T, Kiriyama S, Sone Y, Tanikawa M, Hisanaga Y, Yamaguchi A, Isogai M, Kaneoka Y, Washizu J, Prognostic significance of simultaneous measurement of three tumor markers in patients with hepatocellular carcinoma, Clinical Gastroenterology and Hepatology. 2006;4:111-117.

Boceprevir-Containing Regimens Are Effective in HCV/HIV–Co-infected Patients

SPECIAL IDSA COVERAGE

At the 49th Annual Meeting of the Infectious Diseases Society of America, Mark S. Sulkowski presented results of a phase IIb trial designed to evaluate the efficacy and safety of a boceprevir-containing regimen in patients who were co-infected with HCV and HIV-1.[1] Between November 2009 and December 2010, this study enrolled 100 patients with untreated genotype 1 HCV infection, HIV RNA levels less than 50 copies/mL, and stable HIV disease. Patients were excluded if they were receiving nonnucleoside reverse transcriptase inhibitors, unboosted protease inhibitors, zidovudine, or didanosine.

Patients were stratified by presence of cirrhosis and by baseline HCV RNA level (<800,000 IU/mL vs ≥800,000 IU/mL). During the 4-week lead-in period, all patients received peginterferon α-2b (1.5 µg/kg/week) and weight-based ribavirin (600–1,400 mg/day) alone. Patients were then randomly assigned to 44 weeks of treatment with peginterferon and ribavirin plus either boceprevir (800 mg 3 times daily) or placebo. Ninety-eight patients received at least 1 dose of medication: 64 patients in the boceprevir arm and 34 patients in the control arm. Patients' median age was 43 years; 82% were white, 69% were male, 88% had high HCV RNA levels, 65% had genotype 1a HCV infection, and 5% had cirrhosis.

In an interim analysis of 93 patients who had evaluable Week 24 data, 70.5% of patients receiving boceprevir plus peginterferon and ribavirin had undetectable levels of HCV RNA (using the Taqman v2 assay, with a LOD of

ABSTRACT SUMMARY SVR Rates and Viral Resistance Profiles Following Telaprevir-Based Therapy Are Similar Across Liver Fibrosis Stage

Two randomized, double-blind, placebo-controlled, phase III trials—ADVANCE and ILLUMINATE—demonstrated the efficacy of telaprevir-based therapy in treatment-naïve patients with genotype 1 HCV infection.[1,2] At the 2011 AASLD Annual Meeting, Patrick Marcellin and colleagues presented results of a pooled analysis of these 2 trials in which they evaluated whether liver fibrosis stage affects responses to telaprevir-based therapy and the development of resistant variants.[3]

This analysis included a total of 1,443 patients: 903 patients from the ADVANCE trial and 540 patients from the ILLUMINATE trial. Of the 1,264 evaluable patients, 903 had received telaprevir-based therapy and 361 had received peginterferon and ribavirin alone. Overall, 77% of patients had no/minimal or portal fibrosis (F0–F2) and 23% had bridging fibrosis or cirrhosis (F3–F4). Analyzed separately according to the type of treatment they received, 75% of telaprevir-treated patients had F0–F2 fibrosis, and 80% of patients receiving peginterferon and ribavirin alone had F0–F2 fibrosis. The investigators reported no differences in SVR rates according to pretreatment fibrosis stage, and the increases in SVR rates observed when telaprevir was added to peginterferon and ribavirin were comparable regardless of fibrosis stage. However, relapse and virologic failure were more likely in patients with advanced fibrosis.

The presence of resistant variants was evaluated in 223 patients who did not attain SVR. The incidence of low-level resistant variants was 40% and 43% in patients with F0–F2 and F3–F4 fibrosis, respectively; the incidence of high-level resistant variants was 35% and 41%, respectively. The median time to loss of resistant variants, which was assessed in 152 patients, was similar for patients with F0–F2 fibrosis (9 months) versus patients with F3–F4 fibrosis (10 months).

