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INDICATION

INCIVEK, in combination with peginterferon alfa and ribavirin, is indicated for the treatment of genotype 1 chronic hepatitis C in adult patients with compensated liver disease, including cirrhosis, who are treatment naïve or who have previously been treated with interferon-based treatment, including prior null responders, partial responders, and relapsers.

The following points should be considered when initiating treatment with INCIVEK:

- INCIVEK must not be administered as monotherapy and must only be prescribed with both peginterferon alfa and ribavirin
- A high proportion of previous null responders (particularly those with cirrhosis) did not achieve a Sustained Virologic Response (SVR) and had telaprevir resistance–associated substitutions emerge on treatment with INCIVEK combination treatment
- INCIVEK efficacy has not been established for patients who have previously failed therapy with a treatment regimen that includes INCIVEK or other HCV NS3/4A protease inhibitors

IMPORTANT SAFETY INFORMATION

Contraindications

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

INCIVEK combination treatment is contraindicated in women who are or may become pregnant. Ribavirin may cause fetal harm when administered to a pregnant woman. If ribavirin is used during pregnancy or in the event of a pregnancy while on treatment, inform the patient of the potential hazard to a fetus. INCIVEK combination treatment is also contraindicated in men whose female partners are pregnant.

INCIVEK is contraindicated when combined with drugs that 1) are highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events and 2) strongly induce CYP3A and thus may lead to lower exposure and loss of efficacy of INCIVEK. Contraindicated medications are alfuzosin, rifampin, dihydroergotamine, ergonovine, ergotamine, methylergonovine, cisapride, St. John's wort, atorvastatin, lovastatin, simvastatin, pimozide, sildenafil (Revatio®) or tadalafil (Adcirca®) for pulmonary arterial hypertension, oral midazolam, and/or triazolam.

Warnings and precautions

Pregnancy: 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 just before initiation of therapy.

Female patients of childbearing potential and their male partners as well as male patients and their female partners must use 2 effective contraceptive methods during combination treatment and for 6 months after all treatment has ended. Female patients should have monthly pregnancy tests during treatment and during the 6-month period after stopping all treatment. Female patients may continue hormonal contraceptives but they may not be reliable during INCIVEK dosing and for up to two weeks after stopping INCIVEK. During this time, female patients of childbearing potential should use 2 effective non-hormonal methods of contraception.

INCIVEK HAS ARRIVED

Serious skin reactions, including Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) and Stevens-Johnson syndrome (SJS) were reported in less than 1% of subjects receiving INCIVEK combination treatment. These reactions required hospitalization and all patients recovered. Presenting signs of these reactions may include rash, facial edema, target lesions, mucosal ulcerations, and evidence of internal organ involvement. If serious skin reactions occur, all components of INCIVEK combination treatment must be discontinued immediately and the patient referred for urgent medical care.

Rash developed in 56% of patients who received INCIVEK combination treatment. Severe rash was reported in 4% of patients treated with INCIVEK combination treatment. Severe rash may have a prominent eczematous component. Patients with rash should be followed for progression of rash or development of systemic symptoms. If rash becomes severe or systemic symptoms develop, discontinue INCIVEK. Peginterferon alfa and ribavirin may be continued.

Anemia has been reported with peginterferon alfa and ribavirin treatment. Adding INCIVEK is associated with additional decrease in hemoglobin compared to peginterferon alfa and ribavirin alone. Hemoglobin values of ≤10 g/dL were observed in 36% of subjects, and <8.5 g/dL in 14% of subjects who received INCIVEK combination treatment. Hemoglobin should be monitored at baseline and at weeks 2, 4, 8, and 12, or as clinically appropriate. Use the labeled ribavirin dose modification guidelines to manage anemia; if ribavirin dose reductions are inadequate, consider discontinuing INCIVEK. If ribavirin is permanently discontinued, INCIVEK must also be permanently discontinued. The dose of INCIVEK must not be reduced and must not be restarted if discontinued.

Adverse reactions

The most common adverse reactions seen with an incidence ≥5% with INCIVEK over controls were rash (56%), fatigue (56%), pruritus (47%), nausea (39%), anemia (36%), diarrhea (26%), vomiting (13%), hemorrhoids (12%), anorectal discomfort (11%), dysgeusia (10%), and anal pruritus (6%).

Please see the Brief Summary on the adjacent pages.

INCIVEK combination treatment = INCIVEK + pegIFN-RBV for 12 weeks, and an additional 12 or 36 weeks of pegIFN-RBV.

Visit www.INCIVEK.com for:

- Latest information
- Free resources
- Guidance & Patient Support (GPS) information

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INCIVEK™
(telaprevir) Tablets
Brief Summary of Prescribing Information. See package insert for full prescribing information.

INDICATIONS AND USAGE
INCIVEK™ (telaprevir), in combination with peginterferon alfa and ribavirin, is indicated for the treatment of genotype 1 chronic hepatitis C in adult patients with compensated liver disease, including cirrhosis, who are treatment-naïve or who have previously been treated with interferon-based treatment, including prior null responders, partial responders, and relapsers.
The following points should be considered when initiating treatment with INCIVEK:
- INCIVEK must not be administered as monotherapy and must only be prescribed with both peginterferon alfa and ribavirin.
- A high proportion of previous null responders (particularly those with cirrhosis) did not achieve a Sustained Virologic Response (SVR) and had telaprevir resistance-associated substitutions emerge on treatment with INCIVEK combination treatment.
- INCIVEK efficacy has not been established for patients who have previously failed therapy with a treatment regimen that includes INCIVEK or other HCV NS3/4A protease inhibitors.

CONTRAINDICATIONS
Contraindications to peginterferon alfa and ribavirin also apply to INCIVEK combination treatment.
INCIVEK combination treatment is contraindicated in:
- women who are or may become pregnant. Ribavirin may cause fetal harm when administered to a pregnant woman. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug treatment, the patient should be apprised of the potential hazard to a fetus.
- men whose female partners are pregnant.

INCIVEK is contraindicated when combined with drugs that are highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events (narrow therapeutic index). INCIVEK is contraindicated when combined with drugs that strongly induce CYP3A and thus may lead to lower exposure and loss of efficacy of INCIVEK. Contraindicated drugs are listed below.

Drugs that are Contraindicated with INCIVEK

Drug Class	Drugs within Class that are Contraindicated with INCIVEK	Clinical Comments
Alpha 1-adrenoreceptor antagonist	Alfuzosin	Potential for hypotension or cardiac arrhythmia
Antimycobacterials	Rifampin	Rifampin significantly reduces telaprevir plasma concentrations.
Ergot derivatives	Dihydroergotamine, ergonovine, ergotamine, methylergonovine	Potential for acute ergot toxicity characterized by peripheral vasospasm or ischemia
GI Motility Agent	Cisapride	Potential for cardiac arrhythmias
Herbal products	St. John's wort (*Hypericum perforatum)*	Plasma concentrations of telaprevir can be reduced by concomitant use of the herbal preparation St. John's wort.
HMG CoA reductase inhibitors	Atorvastatin, lovastatin, simvastatin	Potential for myopathy including rhabdomyolysis
Neuroleptic	Pimozide	Potential for serious and/or life-threatening adverse reactions such as cardiac arrhythmias secondary to increases in plasma concentrations of antiarrhythmics
PDE5 inhibitor	Sildenafil (Revatio®) or tadalafil (Adcirca®) [for treatment of pulmonary arterial hypertension][a]	Potential for PDE5 inhibitor-associated adverse events, including visual abnormalities, hypotension, prolonged erection, and syncope
Sedatives/hypnotics	Orally administered midazolam[b], triazolam	Prolonged or increased sedation or respiratory depression

[a] See table under *Drug Interactions* for co-administration of sildenafil and tadalafil when dosed for erectile dysfunction.
[b] See table under *Drug Interactions* 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.
Because INCIVEK must be used in combination with peginterferon alfa and ribavirin, the contraindications and warnings applicable to those drugs are applicable to combination therapy. Female patients of childbearing potential and their male partners as well as male patients and their female partners must use 2 effective contraceptive methods during treatment and for 6 months after all treatment has ended. Female patients should have monthly pregnancy tests during treatment and during the 6-month period after stopping treatment. Extreme care must be taken to avoid pregnancy in female patients and in female partners of male patients as significant teratogenic and/or embryocidal effects have been demonstrated in all animal species exposed to ribavirin. Refer also to the prescribing information for ribavirin.
Female Patients-Hormonal contraceptives may be continued but may not be reliable during INCIVEK dosing and for up to two weeks following cessation of INCIVEK. During this time, female patients of childbearing potential should use two effective non-hormonal methods of contraception. Examples may include barrier methods or intrauterine devices (IUDs). Two weeks after completion of INCIVEK treatment, hormonal contraceptives are again appropriate as one of the two required effective methods of birth control; however, specific prescribing information recommendations should be followed for the contraceptives.
Serious Skin Reactions. Serious skin reactions, including Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) and Stevens-Johnson Syndrome (SJS) were reported in less than 1% of subjects who received INCIVEK combination treatment compared to none who received peginterferon alfa and ribavirin alone. These serious skin reactions required hospitalization, and all patients recovered. The presenting signs of DRESS may include rash, fever, facial edema, and evidence of internal organ involvement (e.g., hepatitis, nephritis). Eosinophilia may or may not be present. The presenting signs of SJS may include fever, target lesions, and mucosal erosions or ulcerations (e.g., conjunctivae, lips).
If a serious skin reaction occurs, all components of INCIVEK combination treatment must be discontinued immediately and the patient should be promptly referred for urgent medical care.
Rash. Rash developed in 56% of subjects who received INCIVEK combination treatment. Severe rash (e.g., a generalized rash or rash with vesicles or bullae or ulcerations other than SJS) was reported in 4% of subjects who received INCIVEK combination treatment compared to less than 1% who received peginterferon alfa and ribavirin alone. The severe rash may have a prominent eczematous component.
Patients with mild to moderate rashes should be followed for progression of rash or development of systemic symptoms. If rash progresses and becomes severe or if systemic symptoms develop, INCIVEK should be discontinued. Peginterferon alfa and ribavirin may be continued. If improvement is not observed within 7 days of INCIVEK discontinuation, sequential or simultaneous interruption or discontinuation of ribavirin and/or peginterferon alfa should be considered. If medically indicated, earlier interruption or discontinuation of ribavirin and peginterferon alfa should be considered. Patients should be monitored until the rash has resolved. INCIVEK must not be reduced or restarted if discontinued due to rash. Treatment of rash with oral antihistamines and/or topical corticosteroids may provide symptomatic relief but effectiveness of these measures has not been established. Treatment of rash with systemic corticosteroids is not recommended.
Anemia. Anemia has been reported with peginterferon alfa and ribavirin therapy. The addition of INCIVEK to peginterferon alfa and ribavirin is associated with an additional decrease in hemoglobin concentrations. Hemoglobin values less than or equal to 10 g/dL were observed in 36% of subjects who received INCIVEK combination treatment compared to 17% of subjects who received peginterferon alfa and ribavirin. Hemoglobin values less than 8.5 g/dL were observed in 14% of subjects who received INCIVEK combination treatment compared to 5% of subjects receiving peginterferon alfa and ribavirin.
In subjects receiving INCIVEK combination treatment, 4% discontinued INCIVEK, 1% discontinued INCIVEK combination treatment, and 32% underwent a ribavirin dose modification (reduction, interruption or discontinuation) due to anemia. In subjects treated with peginterferon alfa and ribavirin alone, there were two discontinuations and 12% underwent ribavirin dose modification due to anemia.
Hemoglobin should be monitored prior to and at least every 4 weeks during INCIVEK combination treatment. For the management of anemia, ribavirin dose reductions should be used (refer to the prescribing information for ribavirin for its dose reduction guidelines). If ribavirin dose reductions are inadequate, discontinuation of INCIVEK should be considered. If ribavirin is permanently discontinued for the management of anemia, INCIVEK must also be permanently discontinued. Ribavirin may be restarted per the dosing modification guidelines for ribavirin. The dose of INCIVEK must not be reduced and INCIVEK must not be restarted if discontinued.
Drug Interactions. See the table above for a listing of drugs that are contraindicated for use with INCIVEK due to potentially life-threatening adverse events or potential loss of therapeutic effect to INCIVEK. Refer to the table included under *Drug Interactions* for established and other potentially significant drug-drug interactions.
Laboratory Tests. HCV-RNA levels should be monitored at weeks 4 and 12 and as clinically indicated. Use of a sensitive real-time RT-PCR assay for monitoring HCV-RNA levels during treatment is recommended. The assay should have a lower limit of HCV-RNA quantification equal to or less than 25 IU/mL and a limit of HCV-RNA detection of approximately 10-15 IU/mL. For the purpose of assessing response-guided therapy eligibility, an "undetectable" HCV-RNA result is required; a confirmed "detectable but below limit of quantification" HCV-RNA result should not be considered equivalent to an "undetectable" HCV-RNA result.
Hematology evaluations (including white cell differential count) are recommended at weeks 2, 4, 8 and 12 or as clinically appropriate thereafter. Chemistry evaluations (electrolytes, serum creatinine, uric acid, hepatic enzymes, bilirubin, and TSH) are recommended as frequently as the hematology evaluations or as clinically indicated. Refer to the prescribing information for peginterferon alfa and ribavirin, including pregnancy testing requirements.
General. INCIVEK must not be administered as monotherapy and must only be prescribed with both peginterferon alfa and ribavirin. Therefore, the prescribing information for peginterferon alfa and ribavirin must be consulted before starting treatment with INCIVEK.
There are no clinical data on re-treating patients who have failed an HCV NS3/4A protease inhibitor-based treatment, nor are there data on repeated courses of INCIVEK.
Hepatic Impairment. INCIVEK is not recommended for patients with moderate or severe hepatic impairment (Child-Pugh B or C, score greater than or equal to 7) or patients with decompensated liver disease. Refer to prescribing information for peginterferon alfa and ribavirin which must be co-administered with INCIVEK.

