

THE GASTRO & HEP REPORT

Presentation summaries in:

9 Hepatology

12 IBS

14 GERD

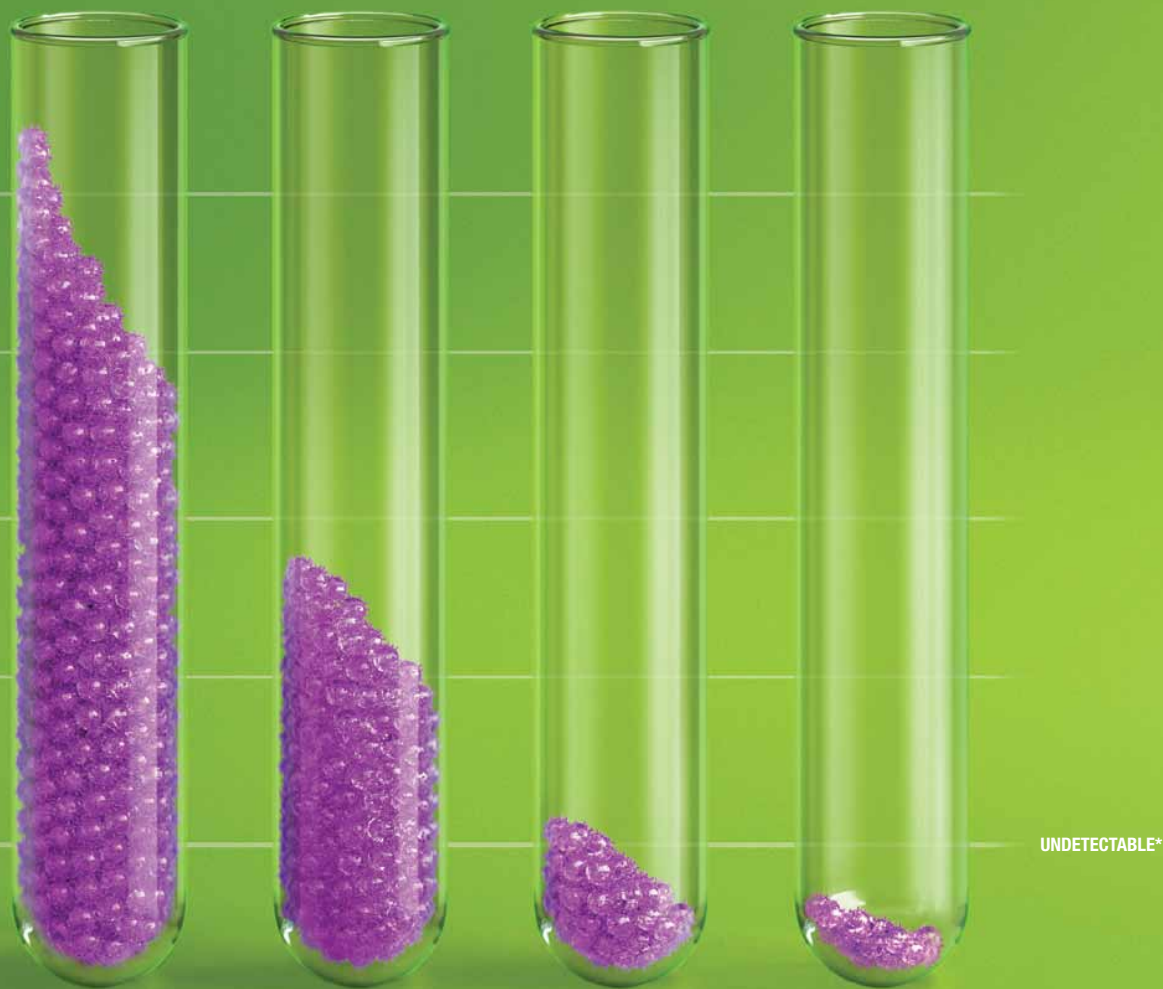
17 IBD

20 Endoscopy

Comprehensive Reports on the Latest Advances in Gastroenterology and Hepatology from:

- The 75th American College of Gastroenterology Annual Scientific Meeting and Postgraduate Course
October 15–20, 2010
San Antonio, Texas
- The 61st Annual Meeting of the American Association for the Study of Liver Diseases
October 29–November 2, 2010
Boston, Massachusetts
- 2010 Advances in Inflammatory Bowel Diseases/Crohn's & Colitis Foundation's Clinical and Research Conference
December 9–12, 2010
Hollywood, Florida

With current HCV therapies, SVR is more likely when viral load reaches undetectable at Week 4



*Illustrative representation of the lower limit of detection.

Monitoring your patients at Week 4 is important

- Undetectability at Week 4 is the best on-treatment positive predictor of SVR¹
 - 11%–20% of G1 HCV patients achieve undetectable at Week 4 with current therapies^{2,3}
- Rapid undetectability is associated with higher SVR rates and lower relapse rates³
- HCV is curable by achieving SVR²

Learn more at HCVInsights.com

G1 = genotype 1. HCV = hepatitis C virus. SVR = sustained virological response.

References: 1. Ferenci P, et al. *J Hepatol.* 2005;43:425-433. 2. Ghany MG, et al. *Hepatology.* 2009;49:1335-1374. 3. McHutchison JG, et al. *N Engl J Med.* 2009;361:580-593.

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Still **0%** resistance at Years 1, 2, and 3
(Studies 102 and 103)

Patients were primarily nucleoside–treatment-naïve with compensated liver disease¹

In Studies 102 (HBeAg–) and 103 (HBeAg+), 641 adult patients with chronic hepatitis B (CHB) and compensated liver disease entered a 48-week, randomized, double-blind, active-controlled treatment period comparing VIREAD 300 mg to Hepsera® (adefovir dipivoxil) 10 mg. 585 patients then rolled over to open-label VIREAD for analysis through Week 144.¹⁻³

Cumulative VIREAD genotypic resistance was evaluated annually with the paired HBV reverse transcriptase amino acid sequences of the pre-treatment and on-treatment isolates from subjects who received at least 24 weeks of VIREAD monotherapy and remained viremic with HBV DNA ≥400 copies/mL at the end of each study year (or at discontinuation of VIREAD monotherapy) using an as-treated analysis.¹

- No specific substitutions occurred at a sufficient frequency to be associated with resistance to VIREAD (genotypic or phenotypic analysis)¹
- From 4 ongoing VIREAD trials (Studies 102, 103, and 106* in subjects with compensated liver disease and Study 108† in subjects with decompensated liver disease), 10% (69/660) of VIREAD recipients with compensated liver disease receiving up to 144 weeks of VIREAD monotherapy and 18% (7/39) of VIREAD recipients with decompensated liver disease receiving up to 48 weeks of VIREAD monotherapy remained viremic at their last time-point on VIREAD monotherapy¹
- Treatment-emergent amino acid substitutions in the HBV reverse transcriptase were identified in 46% (32/69) of those subjects in Studies 102, 103, 106, and 108 with evaluable paired genotypic data; no specific substitutions occurred at a sufficient frequency to be associated with resistance to VIREAD (genotypic or phenotypic analysis)¹

Indication and Important Safety Information

Indication and Usage

VIREAD® (tenofovir disoproxil fumarate) is indicated for the treatment of chronic hepatitis B in adults.

The following points should be considered when initiating therapy with VIREAD for the treatment of HBV infection:

- This indication is based primarily on data from treatment of subjects who were nucleoside–treatment-naïve and a smaller number of subjects who had previously received lamivudine or adefovir dipivoxil. Subjects were adults with HBeAg-positive and HBeAg-negative chronic hepatitis B with compensated liver disease
- VIREAD was evaluated in a limited number of subjects with chronic hepatitis B and decompensated liver disease
- The numbers of subjects in clinical trials who had lamivudine- or adefovir-associated substitutions at baseline were too small to reach conclusions of efficacy

WARNINGS: LACTIC ACIDOSIS/SEVERE HEPATOMEGALY WITH STEATOSIS and POST TREATMENT EXACERBATION OF HEPATITIS

- **Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs, including VIREAD, in combination with other antiretrovirals**
- **Severe acute exacerbations of hepatitis have been reported in HBV-infected patients who have discontinued anti-hepatitis B therapy, including VIREAD. Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in patients who discontinue anti-hepatitis B therapy, including VIREAD. If appropriate, resumption of anti-hepatitis B therapy may be warranted**

* Study 106 is an ongoing Phase 2 study involving Hepsera–treatment-experienced subjects previously treated for 24 to 96 weeks with Hepsera for chronic HBV infection and had plasma HBV DNA ≥1000 copies/mL at screening.¹

† Study 108 was a small, double-blind, randomized, active-controlled trial comparing the safety of VIREAD and other oral antivirals in patients with CHB and decompensated liver disease through 48 weeks.¹

Please see continued Important Safety Information and brief summary of full Prescribing Information for VIREAD on the following pages.

My liver.  My fight. My VIREAD.