The authors concluded that, in terms of SVR rate or viral resistance profiles, pretreatment fibrosis score did not appear to affect the benefit of telaprevir-based therapy over peginterferon and ribavirin. However, patients with more advanced fibrosis were more likely to have virologic failure or relapse compared to patients with no/minimal or portal fibrosis.

References

1. Jacobson IM, McHutchison JG, Dusheiko GM, et al. Telaprevir in combination with peginterferon and ribavirin in genotype 1 HCV treatment-naive patients: final results of phase 3 ADVANCE study. Presented at the Annual Meeting of the American Association for the Study of Liver Diseases; October 29–November 2, 2010; Boston, Massachusetts. Abstract 211.
2. Herman KE, Flamm SL, Afdhal NH, et al. Telaprevir in combination with peginterferon alfa2a and ribavirin for 24 or 48 weeks in treatment-naïve genotype 1 HCV patients who achieved an extended rapid viral response: final results of phase 3 ILLUMINATE study. Presented at the Annual Meeting of the American Association for the Study of Liver Diseases; October 29–November 2, 2010; Boston, Massachusetts. Abstract LB2.
3. Marcellin P, Sullivan J, Fried MW, et al. Sustained virologic response rates and viral resistance profiles were similar in patients treated with a telaprevir-based regimen regardless of liver fibrosis stage. Presented at the Annual Meeting of the American Association for the Study of Liver Diseases; November 4–8, 2011; San Francisco, California. Abstract 2105.

9.3 IU/mL), compared to 34.4% of patients in the control group. Virologic response rates were also higher in the boceprevir-treated group at Week 8 (37.5% vs 14.7%) and Week 12 (56.5% vs 25.0%).

In terms of adverse events, boceprevir-treated patients were more likely than control patients to have pyrexia (34% vs 21%), anorexia (30% vs 18%), headache (28% vs 12%), dysgeusia (25% vs 15%), vomiting (25% vs 15%), and neutropenia (13% vs 3%). Other adverse events, including anemia, occurred at similar rates in both arms (<10% difference). Serious clinical events occurred in 8% of patients in the boceprevir-treated group and 21% of patients in the control group; dose modifications due to adverse events were required in 19% and 21%, respectively; and study discontinuations were required in 14% and 9%, respectively. The study investigators reported no differences between arms in terms of HIV-related parameters, including CD4+ T-cell count or the proportion of patients with an HIV RNA level less than 50 copies/mL.

Reference

1. Sulkowski M, Pol S, Cooper C, et al. Boceprevir plus peginterferon/ribavirin for the treatment of HCV/HIV co-infected patients: interim on-treatment results. Presented at the Annual Meeting of the Infectious Diseases Society of America; October 20–23, 2011; Boston, Massachusetts. Abstract LB-37.

ABSTRACT SUMMARY Peginterferon α-2a Comparable to Peginterferon α-2b in Boceprevir-Based Regimens

Boceprevir-based regimens have demonstrated significant efficacy in patients who failed prior treatment for HCV infection. In the RESPOND-2 trial, the addition of boceprevir to peginterferon α-2b and ribavirin was associated with an SVR rate of 59–66%, compared to an SVR rate of only 21% in patients treated with peginterferon and ribavirin alone.[1]

To evaluate whether the addition of boceprevir was also effective when combined with the alternative peginterferon (α-2a) in combination with ribavirin in patients with previously treated infection, Steven L. Flamm and colleagues designed a randomized, double-blind, placebo-controlled, phase III trial.[2] The entry criteria for this study were identical to those of the RESPOND-2 trial: Patients must have responded to interferon for at least 12 weeks but failed to achieve SVR. Patients were stratified by historical response (nonresponse vs relapse) and by HCV genotype (1a vs 1b).

This study enrolled 201 patients who were randomly assigned to 1 of 2 treatment regimens; 134 patients received boceprevir (800 mg 3 times daily), peginterferon α-2a (180 µg weekly), and weight-based ribavirin (1,000–1,200 mg/day in a divided dose); 67 patients received peginterferon and ribavirin plus placebo. All patients received 4 weeks of peginterferon and ribavirin prior to the 44-week treatment period. Patients with detectable HCV RNA levels at Week 12 discontinued treatment due to futility.