ADVERSE REACTIONS
The following adverse reactions are discussed in greater detail in other sections of the label:
- Pregnancy: Use with Ribavirin and Peginterferon alfa
- Serious Skin Reactions/Rash
- Anemia

INCIVEK must be administered with peginterferon alfa and ribavirin. Refer to their respective prescribing information for their associated adverse reactions.
Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.
The safety assessment is based on data from pooled adequate and well-controlled clinical trials including 1797 subjects who received INCIVEK combination treatment and 493 who received peginterferon alfa and ribavirin.
Serious adverse drug reactions occurred in 3% of subjects who received INCIVEK combination treatment compared to none of the subjects treated with peginterferon alfa and ribavirin. The most frequent serious adverse events in subjects treated with INCIVEK combination treatment were skin disorders (rash and/or pruritus) and anemia. Fourteen percent of subjects discontinued INCIVEK due to adverse drug reactions. Rash, anemia, fatigue, pruritus, nausea, and vomiting were the most frequent adverse drug reactions leading to discontinuation of INCIVEK.

INCIVEK was administered in combination with peginterferon alfa and ribavirin. The following table lists adverse drug reactions that occurred in INCIVEK-treated subjects with an incidence at least 5% greater than in subjects receiving peginterferon alfa and ribavirin alone.

Clinical Adverse Drug Reactions Reported with at Least 5% Higher Frequency Among Subjects Receiving INCIVEK

	INCIVEK, peginterferon alfa, and ribavirin Combination Treatment N=1797	Peginterferon alfa and ribavirin N=493
Rash*	56%	34%
Fatigue	56%	50%
Pruritus	47%	28%
Nausea	39%	28%
Anemia*	36%	17%
Diarrhea	26%	17%
Vomiting	13%	8%
Hemorrhoids	12%	3%
Anorectal discomfort	11%	3%
Dysgeusia	10%	3%
Anal pruritus	6%	1%

*Rash and anemia based on SSC (Special Search Category) grouped terms.

Description of Selected Adverse Drug Reactions
Rash. In controlled clinical trials, rash events (all grades) were reported in 56% of subjects who received INCIVEK combination treatment and in 34% of subjects who received peginterferon alfa and ribavirin. Rash most frequently began during the first 4 weeks, but could occur at any time during INCIVEK combination treatment. Improvement of rash occurs after INCIVEK dosing completion or discontinuation; however, rashes may take weeks for complete resolution.
Rash events led to discontinuation of INCIVEK alone in 6% of subjects and discontinuation of INCIVEK combination treatment in 1% of subjects.
Anemia. In controlled clinical trials, the overall incidence and severity of anemia increased with INCIVEK combination treatment compared to peginterferon alfa and ribavirin alone. The incidence of anemia adverse events was 36% with INCIVEK combination treatment compared to 17% with peginterferon alfa and ribavirin alone. A decrease in hemoglobin levels occurred during the first 4 weeks of treatment, with lowest values reached at the end of INCIVEK dosing. Hemoglobin values gradually returned to levels observed with peginterferon alfa and ribavirin after INCIVEK dosing was completed.
Anorectal Signs and Symptoms. In the controlled clinical trials, 29% of subjects treated with INCIVEK combination treatment experienced anorectal adverse events, compared to 7% of those treated with peginterferon alfa and ribavirin alone. The majority of these events (e.g., hemorrhoids, anorectal discomfort, anal pruritus, and rectal burning) were mild to moderate in severity; less than 1% led to treatment discontinuation and all resolved during or after completion of INCIVEK dosing.
Laboratory abnormalities
White Blood Cells: Treatment with peginterferon alfa is associated with decreases in mean values for total white blood cell, absolute neutrophil, and absolute lymphocyte count. More INCIVEK-treated subjects had decreases in lymphocyte counts to 499/mm^3 or less (15% compared to 5%). Decreases in total white cell counts to 1,499/mm^3 or less were comparable (8% compared to 5%). The incidence of decreases in absolute neutrophil counts to 749/mm^3 or less was 15% in subjects treated with peginterferon alfa and ribavirin alone compared to 12% among those treated with INCIVEK combination treatment.
Platelets: Treatment with peginterferon alfa is associated with decreases in mean platelet counts. More patients treated with INCIVEK combination treatment had decreases in mean platelet values of all grades: 47% compared to 36% treated with peginterferon alfa and ribavirin alone. Three percent of INCIVEK combination treatment subjects had decreases to 49,999/mm^3 or less compared to 1% of those treated with peginterferon alfa and ribavirin-treated alone.
Bilirubin: Forty one percent of INCIVEK-treated subjects compared to 28% of peginterferon alfa and ribavirin-treated subjects had all grade elevations in bilirubin levels; 4% and 2% of subjects, respectively, had greater than or equal to 2.6 x ULN elevations. Bilirubin levels increased most steeply during the first 1 to 2 weeks of INCIVEK dosing, stabilized and between Weeks 12 and 16 were at baseline levels.
Uric Acid: During the INCIVEK combination treatment period, 73% of subjects had elevated uric acid levels compared to 29% for those treated with peginterferon alfa and ribavirin alone. Shifts to greater than or equal to 12.1 mg/dL from baseline in uric acid levels were also more frequent among subjects treated with INCIVEK (7%) compared to peginterferon alfa and ribavirin (1%). Less than 1% of subjects had clinical events of gout/gouty arthritis; none were serious and none resulted in treatment discontinuation.

DRUG INTERACTIONS
Potential for INCIVEK to Affect Other Drugs
INCIVEK is an inhibitor of CYP3A. Co-administration of INCIVEK with drugs that are primarily metabolized by CYP3A may result in increased plasma concentrations of such drugs, which could increase or prolong their therapeutic effect and adverse reactions. INCIVEK is also an inhibitor of P-gp. Co-administration of INCIVEK with drugs that are substrates for P-gp transport may result in increased plasma concentrations of such drugs, which could increase or prolong their therapeutic effect and adverse reactions. **If dose adjustments of concomitant medications are made during INCIVEK treatment, they should be re-adjusted after administration of INCIVEK is completed.**
Potential for Other Drugs to Affect INCIVEK
INCIVEK is a substrate of CYP3A and P-gp; therefore, drugs that induce CYP3A and/or P-gp may decrease INCIVEK plasma concentrations and reduce the therapeutic effect of INCIVEK. Co-administration of INCIVEK with drugs that inhibit CYP3A and/or P-gp may increase INCIVEK plasma concentrations.
Established and Other Potentially Significant Drug Interactions
The table below provides effect of concentration of INCIVEK or concomitant drug with INCIVEK. These recommendations are based on either drug interaction studies (indicated with *) or predicted interactions due to the expected magnitude of interaction and potential for serious adverse events or loss of efficacy.

Established and Other Potentially Significant Drug Interactions: Alterations in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interaction

Concomitant Drug Class: Drug Name	Effect on concentration of INCIVEK or Concomitant Drug	Clinical Comment
ANTIARRHYTHMICS		
lidocaine (systemic), amiodarone, bepridil, flecainide, propafenone, quinidine	↑ antiarrhythmics	Co-administration with telaprevir has the potential to produce serious and/or life-threatening adverse events and has not been studied. Caution is warranted and clinical monitoring is recommended when co-administered with telaprevir.
digoxin*	↑ digoxin	Concentrations of digoxin were increased when co-administered with telaprevir. The lowest dose of digoxin should be initially prescribed. The serum digoxin concentrations should be monitored and used for titration of digoxin dose to obtain the desired clinical effect.
ANTIBACTERIALS		
clarithromycin erythromycin telithromycin	↑ telaprevir ↑ antibacterials	Concentrations of both telaprevir and the antibacterial may be increased during co-administration. Caution is warranted and clinical monitoring is recommended when co-administered with telaprevir. QT interval prolongation and Torsade de Pointes have been reported with clarithromycin and erythromycin. QT interval prolongation has been reported with telithromycin.
ANTICOAGULANT		
warfarin	↑ or ↓ warfarin	Concentrations of warfarin may be altered when co-administered with telaprevir. The international normalized ratio (INR) should be monitored when warfarin is co-administered with telaprevir.
ANTICONVULSANTS		
carbamazepine phenobarbital phenytoin	↓ telaprevir ↑ carbamazepine ↑ or ↓ phenytoin ↑ or ↓ phenobarbital	Concentrations of the anticonvulsant may be altered and concentrations of telaprevir may be decreased. Caution should be used when prescribing carbamazepine, phenobarbital, and phenytoin. Telaprevir may be less effective in patients taking these agents concomitantly. Clinical or laboratory monitoring of carbamazepine, phenobarbital, and phenytoin concentrations and dose titration are recommended to achieve the desired clinical response.
ANTIDEPRESSANTS		
escitalopram*	↔ telaprevir ↓ escitalopram	Concentrations of escitalopram were decreased when co-administered with telaprevir. Selective serotonin reuptake inhibitors such as escitalopram have a wide therapeutic index, but doses may need to be adjusted when combined with telaprevir.
desipramine trazodone	↑ desipramine ↑ trazodone	Concomitant use of trazodone or desipramine and telaprevir may increase plasma concentrations of trazodone or desipramine which may lead to adverse events such as nausea, dizziness, hypotension and syncope. If trazodone or desipramine is used with telaprevir, the combination should be used with caution and a lower dose of trazodone or desipramine should be considered.