Important Safety Information (cont'd)

Warnings and Precautions

- **New onset or worsening renal impairment:** New onset or worsening renal impairment, including cases of acute renal failure and Fanconi syndrome (renal tubular injury with severe hypophosphatemia), have been reported with the use of VIREAD. Assess creatinine clearance (CrCl) before initiating treatment with VIREAD. Monitor CrCl and serum phosphorus in patients at risk, including those who have previously experienced renal events while receiving HEPSERA[®] (adefovir dipivoxil). Avoid administering VIREAD with concurrent or recent use of nephrotoxic drugs. Dosing interval adjustment of VIREAD and close monitoring of renal function are recommended in all patients with CrCl <50 mL/min
- **Coadministration with other products:**
 - Do not use with other tenofovir-containing products (eg, ATRIPLA[®] [efavirenz/emtricitabine/tenofovir disoproxil fumarate] and TRUVADA[®] [emtricitabine/tenofovir disoproxil fumarate])
 - Do not administer in combination with HEPSERA
- **Patients coinfecting with HIV-1 and HBV:** Due to the risk of development of HIV-1 resistance, VIREAD should only be used in HIV-1 and HBV coinfecting patients as part of an appropriate antiretroviral combination regimen. HIV antibody testing should be offered to all HBV-infected patients before initiating therapy with VIREAD
- **Decreases in bone mineral density:** Decreases in bone mineral density (BMD) have been observed in HIV-infected patients. Consider monitoring BMD in patients with a history of pathologic fracture or who are at risk for osteopenia. The bone effects of VIREAD have not been studied in patients with chronic HBV infection. Cases of osteomalacia (associated with proximal renal tubulopathy and which may contribute to fractures) have been reported in association with the use of VIREAD

Adverse Reactions

- **In HBV-infected patients with compensated liver disease:** Most common adverse reaction (all grades) was nausea (9%). Other treatment-emergent adverse reactions reported in >5% of patients treated with VIREAD included: abdominal pain, diarrhea, headache, dizziness, fatigue, nasopharyngitis, back pain, and skin rash
- **In HBV-infected patients with decompensated liver disease:** Most common adverse reactions (all grades) reported in ≥10% of patients treated with VIREAD were abdominal pain (22%), nausea (20%), insomnia (18%), pruritus (16%), vomiting (13%), dizziness (13%), and pyrexia (11%)

Please see full Indication and Important Safety Information for VIREAD, including **boxed WARNING** information about **lactic acidosis, severe hepatomegaly with steatosis, and post treatment exacerbation of hepatitis**, on preceding page.

References: 1. VIREAD Prescribing Information. Foster City, CA: Gilead Sciences, Inc.; October 2010. 2. Study 102, Data on file, Gilead Sciences, Inc. 3. Study 103, Data on file, Gilead Sciences, Inc. VIREAD, HEPSERA, and TRUVADA are registered trademarks of Gilead Sciences, Inc. ATRIPLA is a registered trademark of Bristol-Myers Squibb & Gilead Sciences, LLC.

Drug Interactions

- **Didanosine:** Coadministration increases didanosine concentrations. Use with caution and monitor for evidence of didanosine toxicity (eg, pancreatitis, neuropathy). Didanosine should be discontinued in patients who develop didanosine-associated adverse reactions. In adults weighing >60 kg, the didanosine dose should be reduced to 250 mg when it is coadministered with VIREAD. Data are not available to recommend a dose adjustment of didanosine for patients weighing <60 kg
- **Atazanavir:** Coadministration decreases atazanavir concentrations and increases tenofovir concentrations. Use atazanavir with VIREAD only with additional ritonavir; monitor for evidence of tenofovir toxicity
- **Lopinavir/ritonavir:** Coadministration increases tenofovir concentrations. Monitor for evidence of tenofovir toxicity

Dosage and Administration

- Recommended dose for the treatment of chronic hepatitis B: 300 mg once daily taken orally without regard to food. In the treatment of chronic hepatitis B, the optimal duration of treatment is unknown
- The dosing interval of VIREAD should be adjusted (using recommendations in the table below) and renal function closely monitored in patients with creatinine clearance <50 mL/min

Dosage Adjustment for Patients with Altered Creatinine Clearance

	Creatinine clearance (mL/min) ^a			Hemodialysis patients
	≥50	30-49	10-29	
Recommended 300 mg dosing interval	Every 24 hours	Every 48 hours	Every 72 to 96 hours	Every 7 days or after a total of approximately 12 hours of dialysis ^b

^a Calculated using ideal (lean) body weight.

^b Generally once weekly assuming three hemodialysis sessions a week of approximately 4 hours' duration. VIREAD should be administered following completion of dialysis.

- The pharmacokinetics of tenofovir have not been evaluated in non-hemodialysis patients with creatinine clearance <10 mL/min; therefore, no dosing recommendation is available for these patients
- No dose adjustment is necessary for patients with mild renal impairment (creatinine clearance 50-80 mL/min). Routine monitoring of calculated creatinine clearance and serum phosphorus should be performed in these patients

VIREAD®

(tenofovir disoproxil fumarate) Tablets

Brief summary of full prescribing information. Please see full prescribing information including Boxed WARNINGS, Rx only

WARNINGS: LACTIC ACIDOSIS/SEVERE HEPATOMEGALY WITH STEATOSIS AND POSTTREATMENT EXACERBATION OF HEPATITIS

- Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs, including VIREAD, in combination with other antiretrovirals (See **Warnings and Precautions**).
- Severe acute exacerbations of hepatitis have been reported in HIV-infected patients who have discontinued anti-hepatitis B therapy, including VIREAD. Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in patients who discontinue anti-hepatitis B therapy, including VIREAD. If appropriate, resumption of anti-hepatitis B therapy may be warranted (See **Warnings and Precautions**).

INDICATIONS AND USAGE: VIREAD is indicated for the treatment of chronic hepatitis B in adults. The following points should be considered when initiating therapy with VIREAD for the treatment of HBV infection:

- This indication is based primarily on data from treatment of subjects who were nucleoside-treatment-naïve and a smaller number of subjects who had previously received lamivudine or adefovir dipivoxil. Subjects were adults with HBeAg-positive and HBeAg-negative chronic hepatitis B with compensated liver disease (See **Adverse Reactions**).
- VIREAD was evaluated in a limited number of subjects with chronic hepatitis B and decompensated liver disease.
- The numbers of subjects in clinical trials who had lamivudine- or adefovir-associated substitutions at baseline were too small to reach conclusions of efficacy.

DOSE AND ADMINISTRATION: For the treatment of chronic hepatitis B in adults, the dose is one 300 mg VIREAD tablet once daily taken orally, without regard to food. The optimal duration of treatment is unknown. **Dose Adjustment for Renal Impairment in Adults:** Significantly increased drug exposures occurred when VIREAD was administered to subjects with moderate to severe renal impairment. Therefore, the dosing interval of VIREAD should be adjusted in patients with baseline creatinine clearance <50 mL/min using the recommendations in Table 1. These dosing interval recommendations are based on modeling of single-dose pharmacokinetic data in non-HIV and non-HBV infected subjects with varying degrees of renal impairment, including end-stage renal disease requiring hemodialysis. The safety and effectiveness of these dosing interval adjustment recommendations have not been clinically evaluated in patients with moderate or severe renal impairment, therefore clinical response to treatment and renal function should be closely monitored in these patients (See **Warnings and Precautions**). No dose adjustment is necessary for patients with mild renal impairment (creatinine clearance 50–80 mL/min). Routine monitoring of calculated creatinine clearance and serum phosphorus should be performed in patients with mild renal impairment (See **Warnings and Precautions**).

Table 1 Dose Adjustment for Adult Patients with Altered Creatinine Clearance

	Creatinine Clearance (mL/min) ^a			Hemodialysis Patients
	≥50	30–49	10–29	
Recommended 300 mg Dosing Interval	Every 24 hours	Every 48 hours	Every 72 to 96 hours	Every 7 days or after a total of approximately 12 hours of dialysis ^b

- Calculated using ideal (lean) body weight.
- Generally once weekly assuming three hemodialysis sessions a week of approximately 4 hours duration. VIREAD should be administered following completion of dialysis.

The pharmacokinetics of tenofovir have not been evaluated in non-hemodialysis patients with creatinine clearance <10 mL/min; therefore, no dosing recommendation is available for these patients. No data are available to make dose recommendations in pediatric patients 12 years of age and older with renal impairment.

CONTRAINDICATIONS: None.

WARNINGS AND PRECAUTIONS: Lactic Acidosis/Severe Hepatomegaly with Steatosis: Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs, including VIREAD, in combination with other antiretrovirals. A majority of these cases have been in women. Obesity and prolonged nucleoside exposure may be risk factors. Particular caution should be exercised when administering nucleoside analogs to any patient with known risk factors for liver disease; however, cases have also been reported in patients with no known risk factors. Treatment with VIREAD should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations). **Exacerbation of Hepatitis after Discontinuation of Treatment:** Discontinuation of anti-HBV therapy, including VIREAD, may be associated with severe acute exacerbations of hepatitis. Patients infected with HBV who discontinue VIREAD should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment. If appropriate, resumption of anti-hepatitis B therapy may be warranted. **New Onset or Worsening Renal Impairment:** Tenofovir is principally eliminated by the kidney. Renal impairment, including cases of acute renal failure and Fanconi syndrome (renal tubular injury with severe hypophosphatemia), has been reported with the use of VIREAD (See **Adverse Reactions**). It is recommended that creatinine clearance be calculated in all patients prior to initiating therapy and as clinically appropriate during therapy with VIREAD. Routine monitoring of calculated creatinine clearance and serum phosphorus should be performed in patients at risk for renal impairment, including patients who have previously experienced renal events while receiving HEPSERA. Dosing interval adjustment of VIREAD and close monitoring of renal function are recommended in all patients with creatinine clearance <50 mL/min (See **Dosage and Administration**). No safety or efficacy data are available in patients with renal impairment who received VIREAD using these dosing guidelines, so the potential benefit of VIREAD therapy should be assessed against the potential risk of renal toxicity. VIREAD should be avoided with concurrent or recent use of a nephrotoxic agent. **Coadministration with Other Products:** VIREAD should not be used in combination with the fixed-dose combination products TRUVADA® (emtricitabine/tenofovir disoproxil fumarate) or ATRIPLA® (efavirenz/emtricitabine/tenofovir disoproxil fumarate) since tenofovir disoproxil fumarate is a component of these products. VIREAD should not be administered in combination with HEPSERA® (adefovir dipivoxil) (See **Drug Interactions**). **Patients Coinfected with HIV-1 and HBV:** Due to the risk

of development of HIV-1 resistance, VIREAD (tenofovir disoproxil fumarate) should only be used in HIV-1 and HBV coinfecting patients as part of an appropriate antiretroviral combination regimen. HIV-1 antibody testing should be offered to all HBV-infected patients before initiating therapy with VIREAD. It is also recommended that all patients with HIV-1 be tested for the presence of chronic hepatitis B before initiating treatment with VIREAD.