In an earlier report presented at the 2011 Digestive Disease Week meeting, SVR rates in this study were found to be similar to those in the RESPOND-2 trial (64% with boceprevir-based triple therapy vs 21% with peginterferon and ribavirin alone); however, some adverse events were observed more frequently in the boceprevir arm of this trial.[3] At the 2011 AASLD Annual Meeting, Dr. Flamm and colleagues presented a safety analysis to address this latter issue.[2]

Overall, boceprevir plus peginterferon α-2a and ribavirin was well tolerated, and there were no new safety findings compared with peginterferon α-2b–containing therapy. Compared with peginterferon and ribavirin alone, the boceprevir-based regimen was associated with higher rates (>10% difference between arms) of anemia (50% vs 33%), nausea (39% vs 27%), dysgeusia (39% vs 15%), neutropenia (31% vs 18%), diarrhea (25% vs 7%), and rash (23% vs 7%). Compared to treatment with peginterferon and ribavirin alone, boceprevir-based treatment was associated with a higher rate of dose modifications due to adverse events (43% vs 22%) and a higher rate of discontinuations due to adverse events (17% vs 4%).

Serious adverse events occurred in 13% of patients receiving boceprevir-based therapy compared to 10% of patients receiving peginterferon and ribavirin alone. The only serious adverse event occurring in more than 1 patient was neutropenia, which was reported in 2 boceprevir-treated patients. Grade 3/4 neutropenia, which was reported more often after Week 12, was not associated with an increased risk of infections. Overall, the findings from this trial provide evidence that boceprevir is effective and safe when administered in combination with either of the commercially available pegylated interferons.

References

1. Bacon BR, Gordon SC, Lawitz E, et al. Boceprevir for previously treated chronic HCV genotype 1 infection. *N Engl J Med*. 2011;364:1207-1217.
2. Flamm S, Lawitz E, Jacobson I, et al. Overall safety profile of boceprevir plus peginterferon alfa-2a/ribavirin in genotype 1 previous nonresponders and relapsers to peginterferon/ribavirin. Presented at the Annual Meeting of the American Association for the Study of Liver Diseases; November 4–8, 2011; San Francisco, California. Abstract 1010.
3. Flamm SL, Lawitz EJ, Jacobson IM, et al. High sustained virologic response (SVR) among genotype 1 previous non-responders and relapsers to peginterferon/ribavirin when re-treated with boceprevir (BOC) plus peginterferon alfa-2A/ribavirin. Presented at Digestive Disease Week; May 7–10, 2011; Chicago, Illinois. Abstract 903.

Commentary

John M. Vierling, MD, FACP

The regulatory approval of combination therapy with the HCV-specific NS3/4A protease inhibitors boceprevir and telaprevir, in combination with peginterferon-α and ribavirin, has revolutionized therapy for patients with genotype 1 HCV infection who are either treatment-naïve or who failed prior therapy with peginterferon and ribavirin. Post–hoc analyses of the phase III registration trials of boceprevir and telaprevir continue to refine our understanding of the genetic, virologic, clinical, and histologic variables that affect SVR rates. Studies are now exploring the safety and efficacy of newer protease inhibitors; inhibitors of the NS5A and NS5B components of the polymerase replication complex; host cyclophilin inhibitors of NS5A function; dual, triple, and quadruple combinations of direct-acting antivirals (DAAs) plus peginterferon and ribavirin; and peginterferon-λ and immunomodulators. Currently, there are 10 active phase I trials, 19 phase II trials, and 4 phase III registration trials ongoing in the United States and other countries. Given this research activity, it is no surprise that HCV treatment studies were prominent at both the 49th Annual Meeting of the Infectious Diseases Society of America and the 62nd Annual Meeting of the AASLD. This Special Meeting Review highlights advances in the treatment of HCV infection by summarizing presentations from both meetings.