Concomitant Drug Class: Drug Name	Effect on concentration of INCIVEK or Concomitant Drug	Clinical Comment
ANTIFUNGALS		
ketoconazole* itraconazole posaconazole voriconazole	↑ ketoconazole ↑ telaprevir ↑ itraconazole ↑ posaconazole ↑ or ↓ voriconazole	Ketoconazole increases the plasma concentrations of telaprevir. Concomitant systemic use of itraconazole or posaconazole with telaprevir may increase plasma concentration of telaprevir. Plasma concentrations of itraconazole, ketoconazole, or posaconazole may be increased in the presence of telaprevir. When co-administration is required, high doses of itraconazole or ketoconazole (greater than 200 mg/day) are not recommended. Caution is warranted and clinical monitoring is recommended for itraconazole, posaconazole and voriconazole. QT interval prolongation and Torsade de Pointes have been reported with voriconazole and posaconazole. QT interval prolongation has been reported with ketoconazole. Due to multiple enzymes involved with voriconazole metabolism, it is difficult to predict the interaction with telaprevir. Voriconazole should not be administered to patients receiving telaprevir unless an assessment of the benefit/risk ratio justifies its use.
ANTI GOUT		
colchicine	↑ colchicine	Patients with renal or hepatic impairment should not be given colchicine with telaprevir, due to the risk of colchicine toxicity. A reduction in colchicine dosage or an interruption of colchicine treatment is recommended in patients with normal renal or hepatic function. Treatment of gout flares: co-administration of colchicine in patients on telaprevir: 0.6 mg (1 tablet) for 1 dose, followed by 0.3 mg (half tablet) 1 hour later. Not to be repeated before 3 days. If used for prophylaxis of gout flares: co-administration of colchicine in patients on telaprevir: If the original regimen was 0.6 mg twice a day, the regimen should be adjusted to 0.3 mg once a day. If the original regimen was 0.6 mg once a day, the regimen should be adjusted to 0.3 mg once every other day. Treatment of familial Mediterranean fever (FMF): co-administration of colchicine in patients on telaprevir: Maximum daily dose of 0.6 mg (may be given as 0.3 mg twice a day).
ANTIMYCOBACTERIAL		
rifabutin	↓ telaprevir ↑ rifabutin	Concentrations of telaprevir may be decreased, while rifabutin concentrations may be increased during co-administration. Telaprevir may be less effective due to decreased concentrations. The concomitant use of rifabutin and telaprevir is not recommended.
BENZODIAZEPINES		
alprazolam*	↑ alprazolam	Concomitant use of alprazolam and telaprevir increases exposure to alprazolam. Clinical monitoring is warranted.
parenterally administered midazolam*	↑ midazolam	Concomitant use of parenterally administered midazolam with telaprevir increased exposure to midazolam. Co-administration should be done in a setting which ensures clinical monitoring and appropriate medical management in case of respiratory depression and/or prolonged sedation. Dose reduction for midazolam should be considered, especially if more than a single dose of midazolam is administered. Co-administration of oral midazolam with telaprevir is contraindicated.
zolpidem (non-benzodiazepine sedative)*	↓ zolpidem	Exposure to zolpidem was decreased when co-administered with telaprevir. Clinical monitoring and dose titration of zolpidem is recommended to achieve the desired clinical response.
CALCIUM CHANNEL BLOCKERS		
amlodipine* diltiazem felodipine nicardipine nifedipine nisoldipine verapamil	↑ amlodipine ↑ calcium channel blockers	Exposure to amlodipine was increased when co-administered with telaprevir. Caution should be used and dose reduction for amlodipine should be considered. Clinical monitoring is recommended. Concentrations of other calcium channel blockers may be increased when telaprevir is co-administered. Caution is warranted and clinical monitoring of patients is recommended.
CORTICOSTEROIDS		
Systemic prednisone methylprednisolone	↑ prednisone ↑ methylprednisolone	Systemic corticosteroids such as prednisone and methylprednisolone are CYP3A substrates. Since telaprevir is a potent CYP3A inhibitor, plasma concentrations of these corticosteroids can be increased significantly. Co-administration of systemic corticosteroids and telaprevir is not recommended.
Systemic dexamethasone	↓ telaprevir	Systemic dexamethasone induces CYP3A and can thereby decrease telaprevir plasma concentrations. This may result in loss of therapeutic effect of telaprevir. Therefore this combination should be used with caution or alternatives should be considered.
Inhaled/Nasal fluticasone budesonide	↑ fluticasone ↑ budesonide	Concomitant use of inhaled fluticasone or budesonide and telaprevir may increase plasma concentrations of fluticasone or budesonide resulting in significantly reduced serum cortisol concentrations. Co-administration of fluticasone or budesonide and telaprevir is not recommended unless the potential benefit to the patient outweighs the risk of systemic corticosteroid side effects.
ENDOTHELIN RECEPTOR ANTAGONIST		
bosentan	↑ bosentan	Concentrations of bosentan may be increased when co-administered with telaprevir. Caution is warranted and clinical monitoring is recommended.
HIV-ANTIVIRAL AGENTS: HIV-PROTEASE INHIBITORS (PIs)		
atazanavir/ritonavir*	↓ telaprevir ↑ atazanavir	Concomitant administration of telaprevir and atazanavir/ritonavir resulted in reduced steady-state telaprevir exposure, while steady-state atazanavir exposure was increased.
darunavir/ritonavir*	↓ telaprevir ↓ darunavir	Concomitant administration of telaprevir and darunavir/ritonavir resulted in reduced steady-state exposures to telaprevir and darunavir. It is not recommended to co-administer darunavir/ritonavir and telaprevir.
fosamprenavir/ritonavir*	↓ telaprevir ↓ fosamprenavir	Concomitant administration of telaprevir and fosamprenavir/ritonavir resulted in reduced steady-state exposures to telaprevir and amprenavir. It is not recommended to co-administer fosamprenavir/ritonavir and telaprevir.
lopinavir/ritonavir*	↓ telaprevir ↔ lopinavir	Concomitant administration of telaprevir and lopinavir/ritonavir resulted in reduced steady-state telaprevir exposure, while the steady-state exposure to lopinavir was not affected. It is not recommended to co-administer lopinavir/ritonavir and telaprevir.
HIV-ANTIVIRAL AGENTS: REVERSE TRANSCRIPTASE INHIBITORS		
efavirenz*	↓ telaprevir ↓ efavirenz	Concomitant administration of telaprevir and efavirenz resulted in reduced steady-state exposures to telaprevir and efavirenz.
tenofovir disoproxil fumarate*	↔ telaprevir ↑ tenofovir	Concomitant administration of telaprevir and tenofovir disoproxil fumarate resulted in increased tenofovir exposure. Increased clinical and laboratory monitoring are warranted. Tenofovir disoproxil fumarate should be discontinued in patients who develop tenofovir-associated toxicities.
HORMONAL CONTRACEPTIVES/ESTROGEN		
ethinyl estradiol* norethindrone*	↓ ethinyl estradiol ↔ norethindrone	Exposure to ethinyl estradiol was decreased when co-administered with telaprevir. Two effective non-hormonal methods of contraception should be used during treatment with telaprevir. Patients using estrogens as hormone replacement therapy should be clinically monitored for signs of estrogen deficiency.
IMMUNOSUPPRESSANTS		
cyclosporine* sirolimus tacrolimus*	↑ cyclosporine ↑ sirolimus ↑ tacrolimus	Plasma concentrations of cyclosporine and tacrolimus are markedly increased when co-administered with telaprevir. Plasma concentration of sirolimus may be increased when co-administered with telaprevir, though this has not been studied. Significant dose reductions and prolongation of the dosing interval of the immunosuppressant to achieve the desired blood levels should be anticipated. Close monitoring of the immunosuppressant blood levels, and frequent assessments of renal function and immunosuppressant-related side effects are recommended when co-administered with telaprevir. Tacrolimus may prolong the QT interval. The use of telaprevir in organ transplant patients has not been studied.
INHALED BETA AGONIST		
salmeterol	↑ salmeterol	Concentrations of salmeterol may be increased when co-administered with telaprevir. Concurrent administration of salmeterol and telaprevir is not recommended. The combination may result in increased risk of cardiovascular adverse events associated with salmeterol, including QT prolongation, palpitations and sinus tachycardia.
NARCOTIC ANALGESIC		
methadone*	↓ R-methadone	Concentrations of methadone were reduced when co-administered with telaprevir. No adjustment of methadone dose is required when initiating co-administration of telaprevir. However, clinical monitoring is recommended as the dose of methadone during maintenance therapy may need to be adjusted in some patients.
PDE 5 INHIBITORS		
sildenafil tadalafil vardenafil	↑ PDE 5 inhibitors	Concentrations of PDE5 inhibitors may be increased when co-administered with telaprevir. For the treatment of erectile dysfunction, sildenafil at a single dose not exceeding 25 mg in 48 hours, vardenafil at a single dose not exceeding 2.5 mg dose in 72 hours, or tadalafil at a single dose not exceeding 10 mg dose in 72 hours can be used with increased monitoring for PDE5 inhibitor-associated adverse events. QT interval prolongation has been reported with vardenafil. Caution is warranted and clinical monitoring is recommended. Co-administration of sildenafil and telaprevir in the treatment of pulmonary arterial hypertension is contraindicated. Co-administration of tadalafil and telaprevir in the treatment of pulmonary arterial hypertension is not recommended.

*These interactions have been studied. The direction of the arrow (↑ = *increase*, ↓ = *decrease*, ↔ = *no change)* indicates the direction of the change in PK.

In addition to the drugs included in the table above, the interaction between INCIVEK and the following drug was evaluated in clinical studies and no dose adjustment is needed for either drug: esomeprozole.

USE IN SPECIFIC POPULATIONS

Pregnancy

Because INCIVEK must be used in combination with ribavirin and peginterferon alfa, the contraindications and warnings applicable to those drugs are applicable to combination treatment. Extreme care must be taken to avoid pregnancy in female patients and in female partners of male patients.

INCIVEK/Peginterferon Alfa/Ribavirin Combination Treatment

Pregnancy Category X: Animal studies have shown that ribavirin causes birth defects and/or fetal deaths while peginterferon alfa is abortifacient. See the prescribing information for ribavirin.

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 (see also ribavirin prescribing information). Interferons have abortifacient effects in animals and should be assumed to have abortifacient potential in humans (see peginterferon alfa prescribing information).

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 INCIVEK. Therefore, two alternative effective methods of contraception, including intrauterine devices and barrier methods, should be used in women during treatment with INCIVEK and concomitant ribavirin.

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. Health care providers and patients are encouraged to report such cases by calling 1-800-593-2214.

INCIVEK (telaprevir) Tablets

Pregnancy Category B: Telaprevir treatment alone in mice and rats did not result in harm to the fetus. The highest doses tested produced exposures equal to 1.84- and 0.60-fold the exposures in humans at the recommended clinical dose, respectively. Telaprevir treatment alone had effects on fertility parameters in rats. The no observed adverse effect level (NOAEL) for testicular toxicity was established at exposures 0.17-fold the human exposures at the recommended clinical dose. Potential effects on sperm (e.g., decreased % motile sperm and increased non-motile sperm count) were observed in a rat fertility study at exposures 0.30-fold the human exposures at the recommended clinical dose. Additional effects on fertility include minor increases in percent preimplantation loss, in percent of dams with nonviable embryos and percent of nonviable conceptuses per litter. These effects are likely associated with testicular toxicity in male but contributions of the female cannot be ruled out. There are, however, no adequate and well-controlled studies in pregnant women.

Significant teratogenic and/or embryocidal effects have been demonstrated in all animal species exposed to ribavirin. Extreme care must be taken to avoid pregnancy in female patients and in female partners of male patients—both during treatment and for 6 months after the completion of all treatment. INCIVEK combination treatment should not be started unless a female patient has a negative pregnancy test immediately prior to initiation of treatment. Pregnancy testing should occur monthly during INCIVEK combination treatment and for 6 months after all treatment has ended. Pregnancy testing in non-pregnant female partners is recommended before INCIVEK combination therapy, every month during INCIVEK combination therapy, and for 6 months after ribavirin therapy has ended.

Hormonal contraceptives may be continued but may not be reliable during INCIVEK dosing and for up to two weeks following cessation of INCIVEK. During this time, female patients of childbearing potential should use 2 effective non-hormonal methods of contraception. Examples may include barrier methods or IUDs. Refer also to the prescribing information for ribavirin.

Two weeks after completion of INCIVEK treatment, hormonal contraceptives are again appropriate as one of the 2 required effective methods of birth control; however, specific prescribing information recommendations should be followed for the contraceptives. Refer also to the prescribing information for ribavirin.

Nursing Mothers

It is not known whether telaprevir is excreted in human breast milk. When administered to lactating rats, levels of telaprevir were higher in milk compared to those observed in plasma. Rat offspring exposed to telaprevir in utero showed no effects on body weight at birth. However, when fed via milk from telaprevir-treated dams, body weight gain of pups was lower than pups fed milk from control dams. After weaning, rat pup body weight gain was similar in offspring from telaprevir-treated and control dams. Because of the potential for adverse reactions in nursing infants, nursing must be discontinued prior to initiation of treatment. See also the prescribing information for ribavirin.

Pediatric Use

The safety, efficacy and pharmacokinetic profile of INCIVEK in pediatric patients have not been established.

Geriatric Use

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

Hepatic Impairment

INCIVEK is not recommended for use in patients with moderate or severe hepatic impairment (Child-Pugh B or C, score greater than or equal to 7) because no pharmacokinetic or safety data are available regarding the use of INCIVEK in HCV-infected patients with moderate or severe hepatic impairment, and appropriate doses have not been established. No dose adjustment of INCIVEK is necessary for patients with mild hepatic impairment (Child-Pugh A, score 5-6). Refer also to the prescribing information for peginterferon alfa and ribavirin which must be co-administered with INCIVEK.

Renal Impairment

No dose adjustment is necessary for INCIVEK in HCV-infected patients with mild, moderate or severe renal impairment. INCIVEK has not been studied in HCV-infected patients with CrCl less than or equal to 50 mL/min.

The pharmacokinetics of telaprevir were assessed after administration of a single dose of 750 mg to HCV-negative subjects with severe renal impairment (CrCl less than 30 mL/min). INCIVEK has not been studied in patients with end-stage renal disease (ESRD) or on hemodialysis. Refer also to the prescribing information for peginterferon alfa and ribavirin which must be co-administered with INCIVEK.

Co-infection

The safety and efficacy of INCIVEK have not been established in patients co-infected with HCV/HIV or HCV/HBV.

Solid Organ Transplantation

The safety and efficacy of INCIVEK have not been established in solid organ transplant patients.