Decreases in Bone Mineral Density: Assessment of bone mineral density (BMD) should be considered for adults and pediatric patients 12 years of age and older who have a history of pathologic bone fracture or other risk factors for osteoporosis or bone loss. Although the effect of supplementation with calcium and vitamin D was not studied, such supplementation may be beneficial for all patients. If bone abnormalities are suspected then appropriate consultation should be obtained. In HIV-infected adult subjects treated with VIREAD in Study 903 through 144 weeks, decreases from baseline in BMD were seen at the lumbar spine and hip in both arms of the study. At Week 144, there was a significantly greater mean percentage decrease from baseline in BMD at the lumbar spine in subjects receiving VIREAD + lamivudine + efavirenz (-2.2% ± 3.9) compared with subjects receiving stavudine + lamivudine + efavirenz (-1.0% ± 4.6). Changes in BMD at the hip were similar between the two treatment groups (-2.8% ± 3.5 in the VIREAD group vs. -2.4% ± 4.5 in the stavudine group). In both groups, the majority of the reduction in BMD occurred in the first 24–48 weeks of the study and this reduction was sustained through Week 144. Twenty-eight percent of VIREAD-treated subjects vs. 21% of the stavudine-treated subjects lost at least 5% of BMD at the spine or 7% of BMD at the hip. Clinically relevant fractures (excluding fingers and toes) were reported in 4 subjects in the VIREAD group and 6 subjects in the stavudine group. In addition, there were significant increases in biochemical markers of bone metabolism (serum bone-specific alkaline phosphatase, serum osteocalcin, serum C-telopeptide, and urinary N-telopeptide) in the VIREAD group relative to the stavudine group, suggesting increased bone turnover. Serum parathyroid hormone levels and 1,25 Vitamin D levels were also higher in the VIREAD group. Except for bone-specific alkaline phosphatase, these changes resulted in values that remained within the normal range. In a clinical study of HIV-1 infected pediatric subjects 12 years of age and older (Study 321), bone effects were similar to adult subjects. Under normal circumstances BMD increases rapidly in this age group. In this study, the mean rate of bone gain was less in the VIREAD-treated group compared to the placebo group. Six VIREAD-treated subjects and one placebo-treated subject had significant (>4%) lumbar spine BMD loss in 48 weeks. Among 28 subjects receiving 96 weeks of VIREAD, Z-scores declined by -0.341 for lumbar spine and -0.457 for total body. Skeletal growth (height) appeared to be unaffected. Markers of bone turnover in VIREAD-treated pediatric subjects 12 years of age and older suggest increased bone turnover, consistent with the effects observed in adults. The effects of VIREAD-associated changes in BMD and biochemical markers on long-term bone health and future fracture risk are unknown. Cases of osteomalacia (associated with proximal renal tubulopathy and which may contribute to fractures) have been reported in association with the use of VIREAD (See **Adverse Reactions**). The bone effects of VIREAD have not been studied in patients with chronic HBV infection.

ADVERSE REACTIONS: Clinical Trials in Adult Subjects with Chronic Hepatitis B and Compensated Liver Disease:

Treatment-Emergent Adverse Reactions: In controlled clinical trials in subjects with chronic hepatitis B (0102 and 0103), more subjects treated with VIREAD during the 48-week double-blind period experienced nausea: 9% with VIREAD versus 2% with HEPSERA. Other treatment-emergent adverse reactions reported in >5% of subjects treated with VIREAD included: abdominal pain, diarrhea, headache, dizziness, fatigue, nasopharyngitis, back pain, and skin rash. No significant change in the tolerability profile (nature or severity of adverse reactions) was observed in subjects continuing treatment with VIREAD for up to 144 weeks in these studies.

Laboratory Abnormalities: A summary of Grade 3 and 4 laboratory abnormalities through Week 48 is provided in Table 2. Grade 3/4 laboratory abnormalities were similar in subjects continuing VIREAD treatment for up to 144 weeks in these studies.

Table 2 Grade 3/4 Laboratory Abnormalities Reported in ≥1% of VIREAD-Treated Chronic Hepatitis B Subjects in Studies 0102 and 0103 (0–48 Weeks)

	VIREAD (N=426)	HEPSERA (N=215)
Any ≥Grade 3 Laboratory Abnormality	19%	13%
Creatine Kinase (M: >990 U/L; F: >845 U/L)	2%	3%
Serum Amylase (>175 U/L)	4%	1%
Glycosuria (≥3+)	3%	<1%
AST (M: >180 U/L; F: >170 U/L)	4%	4%
ALT (M: >215 U/L; F: >170 U/L)	10%	6%

The overall incidence of on-treatment ALT flares (defined as serum ALT >2 × baseline and >10 × ULN, with or without associated symptoms) was similar between VIREAD (2.6%) and HEPSERA (2%). ALT flares generally occurred within the first 4–8 weeks of treatment and were accompanied by decreases in HBV DNA levels. No subject had evidence of decompensation. ALT flares typically resolved within 4 to 8 weeks without changes in study medication.

Clinical Trial in Adult Subjects with Chronic Hepatitis B and Decompensated Liver Disease: In a small randomized, double-blind, active-controlled trial (0108), subjects with CHB and decompensated liver disease received treatment with VIREAD or other antiviral drugs for up to 48 weeks. Among the 45 subjects receiving VIREAD, the most frequently reported treatment-emergent adverse reactions of any severity were abdominal pain (22%), nausea (20%), insomnia (19%), pruritus (16%), vomiting (13%), dizziness (13%), and pyrexia (11%). Two of 45 (4%) subjects died through Week 48 of the study due to progression of liver disease. Three of 45 (7%) subjects discontinued treatment due to an adverse event. Four of 45 (9%) subjects experienced a confirmed increase in serum creatinine of 0.5 mg/dL (1 subject also had a confirmed serum phosphorus <2 mg/dL through Week 48). Three of these subjects (each of whom had a Child-Pugh score ≥10 and MELD score ≥14 at entry) developed renal failure. Because both VIREAD and decompensated liver disease may have an impact on renal function, the contribution of VIREAD to renal impairment in this population is difficult to ascertain. One of 45 subjects experienced an on-treatment hepatic flare during the 48 week study.

Postmarketing Experience: The following adverse reactions have been identified during postapproval use of VIREAD. Because postmarketing reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure: allergic reaction, including angioedema, lactic acidosis, hypokalemia, hypophosphatemia, dyspnea, pancreatitis, increased amylase, abdominal pain, hepatic steatosis, hepatitis, increased liver enzymes (most commonly AST, ALT gamma GT), rash, rhabdomyolysis, osteomalacia (manifested as bone pain and which may contribute to fractures), muscular weakness, myopathy, acute renal failure, renal failure, acute tubular necrosis, Fanconi syndrome, proximal renal tubulopathy, interstitial nephritis (including acute cases), nephrogenic diabetes insipidus, renal insufficiency, increased creatinine, proteinuria, polyuria, asthenia. The following adverse reactions listed above, may occur as a consequence of proximal renal tubulopathy: rhabdomyolysis, osteomalacia, hypokalemia, muscular weakness, myopathy, hypophosphatemia.