While combination therapy including either boceprevir or telaprevir has unequivocally increased SVR rates in patients with genotype 1 HCV infection, key questions remain about the long-term durability of SVR, the impact of SVR on liver-related events, and changes in populations of resistance-associated variants (RAVs). To address these questions, patients participating in phase II and phase III studies of telaprevir were eligible for enrollment in the EXTEND trial to observe patients for an additional 3 years. The interim results indicated that over 99% of patients who achieved SVR maintained undetectable levels of HCV RNA long term. Importantly, no liver-related events occurred. In contrast, liver-related events related to portal hypertension or hepatocellular carcinoma occurred in 2.2% of patients who did not achieve SVR. Thus, SVR was durable and appears to reduce the risk of liver-related complications. Population sequence analysis (with a lower LOD of approximately 20%) was used to assess the persistence of RAVs. Overall, 85% of RAVs were no longer detectable after a median period of 29 months. Undetectability was greater in patients with genotype 1b HCV infection (95%) versus genotype 1a HCV infection (77%). Deep sequencing analyses will be required to determine if RAVs revert to their pretreatment levels among the quasispecies. Overall, the loss of detectable RAVs after telaprevir or boceprevir therapy bodes well for re-treatment using DAAs of the same or different classes.

With the advent of DAA therapies, clinicians must interpret the results of sensitive HCV RNA polymerase chain reaction assays and use both LOQ and LOD to make on-treatment decisions about response-guided therapy. The clinical importance of LOQ and LOD was illustrated by results of a pooled analysis of the phase III trials of boceprevir-based combination therapy in treatment-naïve and treatment-experienced patients. Patients were divided into 3 groups based on HCV RNA level: undetectable (below the LOD of 9.3 IU/mL); detectable but below the LOQ (between 9.3 IU/mL and 25 IU/mL); or at or above the LOQ. SVR rates varied according to HCV RNA level at Week 8 (after 4 weeks of peginterferon and ribavirin therapy followed by 4 weeks of boceprevir-based combination therapy): 84–89% when the HCV RNA level was undetectable, 63–75% when it was detectable but below the LOQ, and 13–24% if it was at or above the LOQ. Timing of HCV RNA testing also played a role, since the proportion of patients attaining undetectable HCV RNA levels increased from Weeks 7–9, while the proportion of patients with HCV RNA levels that were detectable but below the LOQ remained constant. These results indicate that the faster a patient achieves HCV RNA undetectability, the higher the SVR rate. Thus, clinicians using DAA therapies must pay close attention to whether HCV RNA levels below the LOQ are detectable or undetectable. This is particularly true for determining a patient's eligibility for the shorter duration of response-guided therapy.

In the era of ART, patients with HIV infection are less likely to succumb to complications of AIDS, but those who are co-infected with HCV disproportionately develop cirrhosis, liver failure, and hepatocellular carcinoma. Previous trials of peginterferon and ribavirin in HIV/HCV co-infected patients showed poor tolerability and inferior SVR rates compared to patients with HCV infection alone. Ongoing, randomized, placebo-controlled, phase IIb trials of combination therapy with boceprevir or telaprevir in patients who are co-infected with HIV and genotype 1 HCV demonstrate significant improvements in SVR rates in this difficult-to-treat population. Studies presented in this supplement provide interim results regarding the proportion of HIV/HCV co-infected patients with undetectable HCV RNA levels (LOD, 9.3–10.0 IU/mL) among patients treated with boceprevir-based

combination therapy, telaprevir-based combination therapy, or peginterferon and ribavirin. HCV RNA levels were undetectable in 70.5% of co-infected patients treated with boceprevir-based therapy, compared to 34.4% of patients treated with peginterferon and ribavirin alone. The 24-week interim analysis of the telaprevir-based triple therapy trial showed that 74% of patients treated with telaprevir-based combination therapy had undetectable HCV RNA levels, compared to 55% of patients treated with peginterferon and ribavirin. It is important to note that only predefined ART regimens were allowed in each of these trials, and the designs of the boceprevir and telaprevir trials differed significantly. Data on SVR rates, tolerability, adverse events, and drug-drug interactions are eagerly awaited. Results of ongoing drug-drug interaction studies with boceprevir and telaprevir plus different ART regimens should lead to a better understanding of how ART doses can be safely adjusted to maintain control of HIV and achieve high rates of SVR.