OVERDOSAGE

The highest documented dose administered is 1875 mg every 8 hours for 4 days in healthy subjects with INCIVEK alone. In that study, the following common adverse events were reported more frequently with the 1875 mg q8h regimen compared to the 750 mg q8h regimen: nausea, headache, diarrhea, decreased appetite, dysgeusia, and vomiting. No specific antidote is available for overdose with INCIVEK. Treatment of overdose with INCIVEK consists of general supportive measures including monitoring of vital signs and observation of the clinical status of the patient. In the event of an overdose, it is reasonable to employ the standard supportive measures, such as, removing unabsorbed material from the gastrointestinal tract, employing clinical monitoring (including obtaining an electrocardiogram), and instituting supportive therapy if required. It is not known whether telaprevir is dialyzable by peritoneal or hemodialysis.

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Presentations in GERD

Comparison of Impedance-pH Monitoring and a Symptom-Based Reflux Disease Questionnaire for the Identification of GERD

The GerdQ is a 6-item, symptom-based reflux disease questionnaire that has been validated to help identify patients with gastroesophageal reflux disease (GERD). At the 2011 American College of Gastroenterology (ACG) Annual Scientific Meeting and Postgraduate Course, Chehade and colleagues presented results from a prospective study that aimed to evaluate the association between the GerdQ and parameters of impedance-pH monitoring.

A total of 85 consecutive patients who were referred for impedance-pH monitoring over an 11-month period were included. The majority of patients were white (99%), half were female (52%), the average age was 53±15 years, and the mean body mass index (BMI) was 27.2±6.2 kg/m^2. Patients had a mean duration of symptoms of 100±108 months, and 59% of patients completed the study while receiving proton pump inhibitor (PPI) therapy.

Abnormal acid exposure occurred in 8% and 18% of patients on and off PPI therapy, respectively (*P*=.19). Abnormal acid and nonacid events, combined, also occurred in a similar number of patients on and off treatment (20% and 21%, respectively; *P*=.99). After controlling for age, sex, and BMI, no significant differences were observed between patients on and off PPI therapy in terms of likelihood of an abnormal impedance-pH monitoring result.

Among patients on and off PPI therapy, mean GerdQ scores were 9.2±2.9 and 8.8±2.6, respectively (*P*=.64). For patients who were on treatment, a GerdQ score of 8 or higher had 75% sensitivity (range, 19–99%) for identifying patients with abnormal acid exposure time. However, the specificity of the GerdQ at this threshold was only 26% (range, 14–41%). In patients off treatment, the sensitivity and specificity were 100% (range, 54–100%) and 37% (range, 19–58%), respectively. The investigators concluded that the GerdQ may be an important tool for differentiating acid versus nonacid reflux disease. Further study in a larger patient population is required for confirmation.

Prevalence, Association, and Effect of Gender on Cough and GERD in Untreated Patients Over Age 65

Cough is a reported symptom of GERD; like GERD, cough is also known to increase with patient age. At the 2011 ACG meeting, DeVault and colleagues presented a study that assessed the effect of gender on cough and GERD in older patients.

A total of 300 consecutive patients older than 65 years (mean age, 72 years; range, 65–88 years) were identified after being referred for screening or surveillance colonoscopy. Patients had not previously undergone an upper endoscopic procedure and were not on antisecretory therapy. Nearly half (46%) of the patients were female.

Approximately one fourth (27%) of the 300 patients reported cough as a symptom, with frequency of cough ranging from 1 to 75 times weekly. Of these 82 patients, 20 were not distressed by their cough, 46 were somewhat distressed, 12 were quite a bit distressed, and 4 were very much distressed. Mucosal disease or symptoms consistent with GERD were identified in 52% of patients, including 19% with Barrett esophagus (BE), 14% with erosive esophagitis (EE), and 19% with other significant reflux symptoms.

Cough was significantly more prevalent among GERD patients versus non-GERD patients (31.2% vs 23.1%; *P*=.006). Cough also occurred more frequently in females than males (28.9% vs 24.2%; *P*=.09). GERD was more common in males than females (57.8% vs 43.0%; *P*<.0001). Among GERD patients, mucosal disease was more common in males than females (76.3% vs 45.3%; *P*<.0001), while cough was more frequent in females (35.9% vs 28.0%; *P*<.0001). The investigators concluded that GERD and cough were indeed associated in older patients, but further study is required to determine the cause of this link.

Increasing Body Mass Index Does Not Diminish Heartburn Relief in Patients Treated for Nonerosive GERD or Erosive Esophagitis

As presented by Peura and colleagues at the 2011 ACG meeting, a post–hoc analysis was performed using data from patients with nonerosive GERD (NERD) or EE who were enrolled in phase III trials. The goal of this analysis was to determine if BMI affected the severity and/or frequency of heartburn symptoms.

A total of 3,369 patients were included in this post–hoc analysis. NERD patients were enrolled in a randomized, double-blind study comparing 4 weeks of dexlansoprazole (Dexilant, Takeda; N=315) versus placebo (N=317) for 24-hour heartburn relief. EE patients (N=2,737) were enrolled in a double-blind, randomized study comparing 8 weeks of dexlansoprazole versus lansoprazole for EE healing.

When patients were distributed by baseline BMI into 1 of 3 groups (<25 kg/m^2, 25 kg/m^2 to <30 kg/m^2, and ≥30 kg/m^2), there were 190, 193, and 238 NERD patients in each group, respectively. The corresponding numbers for EE patients were 547, 1,013, and 1,132, respectively. The severity of heartburn symptoms at baseline rose with increasing BMI in both the NERD and EE patient cohorts. Among NERD patients, heartburn symptom severity (as rated on a 5-point scale from 0=none to 4=very severe) was 1.14–1.32, 1.21–1.42, and 1.36–1.50 for patients with BMIs below 25 kg/m^2, 25 kg/m^2 to less-than-30 kg/m^2, and 30 kg/m^2 or higher, respectively. In EE patients, heartburn symptom severity was 1.00–1.07, 1.17–1.25, and 1.43 for these 3 BMI groups, respectively.

During treatment with either dexlansoprazole or lansoprazole, patients with higher BMIs had lower severity of heartburn (NERD patients: 0.50, 0.33, and 0.38; EE patients: 0.19–0.20, 0.13–0.15, and 0.12–0.14; for BMI <25 kg/m^2, 25 kg/m^2 to <30 kg/m^2, and ≥30 kg/m^2, respectively). Patients with higher BMIs also exhibited a higher percentage of heartburn-free 24-hour days with treatment (NERD patients: 51.9%, 57.7%, and 56.0%; EE patients: 73.6–77.0%, 80.0–82.2%, and 81.8–84.8%; for BMI <25 kg/m^2, 25 kg/m^2 to <30 kg/m^2, and ≥30 kg/m^2, respectively). The investigators concluded that NERD and EE patients with higher BMIs had increased severity and frequency of heartburn at baseline but that these patients may actually derive a greater benefit during dexlansoprazole treatment.

Diagnostic Utility of Major Basic Protein and Eotaxin-3 Staining to Differentiate Eosinophilic Esophagitis From GERD

At the 2011 ACG meeting, Dellon and colleagues presented a report on the potential utility of 2 biomarkers, major basic protein (MBP) and eotaxin-3, that might help to differentiate eosinophilic esophagitis (EoE) from GERD. A total of 51 patients with EoE were enrolled based on a diagnosis of EoE as defined by the criteria in current consensus guidelines. The 55 GERD patients enrolled in this study all had signs of inflammation (including the presence of eosinophils on biopsy) and thus represented a patient group in which diagnostic difficulty is likely. MBP and eotaxin-3 expression in the esophageal epithelium was quantified by immunohistochemistry staining density (positive cells/mm^2); the number of eosinophils per high-power field (hpf) was also determined.

The characteristics of the EoE and GERD patient groups were relatively similar, including mean age (24 years and 34 years, respectively) and sex (69% male and 61% male, respectively). At baseline, patients with EoE had a much higher mean eosinophil count compared to GERD patients (143 eosinophils/hpf vs 20 eosinophils/hpf, respectively). MBP maximum staining density was also significantly higher in patients with EoE versus GERD (1,479±1,290 cells/mm^2 vs 59±103 cells/mm^2; *P*<.001), as was the maximum staining density of eotaxin-3 (2,219±1,782 cells/mm^2 vs 479±777 cells/mm^2, respectively; *P*<.001).

Construction of a receiver operator characteristic (ROC) curve revealed a strong association between MBP expression and eosinophil count (R=.81; *P*<.001) and a weaker association between eotaxin-3 expression and eosinophil count (R=.25; *P*=.01). The area under the ROC curve for diagnosis of EoE based on a combination of MBP and eotaxin-3 staining plus eosinophil count was .99, compared to .96 for MBP staining alone, .87 for eotaxin-3 staining alone, and .96 for MBP plus eotaxin-3 staining. The investigators concluded that eotaxin-3 and MBP expression may have greater diagnostic utility than eosinophil count alone for the differentiation of EoE versus GERD.

Comparison of Aerosolized Swallowed Fluticasone to Esomeprazole for Treatment of Eosinophilic Esophagitis

In a prospective, single-blinded, randomized, controlled trial presented by Moawad and colleagues at the 2011 ACG meeting, aerosolized swallowed fluticasone steroid therapy was compared to the oral PPI esomeprazole for the treatment of EoE. A total of 42 patients with EoE were enrolled; all were diagnosed based on both clinical symptoms (including dysphagia and food impaction) and histologic criteria (>15 eosinophils/hpf). Patients were randomized to 8 weeks of treatment with aerosolized, swallowed, twice-daily fluticasone or oral daily esomeprazole. The vast majority of patients were male (90%) and white (81%), with a mean age of 38+10 years. At randomization, patients with coexisting GERD at baseline (n=8) were equally stratified into each treatment arm.

No significant difference was observed between the 2 treatment groups in terms of resolution of EoE (defined as <7 eosinophils/hpf). The proportion of patients in the fluticasone and esomeprazole treatment groups who achieved resolution of EoE was 19% and 35%, respectively (*P*=.247). Clinical assessment using the Mayo Dysphagia Questionnaire revealed a significant improvement in the esomeprazole group (mean score, 19+21 before therapy vs 1+5 after therapy; *P*<.001) but not in the fluticasone group (mean score, 17+18 before therapy vs 12+16 after therapy; *P*=.162). Neither of the treatment groups exhibited significant changes in endoscopic findings, eosinophil counts, or other histologic markers.

Of the EoE patients who had coexisting GERD, 0% and 100% of patients in the fluticasone and esomeprazole arms, respectively, achieved resolution of EoE (*P*=.029). Among patients with coexisting GERD, neither treatment led to an improvement in the Mayo Dysphagia Questionnaire. The investigators concluded that there seemed to be no overall differences between fluticasone and esomeprazole for resolution of EoE, although patients with coexisting GERD may benefit more from esomeprazole.

Can Proton Pump Inhibitors Prevent Progression to Dysplasia in Barrett Esophagus?

Chemoprevention to limit the progression of BE precursor lesions to esophageal adenocarcinoma is a major topic of interest. PPIs have shown some promise as a chemopreventative agent in this setting; based on a lack of definitive studies, however, current guidelines do not recommend their use for this purpose. In a retrospective review presented at the 2011 ACG meeting, Altawil and colleagues identified several characteristics in patients with BE and used these characteristics to examine the association between PPI therapy and progression to dysplasia or esophageal adenocarcinoma.

A total of 77 patients with pathologically confirmed BE were included; most of these patients were white (75%) and male (96%), with an average age of 60 years. Of the 77 patients in this study, over half (64%) were on PPI therapy. Significantly fewer patients on PPI therapy developed dysplasia or esophageal adenocarcinoma compared to patients who were not on PPI therapy (14% vs 36%; *P*=.03).

Two characteristics were identified as being significantly different in patients on and off PPI therapy: BMI (28.9 kg/m^2 vs 26 kg/m^2; *P*=.03) and use of histamine-$_2$ receptor antagonists (2% vs 29%; *P*=.006). There were no significant differences between these 2 groups in terms of patient age (58.3 vs 61.7 years; *P*=.27), race (78% white vs 71% white; *P*=.53), sex (96% male vs 96% male; *P*=.91), or use of other medications (including aspirin [10% vs 11%; *P*=.95], nonsteroidal anti-inflammatory drugs [NSAIDs; 16% vs 14%; *P*=.82], and statins [37% vs 32%; *P*=.69]). From these retrospective data, the investigators concluded that PPI therapy was indeed a potentially valuable chemopreventative tool in patients with BE, one that should be studied further in larger prospective studies.