DRUG INTERACTIONS: Didanosine: Coadministration of VIREAD and didanosine should be undertaken with caution and patients receiving this combination should be monitored closely for didanosine-associated adverse reactions. Didanosine should be discontinued in patients who develop didanosine-associated adverse reactions. When administered with VIREAD, C_{max} and AUC of didanosine (administered as either the buffered or enteric-coated formulation) increased significantly. The mechanism of this interaction is unknown. Higher didanosine concentrations could potentiate didanosine-associated adverse reactions, including pancreatitis and neuropathy. Suppression of CD4⁺ cell counts has been observed in patients receiving tenofovir disoproxil fumarate (tenofovir DF) with didanosine 400 mg daily. In patients weighing >60 kg, the didanosine dose should be reduced to 250 mg when it is coadministered with VIREAD. Data are not available to recommend a dose adjustment of didanosine for adult or pediatric patients weighing <60 kg. When coadministered, VIREAD and didanosine EC may be taken under fasted conditions or with a light meal (<400 kcal, 20% fat). Coadministration of didanosine buffered tablet formulation with VIREAD should be under fasted conditions. **Atazanavir:** Atazanavir has been shown to increase tenofovir concentrations. The mechanism of this interaction is unknown. Patients receiving atazanavir and VIREAD should be monitored for VIREAD-associated adverse reactions. VIREAD should be discontinued in patients who develop VIREAD-associated adverse reactions. VIREAD decreases the AUC and C_{max} of atazanavir. When coadministered with VIREAD, it is recommended that atazanavir 300 mg is given with ritonavir 100 mg. Atazanavir without ritonavir should not be coadministered with VIREAD. **Lopinavir/Ritonavir:** Lopinavir/ritonavir has been shown to increase tenofovir concentrations. The mechanism of this interaction is unknown. Patients receiving lopinavir/ritonavir and VIREAD should be monitored for VIREAD-associated adverse reactions. VIREAD should be discontinued in patients who develop VIREAD-associated adverse reactions. **Drugs Affecting Renal Function:** Since tenofovir is primarily eliminated by the kidneys, coadministration of VIREAD with drugs that reduce renal function or compete for active tubular secretion may increase serum concentrations of tenofovir and/or increase the concentrations of other renally eliminated drugs. Some examples include, but are not limited to, cidofovir, acyclovir, valacyclovir, ganciclovir, and valganciclovir. Drugs that decrease renal function may also increase serum concentrations of tenofovir. In the treatment of chronic hepatitis B, VIREAD should not be administered in combination with HEPSERA (adefovir dipivoxil).

USE IN SPECIFIC POPULATIONS: Pregnancy: Pregnancy Category B: Reproduction studies have been performed in rats and rabbits at doses up to 14 and 19 times the human dose based on body surface area comparisons and revealed no evidence of impaired fertility or harm to the fetus due to tenofovir. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, VIREAD (tenofovir disoproxil fumarate) should be used during pregnancy only if clearly needed. **Antiretroviral Pregnancy Registry:** To monitor fetal outcomes of pregnant women exposed to VIREAD, an Antiretroviral Pregnancy Registry has been established. Healthcare providers are encouraged to register patients by calling 1-800-258-4263. **Nursing Mothers: The Centers for Disease Control and Prevention recommend that HIV-1-infected mothers not breast-feed their infants to avoid risking postnatal transmission of HIV-1.** Studies in rats have demonstrated that tenofovir is secreted in milk. It is not known whether tenofovir is excreted in human milk. Because of both the potential for HIV-1 transmission and the potential for serious adverse reactions in nursing infants, **mothers should be instructed not to breast-feed if they are receiving VIREAD.** **Geriatric Use:** Clinical studies of VIREAD did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, dose selection for the elderly patient should be cautious, keeping in mind the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. **Patients with Impaired Renal Function:** It is recommended that the dosing interval for VIREAD be modified in patients with creatinine clearance <50 mL/min or in patients with end-stage renal disease (ESRD) who require dialysis (See **Dosage and Administration**).

NONCLINICAL TOXICOLOGY: Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term oral carcinogenicity studies of tenofovir disoproxil fumarate in mice and rats were carried out at exposures up to approximately 16 times (mice) and 5 times (rats) those observed in humans at the therapeutic dose for HIV-1 infection. At the high dose in female mice, liver adenomas were increased at exposures 16 times that in humans. In rats, the study was negative for carcinogenic findings at exposures up to 5 times that observed in humans at the therapeutic dose. Tenofovir disoproxil fumarate was mutagenic in the in vitro mouse lymphoma assay and negative in an in vitro bacterial mutagenicity test (Ames test). In an in vivo mouse micronucleus assay, tenofovir disoproxil fumarate was negative when administered to male mice. There were no effects on fertility, mating performance or early embryonic development when tenofovir disoproxil fumarate was administered to male rats at a dose equivalent to 10 times the human dose based on body surface area comparisons for 28 days prior to mating and to female rats for 15 days prior to mating through day seven of gestation. There was, however, an alteration of the estrous cycle in female rats. **Animal Toxicology and/or Pharmacology:** Tenofovir and tenofovir disoproxil fumarate administered in toxicology studies to rats, dogs, and monkeys at exposures (based on AUCs) greater than or equal to 6 fold those observed in humans caused bone toxicity. In monkeys the bone toxicity was diagnosed as osteomalacia. Osteomalacia observed in monkeys appeared to be reversible upon dose reduction or discontinuation of tenofovir. In rats and dogs, the bone toxicity manifested as reduced bone mineral density. The mechanism(s) underlying bone toxicity is unknown. Evidence of renal toxicity was noted in 4 animal species. Increases in serum creatinine, BUN, glycosuria, proteinuria, phosphaturia, and/or calcium and decreases in serum phosphate were observed to varying degrees in these animals. These toxicities were noted at exposures (based on AUCs) 2–20 times higher than those observed in humans. The relationship of the renal abnormalities, particularly the phosphaturia, to the bone toxicity is not known.

For detailed information, please see full prescribing information. To learn more: call 1-800-GILEAD-5 (1-800-445-3235) or visit www.VIREAD.com. TRUVADA, EMTRIVA, HEPSERA, and VIREAD are registered trademarks of Gilead Sciences, Inc. ATRIPLA is a trademark of Bristol-Myers Squibb & Gilead Sciences, LLC. All other trademarks referenced herein are the property of their respective owners.

REFERENCE: 1. VIREAD® (tenofovir disoproxil fumarate) Prescribing Information. Foster City, CA: Gilead Sciences, Inc.; October 2010.



Presentations in Hepatology

Long-Term Safety and Efficacy of Tenofovir Disoproxil Fumarate for Treatment of Chronic Hepatitis B

Tenofovir disoproxil fumarate (TDF; Viread, Gilead) was approved for treatment of chronic hepatitis B (CHB) in 2008 and is currently under investigation in an 8-year, phase III study. Although this study is not yet completed, interim results were presented at the 2010 meeting of the American Association for the Study of Liver Diseases (AASLD).

In the double-blind phase of this study, patients were randomized to receive 300 mg TDF or 10 mg adefovir dipivoxil (ADV; Hepsera, Gilead) for 1 year; during the open-label phase of the study (Years 1–8), all patients received 300 mg TDF. On or after Week 72, patients with confirmed viral suppression (hepatitis B virus [HBV] DNA <400 copies/mL) could add emtricitabine. Hepatitis B e antigen–negative (HBeAg–) patients and HBeAg–positive (HBeAg+) patients were evaluated separately.

In an interim analysis of HBeAg– patients, Dr. Patrick Marcellin and associates reported on the 84% of patients who completed treatment at the end of Year 4. In the long-term evaluation of TDF only, 87% of patients in the ADV-TDF group and 84% of patients in the TDF-TDF group were found to have maintained viral suppression at Week 192. In the on-treatment analysis, which excluded patients with missing data, 100% of patients in the ADV-TDF group and 99% of patients in the TDF-TDF group had maintained viral suppression at Week 192. At this time point, mean alanine aminotransferase (ALT) levels were 34 U/L in the TDF-TDF group and 31 U/L in the ADV-TDF group; 80% of TDF-TDF patients and 86% of ADV-TDF patients exhibited normalized ALT levels. In terms of safety, 3 patients (1%) in the TDF-TDF group and 0 patients in the ADV-TDF group exhibited study-related serious adverse events. Serum creatinine levels remained stable over time; levels at Week 192 were 0.94 mg/dL and 0.92 mg/dL in the TDF-TDF and ADV-TDF groups, respectively. In addition, HBV DNA from 4 viremic patients was genotyped, and no amino acid substitutions were observed at a conserved site.

In a related analysis, Dr. E. Jenny Heathcote and associates presented efficacy and safety data for TDF treatment in HBeAg+ patients; 74% of these patients remained enrolled in the study at the end of Year 4. In this population, the long-term evaluation of TDF only showed

that 72% of ADV-TDF patients and 68% of TDF-TDF patients had maintained viral suppression at Week 192. The on-treatment analysis reported rates of 99% and 96%, respectively. HBeAg loss occurred in 41% of TDF-TDF patients, and HBeAg seroconversion occurred in 29% at Year 4. The cumulative probability of hepatitis B surface antigen (HBsAg) loss was 10.8% in TDF-TDF patients and 8.5% in ADV-TDF patients. Serious drug-related adverse events occurred in 2 TDF-TDF patients (1%) and 2 ADV-TDF patients (2%). Serum creatinine levels remained stable over time; at Week 192, mean serum creatinine levels were 0.91 mg/dL and 0.90 mg/dL in the TDF-TDF and ADV-TDF groups, respectively. No TDF resistance was detected in the 8 viremic (HBV DNA \geq 400 copies/mL) patient samples that were genotyped.

Finally, a study by Andrea Snow-Lampart and colleagues further examined data from these studies to determine whether monoinfected CHB patients develop resistance to TDF. Previous studies by this group found no resistance-associated amino acid substitutions in the reverse transcriptase domain of HBV DNA polymerase (HBV pol/RT) during 144 weeks of TDF treatment in HBeAg– and HBeAg+ patients. In the present study, the authors sought to identify amino acid substitutions in HBV pol/RT following 192 weeks of treatment and to determine whether these substitutions impacted clinical response to therapy or TDF susceptibility. To address these aims, 528 of the HBeAg+ and HBeAg– patients in the previously discussed studies were genotyped by dideoxy sequencing of serum HBV pol/RT (amino acids 1–344 of pol/RT [amino acids 1–266 of HBsAg]) at baseline and then yearly and/or at discontinuation of TDF monotherapy if HBV DNA was at least 400 copies/mL. After baseline, phenotypic analysis was performed in any patient with conserved site changes in pol/RT, virologic breakthrough (1 log₁₀ increase in HBV DNA and/or HBV DNA \geq 400 copies/mL after being <400 copies/mL), or polymorphic site changes. Conserved site changes in HBV pol/RT were not observed in any of the enrolled patients during Year 4. At the end of Year 4, only 3 patients showed virologic breakthrough; all were HBeAg– patients in the TDF-TDF group, and 2 of these patients had a documented history of nonadherence. Persistent viremia was observed in 3 HBeAg+ patients, but conserved site changes were not observed in more than 1 clone. In conclusion, there was no evidence of resistance in either the TDF monotherapy group or the ADV-TDF group following up to 4 years of treatment.