Other difficult-to-treat patients include those with a null response to prior peginterferon and ribavirin therapy (defined as a less-than-2 $\log_{10}$ decline in HCV RNA level from baseline after 12 weeks of peginterferon and ribavirin therapy) and those with advanced fibrosis. Since null responders were excluded from the phase III RESPOND-2 study, which assessed boceprevir-based combination therapy in patients who had failed previous peginterferon and ribavirin therapy, the efficacy of boceprevir-based therapy in null responders is of particular interest. The PROVIDE study, which allowed patients in the control arms of 4 boceprevir trials to enroll for boceprevir-based triple therapy, provided an opportunity to assess SVR rates in prior null responders. The interim analysis of 42 evaluable null responders who had completed SVR testing showed that 16 (38%) had achieved SVR. Declines in HCV RNA levels during the 4-week peginterferon and ribavirin lead-in period predicted SVR rates: Patients with a decline greater than 1 $\log_{10}$ had an SVR rate of 50%, while those with a decline less than 1 $\log_{10}$ had an SVR rate of 34%.

The impact of advanced fibrosis on SVR rates was assessed in a pooled analysis of 2 phase III trials of telaprevir—ADVANCE and ILLUMINATE. While SVR rates were lower among patients with bridging fibrosis (F3) or cirrhosis (F4), the percent increase in SVR rates above the SVR rate in the peginterferon and ribavirin group was comparable across all fibrosis stages. However, patients with F3–F4 fibrosis were more likely to experience virologic failure or relapse. No significant differences were noted between patients with F0–F2 fibrosis versus those with F3–F4 fibrosis in terms of the frequency of RAVs or the duration of their detectability using population sequencing methods.

Coadministration of boceprevir and drugs metabolized through CYP3A or aldo-keto reductases has the potential to alter their metabolism. Boceprevir is metabolized primarily through aldo-keto reductases and, to a lesser extent, through CYP3A4; however, boceprevir is an inhibitor of CYP3A4/5. Telaprevir is both a substrate and an inhibitor of CYP3A4. Retrospective analyses of phase II and phase III trials of boceprevir assessed the pharmacokinetic effects of boceprevir coadministration on concomitant medications and the impact of concomitant medications on rates of adverse events and SVR. Of note, both boceprevir and telaprevir increase exposure to midazolam, a CYP3A4 substrate, which has important implications for its use in moderate sedation. Coadministration of boceprevir increases the AUC of midazolam 5.3-fold, indicating a need for dose reduction. Boceprevir also increased the AUC of the oral contraceptive drospirenone/ethinyl estradiol 1.99-fold, even though drospirenone does not appear to be a CYP3A4 substrate. Importantly, no drug-drug interactions were identified between boceprevir and the HIV ART drugs ritonavir, EFV, and tenofovir. Coadministration of boceprevir with antidepressants and methadone appeared to be safe. The frequency of several adverse events was increased with specific concomitant medications: Anemia was more frequent in patients taking macrolide antibiotics, dysgeusia and paresthesias were more common in patients taking azole antifungal medications, gastroesophageal reflux disease was more prevalent in women taking oral contraceptives, rash was more common in patients receiving statins, and gastrointestinal symptoms were more likely in patients on calcium channel blockers. However, concomitant medications did not affect SVR rates. Healthcare providers should be sure to obtain detailed information about all medications, including complementary and alternative medications, before initiating therapy with either boceprevir or telaprevir. The package inserts for these drugs contain useful information regarding drug-drug interactions and dose modifications, as does the website www.hep-druginteractions.org.