Helicobacter pylori Gastritis Is Inversely Correlated with Dysplasia in Patients with Barrett Esophagus

A large national study recently demonstrated an inverse association between *Helicobacter pylori* infection and BE.[1] At the 2011 ACG meeting, Trapasso and colleagues presented a follow-up study in which they investigated the role of *H. pylori* on the progression of BE to dysplasia and neoplastic lesions.

A total of 172,329 patients (median age, 56 years; 43.5% male) were identified via electronic medical records from a gastrointestinal pathology laboratory's large nationwide patient population. These individuals had simultaneous esophageal and gastric biopsies. Control patients (N=78,505) had no BE or evidence of cancer; this group included only patients with no history of GERD, in order to avoid a false low rate of *H. pylori* positivity. The control group was used as a reference comparator group in this analysis; the prevalence of *H. pylori* infection in these patients was 7.2%.

BE with no evidence of dysplasia was diagnosed in 13,836 patients, while BE with evidence of low-grade or high-grade dysplasia was diagnosed in 283 and 150 patients, respectively. The prevalence of *H. pylori* infection was 3.7% in the group with BE and no dysplasia (odds ratio [OR], 0.49; 95% confidence interval [CI], 0.45–0.54; *P*<.0001), compared to 3.2% (OR, 0.42; 95% CI, 0.21–0.82; *P*<.01) and 2.7% (OR, 0.35; 95% CI, 0.13–0.95; *P*<.05) in the low-grade and high-grade dysplasia groups, respectively. BE with adenocarcinoma was diagnosed in 104 patients; the prevalence of *H. pylori* infection was 6.7% in these patients (OR, 0.93; 95% CI, 0.42–2.00; *P*=not significant). Esophageal squamous-cell carcinoma was diagnosed in 83 patients; this group had an *H. pylori* prevalence of 9.6% (OR, 1.36; 95% CI, 0.66–2.85; *P*=not significant).

The investigators concluded that *H. pylori* infection is inversely related with both low-grade and high-grade dysplasia in patients with BE. In contrast, the investigators found no such relationship in patients with either adenocarcinoma or squamous-cell carcinoma, possibly due to the inclusion of junctional adenocarcinomas of gastric origin in the former group and similar risk factors (such as lower socioeconomic status, ethnic background, and smoking) in the latter group.

Reference:

1. Sonnenberg A, Lash RH, Genta RM. A national study of *Helicobacter pylori* infection in gastric biopsy specimens. *Gastroenterology*. 2010;139:1894-1901.

Presentations in IBS

Efficacy and Safety of Once-Daily Linaclotide in Patients with IBS with Constipation

At the 2011 ACG meeting, Chey and colleagues reported on pooled results from 2 randomized, double-blind, placebo-controlled, phase III trials that evaluated the investigational agent linaclotide for the treatment of irritable bowel syndrome associated with constipation (IBS-C). In both trials, linaclotide was administered at a dose of 290 µg once daily for 12 weeks. Patients were randomized to treatment with either linaclotide or placebo following a 2-week baseline period.

A total of 1,602 patients were included in the pooled intent-to-treat population (median age, 44 years; 90% female). During baseline assessment, the majority of patients (87%) experienced abdominal pain on a daily basis. No complete spontaneous bowel movements (CSBMs) were reported in 76% of patients.

Following treatment, linaclotide was associated with a significant improvement in abdominal and bowel symptoms, even when controlling for multiplicity (nominal $P<.0001$ for all 14 primary and secondary endpoints). Specifically, linaclotide was associated with significant improvements in the following primary endpoints: 30% or greater reduction in abdominal pain, at least 3 CSBMs, and an increase of at least 1 CSBM from baseline, all within the same week for at least 9 of 12 weeks (12.4% vs 4.0% for linaclotide vs placebo); at least 3 CSBMs and an increase of at least 1 CSBM from baseline, both within the same week for at least 9 of 12 weeks (18.8% vs 5.6% for linaclotide vs placebo); 30% or greater reduction in abdominal pain for at least 9 of 12 weeks (36.6% vs 23.3% for linaclotide vs placebo); and 30% or greater reduction in abdominal pain and an increase of at least 1 CSBM from baseline, both within the same week for at least 6 of 12 weeks (33.7% vs 17.4% for linaclotide vs placebo).

The most common adverse event reported was diarrhea, which led to discontinuation in 5.3% and 0.4% of the linaclotide and placebo groups, respectively. The investigators concluded that linaclotide was associated with sustained and clinically meaningful and significant improvements in abdominal and bowel symptoms in patients with IBS-C.

Subanalysis of the TARGET 1 and TARGET 2 Studies to Evaluate the Efficacy of Rifaximin by Baseline Disease Severity

In a presentation at the 2011 ACG meeting, Pimentel and colleagues evaluated the efficacy of rifaximin (Xifaxan, Salix Pharmaceuticals) for the treatment of nonconstipating IBS (non–C-IBS) in 2 double-blind, placebo-controlled trials (TARGET 1 and TARGET 2). A total of 1,260 non–C-IBS patients from these trials were assessed over a 10-week post-treatment follow-up period. In both TARGET trials, patients were randomized to 2 weeks of treatment with rifaximin (550 mg 3 times daily) or placebo.

No interaction was found between rifaximin and non–C-IBS disease severity, suggesting that patients in all severity categories benefit equally from treatment. Improvement in IBS symptoms, the primary study endpoint, was noted with rifaximin versus placebo in mild non–C-IBS (39.8% vs 30.2%; $P=.0261$), moderate non–C-IBS (39.5% vs 31.6%; $P=.1112$), and severe non–C-IBS (43.0% vs 33.7%; $P=.0643$). When all severity groups were considered together, improvement in symptoms was observed in 40.7% of rifaximin-treated patients versus 31.7% of placebo-treated patients ($P=.0008$); rifaximin also improved several secondary endpoints compared to placebo, including bloating symptoms (40.2% vs 30.3%; $P=.0002$), IBS symptoms from daily data (40.2% vs 29.5%; $P<.0001$), and abdominal pain and stool consistency (46.6% vs 37.4%; $P=.0009$). The investigators concluded that rifaximin was associated with improved symptom relief in the weeks following treatment, and this benefit was apparent in patients with non–C-IBS of all severities.

Probiotic Bifidobacterium infantis 35624 in a Nonpatient Population with a History of Abdominal Discomfort and Bloating

Ringel and colleagues presented results from a double-blind, randomized, placebo-controlled, parallel study at the 2011 ACG meeting. In this trial, the efficacy of the probiotic *Bifidobacterium infantis* 35624 was investigated in nonpatient individuals with IBS.

A total of 275 evaluable individuals who had experienced abdominal discomfort and bloating more than 2 times per week, on average, for at least 3 months were recruited by advertisement from the general population. All subjects had not seen a physician for their symptoms and had not received medication for their symptoms within the prior 12 months. After a 2-week placebo run-in phase, *B. infantis* 35624 was administered in a 4-week intervention phase at 10 clinical centers.

At baseline, the mean severity score was 2.3 for abdominal discomfort and 2.5 for bloating. Over the 4-week intervention period, both the *B. infantis* 35624 and placebo groups demonstrated significant improvements in abdominal discomfort and bloating scores ($P<.05$). However, neither score showed a significant difference between the *B. infantis* 35624 and placebo groups.

Although previous studies had suggested a significant benefit with *B. infantis* 35624 in IBS patients, the authors of this study concluded that a population of nonpatients with IBS did not experience the same trend. Reasons for this finding may include a high placebo effect in IBS, as well as the potential for lower severity, frequency, and impact of IBS symptoms among nonpatients.

Interleukin-10 in the Susceptibility and Pathogenesis of IBS

At the 2011 ACG meeting, Jiang and colleagues presented results of an investigation in which they evaluated a particular single nucleotide polymorphism (SNP) present in the –1082 interleukin-10 allele and assessed its association with particular types of IBS. In their previous studies, these investigators had demonstrated an association between the AA SNP and reduced frequency of IBS.

Fifty patients with postinfectious IBS, 50 patients with idiopathic IBS, and 52 healthy control subjects were included in this study. DNA was extracted from blood samples, amplified by polymerase chain reaction, and analyzed by pyrosequencing. The level of interleukin-10 in the fecal matter was measured by enzyme-linked immunosorbent assay.

The incidence of the AA SNP was 40%, 32%, and 52% for postinfectious IBS, idiopathic IBS, and control subjects, respectively. When the incidence in both IBS groups was combined (35%), it was significantly lower than the incidence of the AA SNP in the control group (P=.037). The median levels of fecal interleukin-10 were also assessed and were found to be 2.78 pg/mL, 2.59 pg/mL, 1.85 pg/mL, and 5.79 pg/mL for the postinfectious IBS, idiopathic IBS, combined IBS, and control groups, respectively (P=.023 for combined IBS vs control). The investigators concluded that both postinfectious and idiopathic IBS were associated with a reduced incidence of this AA SNP in the –1082 interleukin-10 allele, as well as reduced interleukin-10 protein expression in fecal matter.

Questionnaire Evaluation of IBS Patients' Outlook on Diagnosis and Treatment

In a presentation at the 2011 ACG meeting, Lurix and colleagues presented results of a questionnaire they administered to 108 IBS patients to help determine patients' outlooks on diagnosis and treatment. This anonymous questionnaire was distributed to IBS patients who presented to an outpatient tertiary referral gastroenterology clinic.

The vast majority of respondents were female (96%), with a mean age of 42 years. Most patients (81%) self-classified their symptoms as moderate to severe, and patients reported that their symptoms had been present for an average of 40 months. One third of patients (33%) reported a prior diagnosis of IBS, but fewer than half (44%) of these patients agreed with this diagnosis. Almost half (44%) of respondents had seen multiple healthcare providers (2–5) for the same complaint; 50% of these patients had seen another gastroenterologist. Colonoscopy, endoscopy, and/or imaging studies were reported in 58–60% of patients; however, nearly all respondents (95%) felt they required more testing. Of the 84% of patients who reported prior treatment, most (64%) had tried lifestyle changes. A diagnosis was expected either that day or within 1 month by 69% of patients, and nearly three quarters of patients (72%) desired some type of treatment at their current visit. Fewer than half (41%) were willing to see a psychiatrist or psychologist. The investigators concluded from the questionnaire responses that IBS patients utilize a significant amount of resources in gastroenterology clinics, and they recommended that physicians be aware of the expectations of their IBS patients.

A Palpable Bowel Loop Is a Highly Specific Physical Sign in IBS and Other Functional Gastrointestinal Disorders

At the 2011 ACG meeting, McWilliams and colleagues presented a study in which they assessed the diagnostic utility of a palpable bowel loop for diagnosis of functional gastrointestinal disorders and IBS. Among a referral population of 2,115 patients, 947 patients (72% female) had an ultimate diagnosis of a functional gastrointestinal disorder. Patients in this group had a significantly younger mean age at first presentation compared to patients without a functional gastrointestinal disorder (38.5 years vs 44.2 years; P<.001).

Of the 2,115 patients in the referral population, palpable bowel loops occurred with an incidence of 15.8%. The sensitivity and specificity of a palpable bowel loop for diagnosis of a functional gastrointestinal disorder were 23.9% and 90.8%, respectively. Similar sensitivity and specificity were observed for the diagnosis of IBS (25% and 88.8%, respectively). Among the 334 patients with a palpable bowel loop, a tender palpable bowel loop (present in 211 patients) had a sensitivity of 69.5% for diagnosis of any functional gastrointestinal disorder and a sensitivity of 76.1% for the diagnosis of IBS. The investigators concluded that a palpable bowel loop was most useful as a diagnostic tool when absent, although the presence of a tender palpable bowel loop may have utility for aiding in the positive diagnosis of IBS.

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

Presentations in Hepatology

The PROVIDE Study Demonstrates Efficacy of Boceprevir in Prior Null Responders to Peginterferon and Ribavirin

The ongoing, multicenter, single-arm rollover PROVIDE study aims to evaluate the efficacy of boceprevir (Victrelis, Merck), peginterferon, and ribavirin in patients who previously failed to respond to peginterferon and ribavirin. The PROVIDE treatment regimen included 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). During the 2011 Annual Meeting of the American Association for the Study of Liver Diseases (AASLD), Vierling and coworkers presented the results of a subset analysis from the PROVIDE study in which they assessed the efficacy of boceprevir, peginterferon, and ribavirin in 48 hepatitis C virus (HCV)-infected patients classified as prior null responders (defined as a reduction in HCV RNA level <2 $\log_{10}$ from baseline to Week 12 during previous peginterferon and ribavirin treatment). All patients in this subanalysis received 4 weeks of peginterferon and ribavirin, followed by boceprevir plus peginterferon and ribavirin for up to 44 weeks.