Entecavir Is Effective in CHB Patients Previously Treated with ADV

Another study presented at the 2010 AASLD meeting examined whether entecavir (ETV; Baraclude, Bristol-Meyers Squibb) is effective for the treatment of CHB in patients who were previously treated with ADV. Specifically, Dr. Mindie H. Nguyen and colleagues conducted a study to determine whether ETV could achieve complete viral suppression (HBV DNA <60–100 IU/mL) and ALT normalization (<40 U/mL) in patients who were switched from ADV due to suboptimal responses, resistance prevention, or other reasons.

CHB patients were enrolled in this study if pretreatment levels of HBV DNA were at least 2,000 IU/mL and if patients were previously treated with ADV and then switched to ETV. Exclusion criteria included co-infection with hepatitis D virus, hepatitis C virus (HCV), or HIV; lamivudine resistance; and recent or ongoing immunosuppressive therapy. Patients were separated into 2 groups: Group I were ADV partial responders (<2 log₁₀ reduction in HBV DNA at 6 months or incomplete viral suppression after 12 months of ADV treatment); Group II were ADV responders who achieved complete viral suppression on ADV but were switched to ETV due to physician or patient preference.

The study included 106 patients who completed at least 6 months of ETV therapy (71 patients in Group I; 35 patients in Group II). After 6 months of treatment with ETV, 62% of the ADV partial responders achieved complete viral suppression and 79% achieved normalization of ALT levels. By 24 months, these rates were 82% and 87%, respectively. All ADV responders continued to have complete viral suppression and normalized ALT levels on ETV therapy, and the authors indicated that neither side effects nor resistance were issues during ETV treatment.

Sustained Virologic Response Reduces Risk of Death in Patients with HCV Infection

Sustained virologic response (SVR) is a well-recognized goal in the treatment of HCV, but the extent to which SVR reduces the risk of death has not been fully explored in a community setting. Dr. Lisa Backus and colleagues at the Center for Quality Management in Public Health in Palo Alto, California therefore compared patient outcomes according to SVR status; this analysis was presented at the 2010 meeting of the AASLD. All subjects were in the US Department of Veterans Affairs' Clinical Case Registry.

A total of 21,836 patients met all essential inclusion criteria; most patients also had a post-treatment

HCV RNA test. The overall SVR rate in an intent-to-treat (ITT) analysis was 34%; this rate was 26%, 62%, and 52% for patients with HCV genotypes 1, 2, and 3, respectively. Of the 16,864 individuals with a post-treatment HCV RNA test, the overall SVR rate was 44%, with rates of 35%, 72%, and 62% in patients with HCV genotypes 1, 2, and 3, respectively.

During a mean follow-up period of 3.7 years following completion of the post-treatment HCV RNA test, a total of 1,535 patients (9.1%) died. Patients who attained SVR were significantly less likely to die during the follow-up period than patients who did not attain SVR, with relative risk reductions of 55%, 50%, and 70% in patients with HCV genotypes 1, 2, and 3, respectively. SVR remained independently associated with a reduced risk of death from any cause in all 3 genotypes even after a multivariate analysis adjusted for age; sex; race; body mass index; creatinine clearance; HBV co-infection; comorbidities; treatment duration; year of treatment initiation; and levels of albumin, ALT, aspartate aminotransferase, bilirubin, hemoglobin, platelets, and sodium.

Addition of Boceprevir Improves SVR Rates in Patients with HCV Infection

Currently, standard treatment for HCV infection involves peginterferon and ribavirin; however, 2 new drugs, boceprevir and telaprevir, may hold promise for improving SVR rates in HCV-infected patients. In SPRINT-2, a randomized, double-blind, international, phase III trial, boceprevir was evaluated in combination with peginterferon and ribavirin; Dr. Fred Poordad and colleagues presented final results of this study during the 2010 AASLD meeting.

In this study, all patients underwent a 4-week lead-in treatment period with peginterferon and ribavirin, after which patients were randomly assigned to 1 of 3 treatment arms: peginterferon and ribavirin plus placebo for 44 weeks; response-guided therapy (RGT), in which patients received boceprevir plus peginterferon and ribavirin for 24 weeks, with an additional 20 weeks of peginterferon and ribavirin treatment for patients with detectable HCV RNA levels during Weeks 8–24; or fixed-duration triple therapy, which consisted of boceprevir plus peginterferon and ribavirin for 44 weeks. Treatment was discontinued in patients with detectable HCV RNA levels at Week 24.

Overall, SVR rates were significantly higher in the boceprevir-containing treatment arms than the control arm. Among nonblack patients, SVR rates were 67% in patients who received RGT, 68% in patients who received 44 weeks of triple therapy, and 40% in patients who

received peginterferon and ribavirin alone ($P < .0001$ for each boceprevir-containing treatment arm vs control). In black patients, SVR rates were 42%, 53%, and 23%, respectively ($P = .044$ for RGT vs control; $P = .004$ for 44 weeks of triple therapy vs control).

In the overall study population, discontinuations due to adverse events were similar among the 3 treatment arms. Anemia occurred in 49% of patients receiving boceprevir and 29% of patients receiving peginterferon and ribavirin, but treatment discontinuations due to anemia were rare.

Telaprevir Shows Benefit in ADVANCE Study

In another study presented at the 2010 AASLD meeting, Dr. Ira M. Jacobson and colleagues presented the final results of the randomized, placebo-controlled, phase III ADVANCE trial, which evaluated the addition of telaprevir to peginterferon and ribavirin in treatment-naïve patients with genotype 1 HCV infection. A total of 1,088 patients were randomly assigned to receive either peginterferon and ribavirin alone or peginterferon

and ribavirin plus telaprevir for the first 8 or 12 weeks of treatment. Patients in the telaprevir-containing arms who achieved an extended rapid viral response (defined as undetectable HCV RNA levels at Weeks 4 and 12) received a total of 24 weeks of therapy; other patients received a total of 48 weeks of therapy. In this difficult-to-treat population, 77% of patients had HCV RNA levels at or above 800,000 IU/mL, 58% had genotype 1a HCV infection, 58% were male, 11% were Latino or Hispanic, 9% were black, and 21% had bridging fibrosis or compensated cirrhosis.

Rates of SVR (defined as undetectable HCV RNA levels 24 weeks after the last planned treatment dose) were significantly higher in both telaprevir-containing treatment arms compared to the control arm. In an ITT analysis, SVR rates were 75% in patients who received 12 weeks of telaprevir treatment, 69% in patients who received 8 weeks of telaprevir treatment, and 44% in the control arm ($P < .0001$). Adverse events led to discontinuation of treatment in 8% of patients who received telaprevir for 8 weeks, 7% of patients who received telaprevir for 12 weeks, and 4% of patients in the placebo arm.

Presentations in IBS

Addition of Desipramine to Alosetron Improves Pain Relief in Women with Irritable Bowel Syndrome

Although effective for relieving diarrhea associated with irritable bowel syndrome (IBS-D), alosetron (Lotronex, Prometheus) does not always alleviate abdominal pain or discomfort in these patients. Dr. Charles Randall and colleagues therefore examined whether adding the tricyclic antidepressant desipramine to the approved IBS-D agent alosetron can help to manage pain in patients with persistent abdominal pain or discomfort. These results were presented at the 2010 American College of Gastroenterology (ACG) meeting.

This open-label study enrolled 20 patients from an IBS registry. All patients were female, were currently receiving alosetron to treat IBS-D, had been at a stable dose of alosetron for at least 60 days, and had abdominal pain or discomfort at least 3 days per week. Desipramine was initially administered at 10 mg daily; the dosage was increased by 10 mg per month until patients experienced either symptom relief or an adverse event. Patients were followed every 3 months for up to 1 year.

Complete pain resolution was achieved in 75% of patients (N=15); these patients were receiving doses of 10 mg (N=4), 20 mg (N=8), or 30 mg (N=3). The remaining 5 patients experienced partial symptom relief; in these patients, abdominal pain or discomfort was reduced to 1 or fewer episodes per week. A mean of 2 weeks passed between the time when the optimal dosage was initiated and when symptom resolution was achieved. No significant adverse events, including constipation or ischemic colitis, were observed.

Daily Composite Endpoint Correlates with the Traditional Endpoint of Binary Weekly Adequate Relief

To evaluate the validity and responsiveness of several efficacy endpoints used to determine response to IBS treatment, an abstract presented at the 2010 ACG meeting reviewed data from 2 identically designed, double-blind, placebo-controlled, phase III trials (TARGET 1 and TARGET 2).