Black patients have a higher prevalence of HCV infection, especially genotype 1 HCV infection, and lower rates of SVR with peginterferon and ribavirin therapy, boceprevir-based triple therapy, or telaprevir-based triple therapy. The efficacy and safety of boceprevir-based triple therapy in treatment-naïve black patients was analyzed in the phase III SPRINT-2 trial, which prespecified an enrollment of black patients exceeding that expected by chance alone. However, the study was not powered to compare SVR rates between black and nonblack patients. SVR rates with boceprevir-based therapy were significantly higher than the SVR rates achieved with peginterferon and ribavirin. In noncirrhotic patients, SVR rates

of 92–95% were achieved if HCV RNA levels were below the LOD of 9.3 IU/mL at Weeks 8–24. In contrast, noncirrhotic patients who were late responders (defined as a detectable level of HCV RNA at Week 8 and an undetectable level at Week 24) had SVR rates of 58–86%. Unfortunately, the number of patients with cirrhosis was too small for meaningful analysis. No racial differences were noted for anemia or dysgeusia associated with boceprevir-based therapy.

Previous analyses of the phase II and phase III trials of boceprevir and telaprevir indicated that SVR rates in treatment-naïve patients correlate with interferon responsiveness. The safety and efficacy of boceprevir and ribavirin when combined with either peginterferon α-2a or peginterferon α-2b were investigated in a randomized, double-blind, placebo-controlled phase III trial. As also reported at Digestive Disease Week 2011, SVR rates were comparable when boceprevir and ribavirin were combined with either peginterferon α-2a or peginterferon α-2b, and no differences in adverse events or serious adverse events were noted. Thus, boceprevir is both safe and effective when used with either peginterferon.

Goals of newer antiviral therapies include an increase in SVR rates, a decrease in the duration of therapy, and possible elimination of peginterferon and/or ribavirin in order to minimize adverse events. Working toward these goals, the ongoing, phase II ZENITH study was designed to assess 12-week response-guided therapy using a combination of telaprevir and the NS5B polymerase inhibitor VX-222—with or without peginterferon and ribavirin—in treatment-naïve patients with genotype 1 HCV infection. Patients were randomized to receive dual therapy with telaprevir and VX-222 (without peginterferon and ribavirin) or quad therapy with all 4 drugs. The dual regimen was aborted due to unacceptable viral breakthrough, and the trial was continued using the quad regimen and a triple drug regimen consisting of telaprevir, VX-222, and ribavirin. The interim analysis of the Week 24 responses focused on the results of the quad therapy regimen, which allowed patients to discontinue all therapy at Week 12 if they had undetectable levels of HCV RNA (LOD, 10 IU/mL) at Weeks 2 and 8. If the level of HCV RNA was detectable at either Week 2 or Week 8, then peginterferon and ribavirin therapy was extended for an additional 12 weeks. Among patients treated with the highest dose of VX-222, 50% were eligible to stop therapy after 12 weeks and 93% achieved SVR. Of those requiring an additional 12 weeks of peginterferon and ribavirin, 87% had undetectable levels of HCV RNA 12 weeks after cessation of therapy. The most frequent adverse events were similar to those observed with telaprevir, peginterferon, and ribavirin therapy. While it is disappointing that a dual regimen consisting of a protease inhibitor and a polymerase inhibitor was ineffective, the outstanding SVR rates among patients who received the quad regimen and the study's ability to use a response-guided approach to shorten therapy are encouraging.

Despite objective proof of the safety and efficacy of antiviral therapies, patients remain enamored by complementary and alternative therapies for chronic HCV infection. Proponents of the milk thistle plant tout evidence of the anti-inflammatory, immunoregulatory, antioxidant, and antiviral properties of its active ingredient, silymarin, as rationales for its use. It is gratifying that the final results of a randomized, double-blind, placebo-controlled trial assessing the safety and efficacy of pharmaceutical-grade silymarin for the treatment of chronic HCV infection are now available. The trial was limited to adults who had quantifiable levels of HCV RNA, had not achieved SVR with prior interferon-based therapies, and had elevated ALT levels. The results of this study were unequivocal: There were no differences between patients treated with silymarin versus placebo with respect to either the primary study endpoint (reduction in ALT level) or secondary endpoints (including changes in ALT level, HCV RNA level, and quality of life). Silymarin was well tolerated, although 1 patient committed suicide 12 weeks after taking the drug. This carefully designed, rigorously conducted study should serve as a model of future studies of complementary and alternative therapies.

AVAILABLE