The primary study endpoint was sustained virologic response (SVR), defined as an undetectable HCV RNA level at 24 weeks post-therapy. SVR was achieved in 16 of 42 evaluable patients (38%). Twenty of 43 patients (47%) achieved end-of-treatment responses, and relapses following end-of-treatment response were detected in 3 of 19 patients (16%). An association was detected between declines in HCV RNA level after the 4-week lead-in period and the likelihood of subsequent SVR. SVR was achieved in 50% of patients with a decline in HCV RNA level of at least 1 $\log_{10}$ at Week 4 versus an SVR rate of 34% among patients whose HCV RNA decline at Week 4 was less than 1 $\log_{10}$. These results suggest the effectiveness of a treatment regimen consisting of boceprevir, peginterferon, and ribavirin in a group of well-documented prior null responders.

Interim Analysis of the ZENITH Study Demonstrates Efficacy of VX-222 and Telaprevir in Combination with Peginterferon and Ribavirin in Treatment-Naïve Patients

The ZENITH trial is an ongoing, phase II study evaluating 12-week response-guided treatment with the HCV polymerase inhibitor VX-222 plus telaprevir (Incivek, Vertex), with or without peginterferon and/or ribavirin, in treatment-naïve patients with genotype 1 HCV infection. In a presentation at the 2011 AASLD meeting, Nelson and coworkers presented a Week 24 interim analysis of 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). Patients received all 4 drugs for 12 weeks and were allowed to stop treatment at Week 12 if they achieved undetectable levels of HCV RNA at Weeks 2 and 8; patients whose HCV RNA levels were detectable at either Week 2 or Week 8 received additional peginterferon and ribavirin for a total of 24 weeks.

Among patients who received VX-222 at a dose of 400 mg, 50% (15 of 30) were eligible to stop treatment at Week 12; SVR was achieved in 93% (14 of 15) of those patients. Of the 15 patients receiving the 400-mg dose of VX-222 who were assigned to 24 weeks of treatment, 87% (n=13) had undetectable levels of HCV RNA at 12 weeks post-treatment. Among patients receiving the 100-mg dose of VX-222, 38% (11 of 29) were eligible 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, 83% (n=15) had undetectable levels of HCV RNA at 12 weeks post-treatment. An intent-to-treat analysis of all patients revealed undetectable HCV RNA levels at Week 24 in 90% of patients who received the 400-mg dose of VX-222 and 83% of patients who received the 100-mg dose of VX-222. A total of 3 patients experienced relapses: 2 in the 100-mg arm and 1 in the 400-mg arm. Fatigue (56%), nausea (49%), diarrhea (48%), anemia (37%), pruritus (34%), and rash (31%) were among the most commonly reported adverse events. Severe adverse events occurring in more than 1 patient included neutropenia (5.1%), hypomagnesemia (3.4%), and anemia (3.4%).

HCV SPRINT-2 Study Addresses Use of Boceprevir Combined with Peginterferon and Ribavirin 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 meeting, McCone and colleagues presented data on the efficacy and safety of boceprevir-based therapy in black patients enrolled in this study. Of the 159 treatment-naïve black patients who were enrolled in this study, 52 patients were assigned to receive 48 weeks of peginterferon and ribavirin; 52 patients were assigned to receive response-guided

therapy with boceprevir, peginterferon, and ribavirin; and 55 patients were assigned to receive boceprevir-based triple therapy for 48 weeks. All patients 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-based therapy, and 26% for patients treated with peginterferon and ribavirin alone. Among patients without cirrhosis who had an undetectable HCV RNA level at Weeks 8–24, boceprevir-containing treatment yielded SVR rates of 92–95%. Among patients without cirrhosis who were late responders—patients whose HCV RNA level was detectable at Week 8 but undetectable at Week 24—SVR rates were 58–86%.

In terms of adverse events, patients who received 48 weeks of boceprevir-based treatment or response-guided boceprevir-based therapy had higher rates of anemia than patients in the control group (71%, 63%, and 31%, 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).

24-Week Interim Analysis of Telaprevir in Combination with Peginterferon and Ribavirin in HCV/HIV Co-Infected Patients

In a late-breaking abstract at the 2011 AASLD meeting, 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. 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 efavirenz (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.

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). 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 alone.

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, but 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.

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

5 Years of Treatment with Tenofovir for Chronic HBV Infection Is Associated with Sustained Viral Suppression and Significant Regression of Fibrosis and Cirrhosis

Marcellin and colleagues presented 5-year on-treatment virologic and paired histologic assessment data from Study 102 and Study 103 during the 2011 AASLD meeting. These multicenter, randomized, double-blind, phase III trials compared tenofovir disoproxil fumarate (Viread, Gilead Sciences) and adefovir dipivoxil (Hepsera, Gilead Sciences) in chronic hepatitis B virus (HBV)–infected patients with compensated liver disease who were hepatitis B e antigen (HBeAg)-negative (Study 102; n=375) or HBeAg-positive (Study 103; n=266). The majority of patients were treatment-naïve. In both studies, patients who were originally randomized to adefovir dipivoxil

were rolled over to open-label tenofovir disoproxil fumarate (n=196) at Week 48, and patients who were originally randomized to tenofovir disoproxil fumarate continued on open-label treatment (n=389).

Of the 641 patients who were initially randomized and treated in these studies, 91% (n=585) entered the open-label extension phase of the trials. At Year 5, 76% (n=490) remained on study. Normalization of alanine aminotransferase (ALT) levels at Week 240 was achieved in 72% of patients in Study 102 and 50% of patients in Study 103. Across both studies, only 2.1% of patients who received tenofovir disoproxil fumarate for 5 years discontinued treatment due to an adverse event; 0.9% of patients experienced a confirmed increase in serum creatinine level of at least 0.5 mg/dL or a calculated creatinine clearance less than 50 mL/min. Resistance to tenofovir disoproxil fumarate over a 5-year treatment period was not detected. Overall histologic improvement was observed in 88% of the 331 patients who underwent biopsies before therapy and again at 5 years. Of the 94 patients who were cirrhotic at the start of therapy, 73% experienced regression of histologic cirrhosis at 5 years.

BE-LOW Study Shows That Entecavir Monotherapy Is Comparable to Entecavir Plus Tenofovir in Nucleos(t)ide-Naïve Patients with Chronic HBV Infection

In a presentation at the 2011 AASLD meeting, Lok and colleagues presented data from the open-label, multicenter, phase IIIb BE-LOW study, in which treatment-naïve adult patients with HBeAg-positive and HBeAg-negative chronic HBV infection and compensated liver disease were randomized to receive either entecavir monotherapy (Baraclude, Bristol-Myers Squibb) 0.5 mg once daily (n=182) or entecavir 0.5 mg plus tenofovir disoproxil fumarate 300 mg once daily (n=197) for 100 weeks.

Prior to Week 96, 6.5% (n=12) of patients in the entecavir monotherapy arm discontinued treatment, compared to 11.6% (n=23) of patients in the entecavir plus tenofovir arm. A comparable proportion of patients in both treatment arms achieved HBV DNA levels below 50 IU/mL at Week 96 (76.4% in the entecavir monotherapy arm vs 83.2% in the entecavir plus tenofovir arm; 95% CI, –1.0, 14.9; *P*=.0882). Fewer patients in the combination therapy arm experienced ALT normalization or HBeAg seroconversion compared to the entecavir monotherapy arm. Virologic breakthrough was similar in both arms (4% in the entecavir plus tenofovir arm vs 1% in the entecavir monotherapy arm). Both study arms had similar safety profiles, with serious adverse events reported in 6.6% of patients in the entecavir monotherapy arm and 7.1% of patients in the entecavir plus tenofovir arm.

Cirrhotic Patients on Rifaximin Have a Lower Incidence of *Clostridium difficile* Infection and Improved Outcomes

In a study presented at the 2011 AASLD meeting, Zuchelli and coworkers sought to determine the incidence of *Clostridium difficile*–associated diarrhea (CDAD) in patients with cirrhosis who were receiving rifaximin and/or lactulose and to establish outcomes and confounding factors among cirrhotic patients with CDAD. A total of 144 patient charts were retrospectively reviewed, including 69 with CDAD and 75 without CDAD. Among patients with CDAD, 26% (n=18) were receiving lactulose and 9% (n=6) were receiving rifaximin. Of the patients without CDAD, 80% (n=60) were receiving lactulose and rifaximin and 20% (n=15) were receiving rifaximin alone. Although there were no significant differences among patients in regard to gender, age, etiology of cirrhosis, or PPI and/or antibiotic use, cirrhotic patients with CDAD were found to have significantly more chronic kidney disease (*P*<.0001), hypertension (*P*<.03), and cardiac disease (atrial fibrillation, congestive heart failure; *P*<.014) than cirrhotic patients without CDAD.

Among all patients, those treated at home with rifaximin had a significantly lower incidence of CDAD than those treated at home with lactulose (*P*<.007). The incidence of CDAD did not differ significantly among patients receiving rifaximin alone compared to rifaximin and lactulose combined. Cirrhotic patients with CDAD had a longer average length of hospitalization (35 days vs 13 days; *P*<.00004) and higher mortality rate (26% vs 13%; *P*<.19) compared to cirrhotic patients without CDAD. Of the 15 patients with CDAD who died, 33% (n=5) were receiving lactulose and 7% (n=1) were receiving rifaximin at the time of death. The study results suggest the need for future prospective studies to reconfirm that rifaximin is protective against *C. difficile* infection in cirrhotic patients.

Presentations in Endoscopy

Resect-and-Discard Strategy in Real-Time Colonoscopy Using a Validated Classification System Provides Accurate Surveillance Interval Recommendations

At the 2011 ACG meeting, Kaltenbach and colleagues evaluated the use of a resect-and-discard strategy for real-time evaluation of polyp histology during colonoscopy. This strategy has been proposed as a means of improving the cost-effectiveness of colorectal cancer screening; it is based on the fact that histopathologic review of polyps makes up a large proportion of related costs, but most small polyps do not exhibit evidence of dysplasia or neoplasia. In this prospective analysis, the resect-and-discard strategy was applied using the recently validated Narrow-Band Imaging International Colorectal Endoscopic (NICE) classification system; this approach was compared to traditional histopathologic assessment.

The NICE classification system is used to differentiate adenomatous and hyperplastic polyps in real time without magnification during endoscopy. This classification scheme differentiates type I (hyperplastic) polyps from type II (adenomatous) polyps based on 3 criteria: color, vessels, and surface pathology.

In this study, endoscopists used the NICE classification system to differentiate polyps less than 1 cm in diameter as type I or type II; they also assigned either a high or low level of confidence to this differentiation. A total of 220 patients were enrolled in the study; 49% had at least 1 polyp that was less than 1 cm in diameter. A high-confidence assignment was made in 75% of the 236 consecutive polyps that were less than 1 cm in diameter. These high-confidence assignments were correlated with 89% accuracy, 98% sensitivity, and a 95% negative predictive value.

In the vast majority of cases (98%), the endoscopists made accurate recommendations for follow-up surveillance colonoscopy intervals. Importantly, most of the incorrect recommendations erred on the side of a recommendation for a shorter surveillance interval (3–5 years vs 10 years). The investigators concluded that use of the NICE classification scheme for evaluation of polyps in real time during colonoscopy could provide a high-confidence prediction of colorectal polyp histology in most cases, resulting in accurate surveillance interval recommendations.

Retrograde Visualization Improves Adenoma Detection Rate Among Individuals Undergoing Surveillance or Diagnostic Colonoscopy

Two thirds of the adenomas missed during colonoscopy are located behind haustral folds. Thus, the TERRACE trial evaluated the ability of the Third Eye Retroscope to provide a retrograde view of areas behind these folds.[1] In the TERRACE study, an additional 23.2% of adenomas were detected using this system, compared to standard colonoscopy; the relative risk (RR) of missing adenomas with standard colonoscopy versus the Third Eye Retroscope was significant (1.92; P=.029).[1] Siersema and colleagues presented a subanalysis of the TERRACE trial at the 2011 ACG meeting. In this report, the TERRACE study results were reviewed to determine if the indication for colonoscopy was correlated with adenoma detection rate using the Third Eye Retroscope.

A total of 448 individuals were enrolled in the prospective, multicenter, randomized TERRACE trial; 349 subjects were included in the per-protocol population. These individuals were randomized to same-day, tandem examinations with either standard colonoscopy followed by the Third Eye Retroscope (group A) or the Third Eye Retroscope followed by standard colonoscopy (group B). Because tandem colonoscopy studies generally result in the discovery of additional lesions during the second procedure, the adenoma detection rate of group B was subtracted from the adenoma detection rate in group A, resulting in a net additional detection rate that could be attributed to the Third Eye Retroscope.