This analysis, by Dr. William Chey and colleagues, examined the endpoints of the TARGET 1 and TARGET 2 studies: 2 traditional binary measurements—weekly adequate relief of global IBS symptoms, and bloat-

ing—and a composite endpoint of daily assessments that was recently proposed by the US Food and Drug Administration (FDA). In addition to responding to questions regarding weekly relief of global IBS symptoms and IBS-related bloating, patients in these studies also provided daily ratings for IBS symptom severity, stool consistency, and urgency.

A total of 1,260 patients with mild-to-moderate IBS without constipation were randomized to receive either 550 mg rifaximin (Xifaxan, Salix) 3 times daily or placebo for 2 weeks. Patients were evaluated at a 10-week post-treatment follow-up visit. Weekly responder endpoints (including adequate relief of global IBS symptoms, adequate relief of IBS-related bloating, abdominal pain, and stool consistency) were found to be valid, and responsiveness of the endpoints was demonstrated by their consistent association with daily symptom severity scores. Significant improvements ($P<.0001$) in all daily symptom severity scores occurred in responders versus nonresponders at each week. The authors concluded that both the traditional endpoint of binary weekly adequate relief and the new FDA-proposed daily composite endpoint were valid, and the 2 endpoints were significantly correlative ($P<.001$).

Psychiatric Comorbidities Reduce Quality of Life in IBS Patients

IBS has been shown to exert multiple negative effects on quality of life (QOL). Many of these effects are comparable to the QOL impacts resulting from other gastrointestinal disorders, such as inflammatory bowel disease (IBD; ulcerative colitis [UC] and/or Crohn's disease [CD]), or chronic hepatitis. Importantly, up to half of IBS patients experience comorbid psychiatric conditions, including depression, anxiety, and somatization. In some instances, these comorbid conditions may compound the negative effect that IBS has on QOL. In an abstract presented at the 2010 ACG meeting, Dr. Gregory Sayuk and colleagues aimed to evaluate this possibility.

This study enrolled 279 IBS patients (mean age=49.5±4.7 years) who consecutively presented to a tertiary gastrointestinal outpatient clinic over a 52-month period. Patients completed several instruments to measure QOL, including the Rome III Research Diagnostic Questions, Beck Depression and Anxiety Inventories (to measure mood), SF-86 Health-Related QOL Index, and

Patient Health Questionnaire-15 Somatization Scale. The investigators controlled for the effect of IBS symptoms by measuring bowel symptom severity and the number of symptomatic days over the preceding 2 weeks.

Approximately half of the patients (52.3%) had at least 1 psychiatric comorbidity. These patients had particularly poor QOL, as evidenced by significantly lower SF-86 scores compared to IBS patients without psychiatric comorbidities (38.3 ± 19.8 vs 64.7 ± 19.0 ; $P < .001$). In a multivariate analysis, worsened QOL was significantly associated with depression and somatization scores as well as with older age; QOL was not significantly associated with bowel symptom severity or frequency, gender, or anxiety.

Safety and Efficacy of Linaclotide for Treatment of Chronic Constipation

Linaclotide is a guanylate cyclase type C receptor agonist that is currently under investigation as a treatment for chronic constipation. In an abstract from the 2010 ACG meeting, Dr. Anthony Lembo and colleagues presented the combined results of 2 randomized, double-blind, placebo-controlled, phase III trials that evaluated the activity and safety of this drug.

A total of 1,272 patients with chronic constipation were included in this ITT analysis. All patients met modified Rome II criteria for chronic constipation, with fewer than 3 complete spontaneous bowel movements weekly and 6 or fewer spontaneous bowel movements in the 2-week period prior to randomization. Patients were randomized to receive 133 μ g linaclotide once daily (N=430), 266 μ g linaclotide once daily (N=418), or placebo (N=424); all treatments were continued for 12 weeks. The primary endpoint of both studies was 12-week overall response in terms of complete spontaneous bowel movements (defined as ≥ 3 per week, with an increase of ≥ 1 per week from baseline for 9 of 12 weeks).

This primary endpoint was met in a significantly higher percentage of patients treated with either low- or high-dose linaclotide than those treated with placebo (18.6% and 20.3% vs 4.7%, respectively; $P < .0001$ for both comparisons against placebo). An improvement in the number of spontaneous bowel movements was evident within 24 hours of linaclotide treatment. Both

doses of linaclotide were also associated with significant improvements in secondary endpoints, including stool consistency, straining, constipation severity, abdominal discomfort, and bloating ($P < .0001$ vs placebo for all comparisons). The most frequently reported treatment-related adverse event was diarrhea, which occurred in 16.0% and 14.2% of patients treated with 133 μ g and 266 μ g linaclotide, respectively, compared to 4.7% of patients who received placebo.

Measuring the Economic Burden of Chronic Constipation

The effects of chronic constipation can be significant and far-reaching, as they include not only the burden on individual patients but also broader economic effects. A study presented at the 2010 ACG meeting by Dr. Shawn Sun and colleagues sought to quantify the economic impact of chronic constipation by analyzing data from the EXCEED registry. This 12-month, observational, multicenter dataset includes patients from 60 community and academic primary care centers throughout the United States (N=691, mean age= 52.7 ± 16.9 years). Registry data include patient medical history, constipation symptoms, health-related QOL, and impairment of work productivity and activity. All patients in this study had had symptoms related to constipation for at least 3 months; patients with a preexisting IBS diagnosis or moderate or severe abdominal pain or discomfort were excluded from the study.

Several instruments were used to assess the personal burden of chronic constipation; patients reported negative effects related to physical discomfort, psychological discomfort, worries and concerns, and satisfaction. Chronic constipation was determined to affect 33.7% of normal daily activities and 34.0% of overall work productivity. Approximately one third (32.3%) of patients who were employed exhibited absenteeism, and two thirds (67.8%) of employed patients experienced reduced productivity at work. This amounted to a loss of 13.4 hours per week due to chronic constipation (1.9 hours due to absenteeism and 11.5 hours due to reduced productivity while at work). Overall, the estimated economic impact of chronic constipation (based on the 2008 average national hourly wage) was \$272 per patient each week.

Presentations in GERD

Esomeprazole Improves Sleep Disorders Associated with Gastroesophageal Reflux Disease

Gastroesophageal reflux disease (GERD) is associated with sleep disorders that can result in worsened next-day function, including impaired work productivity and poor psychomotor function. In an abstract presented at the 2010 ACG meeting, Dr. David Johnson and colleagues conducted a prospective pilot study to assess the impact of GERD-induced sleep disorders on a simulated driving exercise and to evaluate the effect of the proton pump inhibitor (PPI) esomeprazole on patients' performance of this task.

A total of 11 GERD patients (mean age=49 years, range 32–60 years) who had nocturnal symptoms and no known sleep disorders were enrolled in this study; most patients were female (N=9). Driving skills were assessed in a validated commercial driving simulator that responds to driver input and projects realistic roadway images. Driving performance, defined as the standard deviation of lateral position subtracted from the standard deviation of lane variation, was measured every 0.5 seconds over 1 hour. Patients were assessed at baseline, at which time all patients had not received PPI treatment for at least 14 days, and again following 4 weeks of esomeprazole treatment (40 mg every morning).

This study found that the standard deviation of lateral position increased significantly over time ($P=.002$). However, this outcome was significantly improved following esomeprazole treatment ($P=.004$). Esomeprazole was also associated with significant improvements in GERD-induced sleep disorders, as shown by a decrease from baseline in the overall average proportion of nights that patients experienced sleep disorders (62.5% vs 9.5% at baseline and after treatment, respectively; $P<.001$) and decreases on the Epworth Sleepiness Scale, an assessment of daytime sleepiness (7.9+2.5 vs 5.9+3.5 at baseline and after treatment, respectively; $P=.056$). Furthermore, patients experienced a significant improvement in GERD symptom score following treatment with esomeprazole (2.10 vs 0.33 at baseline and after treatment, respectively; $P<.001$).

Baclofen Can Decrease Reflux and Improve Sleep Quality in GERD Patients

In another abstract presented at the 2010 ACG meeting, Dr. William Orr and colleagues reported on a study in

which the gamma aminobutyric acid-B agonist baclofen was evaluated to determine its effect on reflux during sleep and its potential for improving objective and subjective measures of sleep. A total of 22 patients were included in this study. All patients had complained of nighttime heartburn at least twice per week, had a Carls-son GERD score of at least 5, and were categorized as having disturbed sleep (defined as an abnormal score on the Pittsburgh Sleep Quality Index). Patients with symptoms of a primary sleep disorder were excluded. Polysomnography with simultaneous pH monitoring was performed twice (separated by approximately 2 weeks); on the night of each study, patients consumed a refluxogenic meal. Ninety minutes prior to the initiation of the polysomnography, patients were randomly administered either baclofen (40 mg) or placebo.

There was no significant difference between baclofen and placebo in terms of upright or supine acid contact time. However, patients who received baclofen had significantly fewer reflux events compared to patients who received placebo (1.3 vs 4; $P<.05$). Compared to the placebo group, patients in the baclofen group also achieved improved sleep outcomes as measured by an increase in total sleep time (379 minutes vs 434 minutes; $P<.001$), improved sleep efficiency (79% vs 91%; $P<.001$), and decreased wake time after sleep onset (83 minutes vs 31 minutes; $P<.001$). There was no significant difference in the proportion of patients in each group who reached rapid eye movement sleep; however, fewer patients in the baclofen group were in stage 1 sleep (6.8% vs 10.6%; $P<.05$).