Among the study population, indications for colonoscopy were screening (51.0%), surveillance following prior polypectomy (25.2%), and diagnostic work-up (23.8%). The additional adenoma detection rates for the Third Eye Retroscope compared to standard colonoscopy were 4.4%, 35.7%, and 55.4% for the screening, surveillance, and diagnostic groups, respectively. The RRs for missing adenomas with standard colonoscopy versus the Third Eye Retroscope were 1.11 (P=.81), 3.15 (P<.05), and 8.64 (P<.05), respectively. When the surveillance and diagnostic groups were combined, an additional 17.5% of patients were determined to have at least 1 adenoma due to the Third Eye Retroscope. Further, an additional 27.3% of patients in the combined surveillance and diagnostic group were advised (per guidelines) to return for a 3-year follow-up colonoscopy due to the use of the

Third Eye Retroscope. The investigators concluded that individuals undergoing colonoscopy for an indication of either surveillance or diagnostic work-up benefited most from the use of the Third Eye Retroscope.

Reference:

1. Leufkens AM, DeMarco DC, Rastogi A, et al; Third Eye Retroscope Randomized Clinical Evaluation [TERRACE] Study Group. Effect of a retrograde-viewing device on adenoma detection rate during colonoscopy: the TERRACE study. *Gastrointest Endosc*. 2011;73:480-489.

Indigocarmine Added to the Water Method Enhances Adenoma Detection Rate in Screening Colonoscopy

In a late-breaking abstract presented at the 2011 ACG meeting, Leung and colleagues reported the results of a randomized controlled trial in which they evaluated whether the addition of indigocarmine to the water method could improve adenoma detection rates during screening colonoscopy.

After receiving intravenous (IV) conscious sedation, 168 patients underwent screening colonoscopy with the water method, either with or without 0.008% indigocarmine. Overall, the adenoma detection rate was 62% in the indigocarmine group versus 44% in the group evaluated with the water method alone (P=.0302). One incidence of cancer was detected in each group, and the number of patients with normal biopsies was comparable (12 in the water method group vs 18 in the indigocarmine group; P=.3139). The investigators concluded that detection of adenomas could be significantly improved by the addition of indigocarmine to the water method for screening colonoscopy.

Correlation Between Endoscopic Ultrasound and Histopathology for Diagnosis of Minimal Change Chronic Pancreatitis

Although endoscopic ultrasound (EUS) has been widely used to diagnose minimal change (noncalcific) chronic pancreatitis (MCCP), the 9 criteria used for diagnosis of MCCP via EUS are derived from patients undergoing resection for non–MCCP-related conditions. Therefore, Vega-Peralta and colleagues presented a retrospective study at the 2011 ACG meeting in which they assessed the relationship between EUS findings and histopathology in patients with MCCP.

A total of 50 adults and children with MCCP were identified from a total of 141 patients who underwent total pancreatectomy with islet autotransplantation at a single center between 2008 and 2010. EUS findings obtained within 1 year prior to surgery and histopathology records were examined.

MCCP was identified via histopathology in 90% of cases using a composite of any of 3 abnormalities: fibrosis, atrophy, or inflammation. All of the patients identified via histopathology had fibrosis. The 10% of patients with normal histology had a documented history of acute recurrent pancreatitis in addition to disabling pain. More than half (60%) of the patients with MCCP identified via histopathology fulfilled 4 or more of the 9 EUS criteria. A minority (7%) of patients with 4 or more of 9 EUS criteria had normal histology. A total of 85% of patients with 3 or fewer EUS criteria and 80% of patients with no EUS criteria had fibrosis and histologically identified MCCP.

The negative predictive value of a normal EUS was 38%, and the positive predictive value of an abnormal EUS only exceeded 72% with a threshold of 6 or more EUS criteria. The investigators concluded that there was little correlation between EUS and histopathology for MCCP diagnosis in patients undergoing total pancreatectomy with islet autotransplantation.

Does Timing of Endoscopic Retrograde Cholangiopancreatography Affect Outcomes in Patients with Cholangitis?

While cholangitis is a serious medical issue, patients can improve with antibiotics, and some patients do not undergo endoscopic retrograde cholangiopancreatography (ERCP) until several days after presentation. There is a question of whether ERCP should be performed within 24 hours or whether it is more prudent to wait for sicker patients to recover and/or to wait for weekdays when supportive care is more routine. A presentation at the 2011 ACG meeting by Craft and colleagues addressed these questions by retrospectively reviewing patient outcomes with either immediate versus conservative implementation of ERCP.

Patients from a single institution were identified; cholangitis was either the preliminary diagnosis or the indication following ERCP. Only patients with clinical cholangitis were included, manifested as fevers, elevated white blood cell counts, and evidence of biliary obstruction. Patients were stratified into 4 groups according to when they underwent ERCP: 0-day delay; 1–2-day delay; 2–5-day delay; and more-than-5-day delay. A total of 53 patients were included; 43% had stones, and 28% had blocked stents. All patients received IV fluid resuscitation and antibiotic therapy during the interval prior to ERCP. Most patients (89%) had a fever, and 81% showed improvement in fever with antibiotic therapy.

The average time from presentation to ERCP was 2.61 days (range, 0–17 days). Organ failure was identified in 6 patients prior to ERCP and in an additional 4 patients after ERCP. One patient died, 6 patients required management in an intensive care unit, and 2 adverse events occurred

post-ERCP (bleeding and pneumonia). ERCP was unsuccessful in 2 patients, who then required percutaneous transhepatic cholangiography; 5 patients required repeat ERCP during their hospital admission. Death, organ failure, and length of hospital stay were not found to differ among the time stratifications for ERCP implementation. The investigators concluded that there were no significant differences in patient outcomes when comparing immediate versus conservative (delayed) use of ERCP for cholangitis.

Is Ablation Needed After Endoscopic Mucosal Resection in Patients with Short-Segment Barrett Esophagus?

At the 2011 ACG meeting, Tian and colleagues investigated the role of ablative therapies following endoscopic mucosal resection (EMR) in patients with short-segment BE. While EMR followed by ablation is widely used to treat BE patients with either high-grade dysplasia or early esophageal adenocarcinoma, the benefit of this strategy is less clear in the setting of limited residual intestinal metaplasia, as seen in short-segment BE.

In this study, EMR followed by ablation was compared to EMR alone in patients with short-segment BE. Ablative therapies included radiofrequency ablation, photodynamic therapy, multipolar/bipolar electrocautery, cryotherapy, and argon plasma coagulation. All short-segment BE patients with high-grade dysplasia or early esophageal adenocarinoma who underwent EMR at a single center between 2006 and 2011 were included. A total of 213 patients met these criteria and were identified as having a complete response for intestinal metaplasia or dysplasia. Most of these patients were male (86.9%), with a mean age of 65.4±10.3 years. EMR was used alone in 43.7% of patients and in combination with ablation in 56.3% of patients.

All-cause mortality was 16.4%. Recurrence, defined as a finding of either dysplasia or esophageal adenocarcinoma after 2 consecutive, negative esophagogastroduodenoscopy examinations with complete response for intestinal metaplasia or dysplasia, occurred in 10.8% of patients during a mean follow-up period of 39.1 months. No differences were found between EMR alone and EMR followed by ablation in regard to age, sex, Charlson comorbidity index, recurrence rate, or mortality rate. After adjusting for age, sex, comorbidity index, and complete response, the use of ablative therapies post-EMR did not result in differences in recurrence or mortality rates. These results led the investigators to conclude that short-segment BE patients with high-grade dysplasia or early esophageal adenocarcinoma did not benefit from the addition of ablative therapies following EMR if they had achieved a complete response.

Utility of Biomarkers in Predicting Response to Radiofrequency Ablation Among Patients with Barrett Esophagus

Although largely considered to be effective for the treatment of BE with dysplasia, radiofrequency ablation does not yield a response in up to 30% of patients. In a presentation at the 2011 ACG meeting, Prasad and colleagues noted that biomarkers detected by fluorescence in situ hybridization (FISH) were able to predict response to photodynamic therapy. Therefore, they sought to determine if FISH-detected biomarkers could serve a similar function in predicting response to radiofrequency ablation.

A total of 99 patients who underwent radiofrequency ablation for dysplastic BE at a single center between 2007 and 2010 were identified. The mean patient age was 63.7±10.7 years, and 86% of patients were male. At baseline, 29% and 62% of patients had low-grade or high-grade dysplasia, respectively; intramucosal adenocarcinoma was identified in 8% of patients. Prior to radiofrequency ablation, the mean BE segment length was 6±2.5 cm. Approximately two thirds (69%) of patients underwent EMR prior to radiofrequency ablation. Most patients (n=81) were treated with Halo^{360} followed by Halo^{90}; the remaining 18 patients received only Halo^{90} ablation. Total elimination of dysplasia was achieved in 61% of patients, and an additional 30% of patients achieved elimination of intestinal metaplasia.

FISH was performed on archived, paraffin-embedded biopsies taken prior to radiofrequency ablation. FISH was performed using a validated set of fluorescently labeled probes directed against the *p16* tumor suppressor gene (chromosome 9p21) and the proto-oncogenes *HER2* (chromosome 17q12), *Myc* (chromosome 8q24), and *ZNF217* (chromosome 20q13.2). FISH signal patterns were evaluated in 50 consecutive cells. Loss of *p16* was hemizygous or homozygous in 14% and 16% of patients, respectively. Gains in *HER2*, *Myc*, and *ZNF217* occurred in 13%, 4%, and 9% of patients, respectively. Polysomy was observed in about half (53%) of cases.

In a multivariate analysis that adjusted for age, sex, and length of BE segment, only polysomy was significant for predicting the elimination of dysplasia (OR, 0.4; 95% CI, 0.2–0.9; *P*=.03) and the elimination of intestinal metaplasia (OR, 0.5; 95% CI, 0.2–1.1; *P*=.08) with radiofrequency ablation. The investigators concluded that the presence of polysomy, detected by FISH, could independently predict a lack of response (elimination of dysplasia) following radiofrequency ablation in patients with BE.

Presentations in IBD

Nonsteroidal Anti-Inflammatory Drugs Are Associated with Risk of Crohn's Disease and Ulcerative Colitis

At the 2011 ACG meeting, Ananthakrishnan and colleagues presented a study in which they prospectively evaluated whether the risk of inflammatory bowel disease (IBD) was associated with use of aspirin or NSAIDs.

A total of 76,814 women enrolled in the Nurses' Health Study were prospectively evaluated in this report. The mean age of these women in 1990 was 57 years. These women have provided data on their use of aspirin and NSAIDs twice per year since 1990. Medical records were used to determine a diagnosis of either Crohn's disease (CD) or ulcerative colitis (UC), which was confirmed by 2 gastroenterologists. A total of 1,295,317 person-years of follow-up over a total of 18 years were included in this assessment.

A total of 240 IBD cases were identified and confirmed, including 123 cases of CD and 117 cases of UC. At baseline, regular aspirin use and regular NSAID use were reported by 44% and 37% of women, respectively. Women who reported using NSAIDs for more than 15 days per month had an increased risk of both CD (RR, 1.59; 95% CI, 0.99–2.56) and UC (RR, 1.87; 95% CI, 1.16–2.99). Risks of CD (RR, 1.71; 95% CI, 1.05–2.77) and UC (RR, 1.78; 95% CI, 1.10–2.89) were also heightened among women who used more than 5 NSAID tablets per week. A longer duration (>6 years) of NSAID use was also associated with a greater risk of CD (RR, 2.83; 95% CI, 1.65–4.85) and UC (RR, 2.00; 95% CI, 1.15–3.49). In contrast, neither dose, duration, nor frequency of aspirin use was associated with a risk of developing CD or UC. The investigators concluded that increased frequency, longer duration, and higher doses of NSAIDs, but not aspirin, were associated with a greater risk of both CD and UC in women.

Over 5 Years of Follow-Up Data From the TREAT Registry Confirms No Increased Risk of Malignancy in Crohn's Disease Patients Treated with Infliximab

The TREAT Registry is an ongoing, large-scale, observational effort aimed at determining long-term outcomes of various treatments for CD; it includes both community-based and academic clinical practices throughout North America. At the 2011 ACG meeting, Lichtenstein and colleagues provided an updated analysis of data from the TREAT Registry that focused on the incidence of malignancy in CD patients treated with anti–tumor necrosis factor α (anti-TNFα) therapy.

This prospective evaluation with over 5 years of follow-up data included 6,273 patients, of whom 3,764 received infliximab (Remicade, Janssen Biotech) and 2,509 received other treatments. A standardized incidence ratio (observed/expected) was calculated by dividing the number of patients in the TREAT Registry in whom malignancies were observed by the expected number of malignancies for the general US population as estimated by the Surveillance, Epidemiology, and End Results 2009 database.

The incidences of malignancies were found to be comparable between patients who received infliximab and those who received other treatments. Several baseline factors were significantly associated with risk of malignancy, including increased age, disease duration at enrollment, smoking status, and use of immunomodulatory therapy. However, infliximab use was not found to be a significant predictor of malignancy (hazard ratio, 0.79; 95% CI, 0.56–1.10; P=.17). The investigators concluded that the risk of malignancy was not significantly increased with infliximab use, based on this longer follow-up analysis of data from the TREAT Registry. However, the researchers did note an increased risk of lymphoma irrespective of infliximab treatment, confirming reports that CD patients have a heightened risk of lymphoma compared to the general population.

US Food and Drug Administration Review of Primary Efficacy Endpoints in Ulcerative Colitis Registration Trials

In an abstract presented at the 2011 Advances in IBD meeting, Johnson and colleagues discussed the US Food and Drug Administration (FDA) review of the various primary efficacy endpoints used in registration trials of recently approved UC treatments. The goal of this review was to evaluate these primary efficacy endpoints and to determine the consistency and use of drug development approaches.

Six recent registration trials were included in this analysis; all of these trials had led to the FDA approval of a therapy for adult or pediatric UC. The agents evaluated in these trials were delayed-release mesalamine (Asacol, Warner Chilcott), high-dose delayed-released mesalamine (Asacol HD, Warner Chilcott), balsalazide (Colazal, Salix Pharmaceuticals), once-daily delayed-release mesalamine (Lialda, Shire), infliximab, and controlled-release mesalamine caplets (Pentasa, Shire).

Primary efficacy was most frequently assessed at Week 8 of therapy in these studies. Studies of delayed-release mesalamine and high-dose delayed-released mesalamine used treatment success as a primary endpoint, defined as improvement in the Physician's Global Assessment score. Balsalazide studies used reduction in rectal bleeding and improvement in at least 1 other symptom as the primary efficacy endpoint in adult trials, while clinical improvement as assessed by the modified UC Disease Activity Index (UCDAI) was the primary efficacy endpoint in pediatric trials. Once-daily delayed-release mesalamine was evaluated in a registration trial that used remission as measured by the UCDAI as the primary efficacy endpoint, while the infliximab adult registration trials used clinical response as defined by the Mayo score as the primary efficacy endpoint. In the registration trials of controlled-release mesalamine caplets, the primary efficacy endpoint was comprised of the Physician's Global Assessment score, treatment failure rate, and sigmoidoscopic index score.

The primary efficacy endpoints in these 6 registration trials differed, and the investigators attributed this difference to the availability of numerous disease activity indices, historical precedence, and evolving science. The authors concluded by stating the FDA "seeks consensus on the definition of successful treatment outcome (disease response and/or remission) and development of a standardized UC activity index that defines the outcome."

Induction of Clinical and Endoscopic Remission with 9-mg Budesonide MMX in Patients with Mild-to-Moderate Ulcerative Colitis

In a presentation at the 2011 ACG meeting, Sandborn and colleagues reported an analysis of pooled data from 2 phase III trials that evaluated the efficacy and safety of Budesonide MMX (Cosmo Pharmaceuticals) in patients with mild-to-moderate UC. A total of 672 patients were pooled from the modified intent-to-treat populations; all patients received at least 1 dose of the study agent and were randomized to receive placebo, 6-mg Budesonide MMX, or 9-mg Budesonide MMX for 8 weeks.

The rate of clinical and endoscopic remission at Week 8 was higher in patients treated with 9-mg Budesonide MMX and 6-mg Budesonide MMX versus placebo (17.7% and 10.9% vs 6.2%; *P*=.0002 and *P*=.0809 for comparison of 9-mg and 6-mg Budesonide MMX vs placebo, respectively). Accordingly, more patients in the 9-mg Budesonide MMX and 6-mg Budesonide MMX groups experienced symptom resolution compared to the placebo group (26.3% and 21.7% vs 14.3%; *P*=.0018 and *P*=.0429 for comparison of 9-mg and 6-mg Budesonide MMX vs placebo, respectively). Patients treated with 9-mg Budesonide MMX showed clinical improvements compared to patients treated with placebo (37.5% vs 28.6%; *P*=.0466); the 9-mg Budesonide MMX group also showed endoscopic improvements compared to the control group (41.8% vs 32.4%; *P*=.0407). In contrast, patients treated with 6-mg Budesonide MMX were not significantly different from placebo-treated patients in terms of either clinical improvement (28.3% vs 28.6%; *P*=.9425) or endoscopic improvement (30.9% vs 32.4%; *P*=.7334). Similar incidences of treatment-related adverse events were reported across the study groups. From these pooled data, the investigators concluded that a 9-mg dose of Budesonide MMX is both safe and effective in patients with mild-to-moderate UC, resulting in both clinical and endoscopic remission and symptom resolution.

Long-Term Clinical Experience with Vedolizumab in Patients with Mild-to-Moderate Ulcerative Colitis

The integrin molecule α4β7 binds the mucosal addressin cell adhesion molecule 1 and mediates leukocyte migration into the gastrointestinal mucosa and lymphoid tissue. Vedolizumab is an investigational monoclonal antibody directed against α4β7. In an abstract presented at the 2011 ACG meeting, Parikh and colleagues reported on the long-term clinical experience of 53 UC patients treated with vedolizumab.

All patients had mild-to-moderate UC and had received vedolizumab for up to 2.5 years. A total of 38 patients received vedolizumab in a randomized dose-ranging study in which vedolizumab was given at doses of 2 mg/kg, 6 mg/kg, or 10 mg/kg on Days 1, 15, 29, and 85. After completion of the dose-ranging portion of the study (Day 253), all of these patients then continued to receive vedolizumab (2 mg/kg) every 8 weeks for up to 547 additional days as part of an open-label extension study. Fifteen treatment-naïve patients who had not participated in the dose-ranging study were also enrolled into the extension study, resulting in a total of 53 patients for this long-term analysis. Following completion of the extension study, patients were eligible to continue to receive vedolizumab in an ongoing, phase III safety extension trial; 55% of patients elected to continue in the phase III trial.

A total of 81% of patients completed the extension study, with a mean vedolizumab exposure of 580.3 days. Discontinuation was due to lack of efficacy (5 patients), adverse events (3 patients), and withdrawal of consent (2 patients). The mean Partial Mayo Score, used to measure response to therapy, was 3.7±1.43 at the initiation of the dose-ranging study and 5.4±1.88 at the initiation of the extension study. At Day 491 of the extension study (prior to enrollment in the phase III safety trial), the mean Partial Mayo Score had dropped

to 0.8±1.15. At that time point, 88% of patients were in clinical remission.

Adverse events were reported in 70% of patients during the extension study; 9% reported a serious adverse event. The most frequently observed adverse events included nasopharyngitis (15%), headache (8%), cough (8%), arthralgia (4%), and upper respiratory infection (4%). One serious infection was reported (self-limited viral gastroenteritis requiring hospitalization). A serious infusion reaction occurred in 1 patient who had previously been exposed to vedolizumab in another clinical trial. Anti–human vedolizumab antibodies were found in 3 patients. The investigators concluded that long-term administration of vedolizumab was well tolerated and associated with durable decreases in UC disease activity.

Phase IIb Study of Ustekinumab in Patients with Moderate-to-Severe Crohn's Disease: Results Through Week 36 From the CERTIFI Trial

Ustekinumab is a novel human monoclonal antibody directed against interleukins 12 and 23. At the 2011 ACG meeting, Feagan and colleagues provided Week 36 results of ustekinumab therapy in the CERTIFI trial. This trial was a multicenter, randomized, double-blind, placebo-controlled, phase IIb study that investigated the safety and efficacy of ustekinumab in patients with moderate-to-severe CD who had previously failed anti-TNFα therapy.

Patients were randomized to receive either IV placebo or IV ustekinumab (1 mg/kg, 3 mg/kg, or 6 mg/kg) at Week 0. At Week 8, patients in the ustekinumab arm were separately rerandomized to receive maintenance therapy with ustekinumab (90 mg) or placebo (regardless of Week 6 response); maintenance therapy was administered subcutaneously at Weeks 8 and 16. Steroid tapering was required during maintenance therapy. Patients were followed through Week 36. The primary study endpoint was clinical response rate at Week 6.

All 526 patients included in this study had a Crohn's Disease Activity Index (CDAI) score of 220–450 (baseline mean CDAI score=324). Nearly half of patients (49.6%) were on steroid therapy (including budesonide), and 48.8% had failed more than 2 prior anti-TNFα therapies.

The clinical response rates at Week 6 were 39.7% for 6-mg/kg ustekinumab versus 23.5% for placebo (P<.05). The clinical response rate at Week 6 for all ustekinumab dosage groups combined was also significantly higher than the response rate in the placebo group (36.8% vs 23.5%; P<.05). During the maintenance phase of the study, 41.7% of the patients who had achieved a response with ustekinumab at Week 6 and had continued with ustekinumab maintenance therapy were in remission at Week 22, compared to 27.4% of patients who had continued with placebo during the maintenance phase of the study (P=.029). The median dose of systemic steroids at baseline was 20 mg; at Week 36, it was reduced to 5 mg in ustekinumab-treated patients and 15 mg in placebo-treated patients (P<.05).

No major adverse events were reported in this study, and the toxicity profiles of the ustekinumab and placebo arms remained similar during both the induction and maintenance phases of the study. The investigators concluded that ustekinumab therapy was well tolerated and resulted in induction and maintenance of clinical response in patients with moderate-to-severe CD who had previously failed anti-TNFα therapy.

Narrow-Band Imaging and Chromoendoscopy for the Detection of Colonic Dysplasia in Patients with IBD

In a presentation at the 2011 Advances in IBD meeting, Feitosa and colleagues presented data from a study that evaluated the use of narrow-band imaging and chromoendoscopy for the detection of colonic dysplasia in patients with IBD. This prospective, randomized study compared narrow-band imaging with chromoendoscopy as a diagnostic technique in 29 patients who had been diagnosed with IBD at least 8 years previously. Baseline patient characteristics were well balanced between the intervention groups, including sex (61.5% female vs 68.75% female) and mean age (50.3 years vs 49.5 years) for the chromoendoscopy and narrow-band imaging groups, respectively. The mean duration of disease was 15.9 years for the narrow-band imaging group and 15.3 years for the chromoendoscopy group. Patients had a diagnosis of CD in 56.3% and 53.8% of the narrow-band imaging and chromoendoscopy groups, respectively. No significant differences were noted in terms of patient demographics, disease behavior, medication use, endoscopic grade of disease activity, or symptoms at the time of examination.

Thirty percent of patients in the chromoendoscopy group exhibited evidence of dysplastic lesions on histologic examination (biopsies of mucosal lesions). In contrast, no patients in the narrow-band imaging group showed signs of dysplastic lesions (chi-square=4.13, ∑critical >3.841, considering a 5% error). Two adenomas and 1 dysplastic lesion were observed, both of which are typical of IBD. While these results are preliminary, the investigators concluded that there was a strong statistical tendency for superiority of chromoendoscopy versus narrow-band imaging. This study was limited by a small sample size, and increasing the number of patients would help to confirm this suspected superiority.

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References:
1. Stravitz RT, et al. Surveillance for hepatocellular carcinoma in patients with cirrhosis improves outcome. Am J Med. 2008;121:119-26.
2. Kumada T, et al. Clinical utility of *Lens culinaris* agglutinin-reactive alpha-fetoprotein in small hepatocellular carcinoma: Special reference to imaging diagnosis. J Hepatol. 1999;30:125-30.
3. Shiraki K, et al. A clinical study of lectin-reactive alpha-fetoprotein as an early indicator of hepatocellular carcinoma in the follow-up of cirrhotic patients. Hepatology. 1995;22:802-7.
4. Taketa K, et al. A collaborative study for the evaluation of lectin-reactive alpha-fetoproteins in early detection of hepatocellular carcinoma. Cancer Res. 1993;53:5419-23.
5. Shimauchi T, et al. A simultaneous monitoring of *Lens culinaris* agglutinin A-reactive alpha-fetoprotein and des-gamma-carboxy prothrombin as an early diagnosis of hepatocellular carcinoma in the follow-up of cirrhotic patients. Oncol Rep. 2000;7:249-56.
6. Toyoda H, et al. Prognostic significance of simultaneous measurement of three tumor markers in patients with hepatocellular carcinoma. Clin Gastroenterol and Hepatol. 2006;4:111-7.
7. Arii S, et al. Management of hepatocellular carcinoma: Report of Consensus Meeting in the 45th Annual Meeting of the Japan Society of Hepatology (2009). Hepatol Res. 2010;40:667-85.