Multichannel Intraluminal Impedance and pH Testing Versus Esophageal pH Testing

Combined multichannel intraluminal impedance and pH (MII-pH) testing has emerged as the preferred method for evaluation of GERD and GERD-related symptoms. MII-pH testing detects reflux by measuring changes in intraluminal resistance and uses pH data to classify this reflux as acidic or nonacidic. However, this technique requires a specialist to evaluate the data, potentially delaying evaluation and treatment. In this abstract from the 2010 ACG meeting, Dr. Erick Singh and colleagues conducted a retrospective review to compare automated MII-pH testing with esophageal pH testing for evaluation of GERD in symptomatic individuals.

MII-pH tracings from 200 GERD patients were included in this analysis; half of these patients (N=100)

were receiving PPI therapy, and half (N=100) were not. Patient tracings were categorized as having either typical or atypical symptoms. Esophageal pH testing and automated MII-pH testing were separately used to interpret each tracing, and the results were blindly compared with the final expert analysis.

Tracings interpreted using automated MII-pH testing had a higher agreement between symptom index and symptom-associated probability among patients with typical GERD symptoms who were not receiving PPI treatment. For patients with typical GERD symptoms who were receiving PPI therapy, the agreement between symptom index and symptom-associated probability was also higher with automated MII-pH testing than with esophageal pH testing. In contrast, tracings from patients with atypical GERD symptoms who were not on PPI treatment were similarly interpreted for symptom index and symptom-associated probability using either method. For all GERD patients with atypical symptoms (both those on and off PPI therapy), a significant association was found between symptom index and symptom-associated probability values as determined using automated MII-pH testing (both $P<.01$). For patients with atypical GERD symptoms who were on PPI therapy, there was also a significant association between symptom index and symptom-associated probability values ($P<.01$). However, there was no significant association between symptom index and symptom-associated probability values for patients with typical GERD symptoms who were on PPI therapy when esophageal pH testing was used for the interpretation. Together, these findings led the authors to conclude that automated MII-pH testing was more reliable than esophageal pH testing in symptomatic GERD patients, especially in patients with typical symptoms who were on PPI therapy.

Rabeprazole and Esomeprazole Are Comparable for Treatment of Esophagitis in Most Patients

Dr. Loren Laine and colleagues presented an abstract at the 2010 ACG meeting in which they analyzed the results of 2 identically designed, double-blind, randomized trials that evaluated the extended-release formulation of the PPI rabeprazole. In both studies, patients with Los Angeles (LA) grade C or D symptomatic esophagitis were randomized to receive 50 mg extended-release rabeprazole (study 1: N=524; study 2: N=528) or 40 mg esomeprazole (study 1: N=531; study 2: N=537); both drugs were administered every morning. Upper endoscopy was performed at 4 weeks to determine if the esophagitis had healed ($P<.05$ used for superiority comparison); if the patient had not healed, another

endoscopy was performed at 8 weeks (8% noninferiority margin used for comparison).

In both studies, there was no significant difference in the proportion of patients who achieved healing at Week 4 with either extended-release rabeprazole or esomeprazole (study 1: 54.8% vs 50.3%; $P=.162$; study 2: 50.9% vs 50.7%; $P=.828$). Similarly, a comparable proportion of patients in both the extended-release rabeprazole and esomeprazole treatment arms achieved healing at Week 8 in both studies (study 1: 80.0% vs 75.0%; 95% confidence interval [CI]: 0–10%; study 2: 77.5% vs 78.4%; 95% CI: –5.9% to 4.0%).

A subgroup analysis suggested a potential benefit for extended-release rabeprazole compared to esomeprazole among patients with grade D esophagitis in study 1, as shown by an improved healing rate at Week 4 (49.1% vs 30.8%; $P=.038$) and Week 8 (75.4% vs 61.5%; 95% CI: –2.4% to 30.2%). In contrast, study 2 found no significant difference in healing among patients with grade D esophagitis at Week 4, although these patients did achieve an improved rate of healing at Week 8 (64.7% vs 56.7%, 95% CI: –8.9% to 25.0%).

Swallowed Fluticasone for Treatment of Eosinophilic Esophagitis Achieves Histologic Response But Not Symptomatic or Endoscopic Improvement

Topical steroid treatment has previously been shown to elicit a histologic response, but not a symptomatic benefit, in children with eosinophilic esophagitis. At the 2010 ACG meeting, Dr. Jeffrey Alexander and colleagues presented results from a trial designed to evaluate the aerosolized, swallowed corticosteroid fluticasone for treatment of eosinophilic esophagitis in adults.

This was a double-blind study that randomized 42 adults (mean age=37.5 years) to receive either 880 µg fluticasone twice daily (N=21) or placebo (N=21) for 6 weeks. All patients had persistent dysphagia following 4 weeks of twice-daily PPI treatment and an esophageal biopsy that showed at least 15 eosinophils per high-power field. Patients were enrolled in this study between 2005 and 2009, and baseline characteristics were well balanced between the treatment and placebo arms. Patients were followed for 6 weeks after treatment; a total of 34 patients completed the study protocol (19 in the fluticasone group and 15 in the placebo group). Thus, both ITT and per-protocol analyses were performed.

Both the ITT and per-protocol analyses showed that a significantly higher proportion of individuals in the fluticasone arm exhibited a histologic response compared to the control arm (ITT: 71% vs 10%; $P<.01$; per-protocol: 79% vs 13%; $P<.01$). However, the rate of

symptom response and the frequency of abnormal endoscopic findings were similar in the 2 arms. The rates of symptom response in the ITT population were 71% and 48% for the fluticasone and placebo arms, respectively; in the per-protocol population, these rates were 68% and 74%, respectively. Abnormal endoscopic findings were seen in 79% and 68% of patients pre- and postfluticasone treatment, respectively, and in 80% and 88% of patients pre- and postplacebo treatment, respectively. Persistently abnormal endoscopic findings occurred in the majority of patients (82%) who had fewer than 15 eosinophils per high-power field following treatment.

No difference in 24-hour, post-treatment urine cortisol levels was observed between the 2 arms. Interestingly, oral thrush was more common in patients treated with placebo compared to fluticasone (26% vs 0%; $P=.05$).

Effect of Dosing Schedule on Efficacy of Omeprazole/Sodium Bicarbonate

In another abstract from the 2010 ACG meeting, Dr. Yvonne Romero and colleagues presented results from a prospective, randomized, open-label trial that compared 2 dosing schedules for immediate-release omeprazole/sodium bicarbonate (Zegerid, Santarus). A total of 88 patients (mean age=58 years, range 22–86 years) were randomized to receive 40 mg immediate-release omeprazole/sodium bicarbonate either 20–60 minutes prior to breakfast (N=41) or prior to bedtime, regardless of mealtime (N=47). All patients were diagnosed with LA grade C or D reflux esophagitis. Endoscopy was performed at baseline and following 8 weeks of treatment.

Of the patients randomized to the prebreakfast dosing schedule, 84% had healed after 8 weeks of treatment; the remaining individuals in this group all exhibited a 1–2 grade improvement in disease severity. Similarly, 85% of patients in the prebedtime dosage group had healed after 8 weeks of treatment; only 2 of the remaining patients in this group had the same or worsened disease severity. While on treatment, approximately 23% of patients (N=18) were selected to undergo pH testing; of these patients, 6 discontinued treatment prior to pH probe placement and were excluded from the subgroup analysis. Of the remaining 12 patients (7 in the

prebreakfast dosage group and 5 in the prebedtime dosage group), normalization of pH levels was achieved in 86% of patients in the prebreakfast group and 60% of patients in the prebedtime dosage group. The dosing schedule made no difference in terms of the PPI's effect on a pH level less than 4. In conclusion, the dosing schedule for omeprazole/sodium bicarbonate (prebreakfast vs prebedtime) did not alter the drug's ability to heal severe erosive reflux esophagitis following 8 weeks of treatment. Thus, patients may be able to use a more convenient alternative schedule while achieving similar efficacy.

Meta-Analysis Finds No Protective Benefit for *Helicobacter pylori* in Patients with GERD

Based on the results of previous studies, the presence of *Helicobacter pylori* has been hypothesized to have a protective role in patients with GERD, although this benefit has been disputed by other studies that did not show any benefit. To address this question, Dr. Abdo Saad and colleagues performed a meta-analysis that evaluated the role of *H. pylori* in the pathogenesis of GERD; their results were presented at the 2010 ACG meeting.

A total of 8 randomized controlled trials were included in this meta-analysis; all studies compared *H. pylori* eradication with no eradication and evaluated the intervention's effect on GERD in terms of both symptomatic and endoscopic changes. All 8 trials were scored as adequate in quality (Jadad score ≥ 2), and I² calculation found no significant heterogeneity among the studies for the primary outcome.

A slight decrease in the incidence of esophagitis was observed among patients in the noneradicated group versus the eradicated group (3.97% vs 4.77%), but this difference did not reach statistical significance (odds ratio [OR] 1.26; 95% CI: 0.81–1.99; $P=.31$). Similar nonsignificant decreases were also observed for noneradication when the analysis was confined to patients with either new-onset esophagitis or worsening of existing esophagitis. Non-eradication of *H. pylori* also had a nonsignificant effect in patients with symptomatic GERD (OR 0.82; 95% CI: 0.48–1.38; $P=.45$). Based on these data, the investigators concluded that *H. pylori* did not have a protective role in patients with GERD.

Presentations in IBD

Population-Based Cohort Study Provides New Data on IBD

Several abstracts presented at the 2010 ACG annual meeting were based on the prospective, population-based Ocean State Crohn's and Colitis Area Registry (OSCCAR), a novel inception cohort of patients with IBD living in Rhode Island. Since January 1, 2008, OSCCAR has enrolled 180 Rhode Island residents newly diagnosed with CD, UC, or indeterminate colitis (IC). Data collected from enrolled individuals include demographic data, medical history, information related to IBD, and responses to questionnaires on QOL and disease activity; blood, urine, and stool samples were also collected.

In a study analyzing these data, Dr. Samir Shah and colleagues reported on the incidence of new cases of IBD in Rhode Island. Between January 1, 2008 and December 31, 2009, 237 new cases of CD and 274 new cases of UC/IC were identified. These numbers translated to unadjusted incidence rates of 21–27 cases per 100,000 individuals for IBD, 10.4–11.6 cases per 100,000 individuals for CD, 9.3–14.3 cases per 100,000 individuals for UC, and 0.8–1.1 cases per 100,000 individuals for IC. Overall, 103 of 237 patients with CD and 77 of 274 patients with UC/IC enrolled in OSCCAR. The enrollees were primarily white (86.4% of CD patients and 93.5% of UC/IC patients) and had no history of smoking (68.9% and 63.6%, respectively) or nonsteroidal anti-inflammatory drug use (87.3% and 79.2%, respectively). Adults comprised 67.0% of patients with CD and 79.2% of those with UC/IC.

In a second analysis of the OSCCAR data, Dr. Mitul Patel and colleagues evaluated presenting symptoms in patients with CD (97 patients at baseline and 39 patients at Year 1) and UC/IC (71 patients at baseline and 23 patients at Year 1). The most common symptoms reported by individuals with CD were abdominal pain and fatigue, present in 83.5% and 81.4%, respectively, at baseline; at Year 1, each symptom was present in 61.5%. The 5 most common presenting symptoms in patients with UC and IC were loose stools/watery bowel movements (93%), urgent bowel movements (90.1%), increased number or frequency of bowel movements (88.6%), passage of blood with bowel movements (87.0%), and cramping with a bowel movement (75.0%). At Year 1, the 5 most common symptoms were fatigue, abdominal pain, and loose stools/watery bowel movements (69.6% each), urgent bowel

movements (52.2%), and uncertainty whether gas or a bowel movement is about to be passed (52.2%).

Efficacy of Adalimumab in UC Patients Who Failed Corticosteroids and/or Immunosuppressants

In another study presented at the 2010 ACG meeting, Dr. Walter Reinisch and colleagues reported Week 52 results from an open-label extension study designed to evaluate the safety and efficacy of adalimumab (Humira, Abbott) in patients with moderately to severely active UC. This study enrolled 390 biologic-naïve UC patients with a Mayo score of 6–12 and an endoscopy subscore of 2–3 despite concurrent use or prior failure of oral corticosteroids and/or immunosuppressants. During the study's double-blind induction period, patients received 1 of 3 treatments: 80/40 mg adalimumab, 160/80 mg adalimumab, or placebo. At Week 8, patients moved into the study's open-label extension phase, during which patients received 40 mg adalimumab every other week, with dose escalation to 40 mg weekly being permissible beginning at Week 12.

The primary endpoint for this study was the proportion of patients who attained clinical remission (Mayo score ≤ 2 with no individual subscore > 1) at Week 8; this endpoint was achieved in a significantly higher proportion of patients treated with 160/80 mg adalimumab than those who received placebo (18.5% vs 9.2%; $P=.031$). The investigators also assessed the response to open-label adalimumab at Week 52 in a pooled analysis of all randomized patients. In a nonresponder imputation (NRI) analysis, in which a missing Week 52 Mayo score or escalation to weekly dosing was counted as lack of remission or response, 25.6% of patients attained clinical remission with open-label adalimumab; in a modified NRI analysis that did not count dose escalations as failures, the Week 52 clinical remission rate was 29.5%. Finally, in the as-observed analysis, 42.0% of patients attained clinical remission at Week 52.

CD Patients Treated with Adalimumab Can Achieve "Deep Remission" Regardless of Disease Duration

In another study involving adalimumab, Dr. Jean-Frederic Colombel and colleagues evaluated patients from the EXTEND study to determine the relationship

between CD duration and rate of “deep remission” (defined as mucosal healing and a Crohn’s Disease Activity Index score <150 points). These data were presented at the 2010 Advances in IBD Crohn’s and Colitis Foundation’s National Clinical and Research Conference.

In the EXTEND trial, 135 patients received open-label adalimumab at Week 0 (160 mg) and Week 2 (80 mg). At Week 4, patients were randomized to receive either adalimumab (40 mg every other week) or placebo, and this treatment was continued until Week 52. After Week 8, patients who experienced a flare or nonresponse were eligible to receive open-label adalimumab (40 mg every other week); those with continued flares or nonresponse could receive 40 mg weekly. All patients in this study had been diagnosed with CD at least 4 months previously; disease durations were 2 years or less (14%), more than 2 years to 5 years (20%), and more than 5 years (66%).

After stratifying by CD duration, more patients in the adalimumab group compared to the placebo group achieved deep remission at Week 52: 25% versus 0% in patients with a disease duration of 5 years or less ($P=.009$) and 16% versus 0% in patients with a disease duration greater than 5 years ($P=.008$). At Week 12, there was a trend toward improved rates of deep remission for adalimumab versus placebo among patients with a shorter duration of CD, but this difference was not statistically significant ($P<.191$).

Long-Term Remission with Certolizumab Pegol in CD

Another drug that is commonly used to treat IBD, certolizumab pegol (Cimzia, UCB), has been evaluated in several clinical trials in the PRECiSE series: PRECiSE 1 demonstrated the efficacy of certolizumab pegol for induction and maintenance of CD in patients with moderately to severely active disease; PRECiSE 2 showed that certolizumab pegol was effective as maintenance therapy in patients who responded to open-label induction therapy with certolizumab pegol; and the ongoing studies PRECiSE 3 and PRECiSE 4 are evaluating the long-term safety and efficacy of certolizumab pegol in CD. In an abstract presented at the 2010 Advances in IBD meeting, Dr. Gary Lichtenstein and colleagues reported interim results from PRECiSE 3.

The PRECiSE 3 study included 141 patients (mean age=37.6±11.9 years) who were randomized to certolizumab pegol and completed an initial 26 weeks of therapy during the PRECiSE 2 study. During the PRECiSE 3 study, patients continued to receive open-label certolizumab pegol at a dose of 400 mg every 4 weeks. Approximately 80% of patients in the PRECiSE 3 study had not been previously treated with

infliximab (Remicade, Centocor). In this interim analysis, the data cutoff was at 4.5 years (4 years after completing PRECiSE 2); at this time, only 32% of patients were still on study.

At the beginning of PRECiSE 3, remission was attained in 75% and 78% of total and infliximab-naïve patients, respectively. Clinical remission (defined as a Harvey-Bradshaw Index score ≤4) was maintained over the next 4.5 years and was similar between the total and infliximab-naïve patient populations. Remission rates at 1, 2, 3, 4, and 4.5 years were 69%, 69%, 64%, 64%, and 63%, respectively, among the total population and 69%, 68%, 65%, 65%, and 63%, respectively, among the infliximab-naïve population.

Certolizumab Pegol Improves QOL in Patients with CD

Health-related QOL is an important indicator in CD, as it has been shown to directly correlate with CD activity. In a study presented at the 2010 Advances in IBD meeting, Dr. Xavier Hébuterne and colleagues assessed health-related QOL among patients in the MUSIC study, a prospective, open-label trial of patients with severely active CD.

All 89 patients in the MUSIC study (mean age=30.2±9.9 years) were treated with open-label certolizumab pegol at a dose of 400 mg; patients received 3 doses at 2-week intervals and then were dosed every 2–4 weeks for up to 54 weeks. Inflammatory Bowel Disease Questionnaire (IBDQ) scores were used to measure QOL at baseline and at Weeks 10 and 54; missing data were counted as a nonresponse. Endoscopies were also performed at baseline and at Weeks 10 and 54; endoscopies were scored using the Crohn’s Disease Endoscopic Index of Severity (CDEIS). IBDQ response was defined as an increase in total IBDQ score of at least 16 points, and IBDQ remission was defined as a total IBDQ score of at least 170 points.

At baseline, the mean total IBDQ score was 120.4±28.9 points. Mean changes in total IBDQ scores from baseline were 43.8 points and 44.1 points at Weeks 10 and 54, respectively; improvements occurred in all 4 IBDQ subscores and were similar between Weeks 10 and 54. A large proportion of patients at Weeks 10 and 54 achieved IBDQ response (66.3% and 43.8%, respectively) and IBDQ remission (43.8% and 29.2%, respectively). Importantly, rates of IBDQ remission correlated with rates of CDEIS remission among the ITT population with available endoscopic assessments at Weeks 10 and 54; 69.7% of patients in CDEIS remission at Week 10 were also in IBDQ remission, and 60.0% of patients in CDEIS remission at Week 54 were also in IBDQ remission.

Benefits of Mucosal Healing in Patients with UC

Mucosal healing is a clinical indicator that is thought to be important for measuring treatment response in patients with UC. Dr. William Sandborn and colleagues therefore analyzed data from patients enrolled in the ACT 1 and ACT 2 studies to determine the association between mucosal healing at Week 8 and clinical outcomes; this analysis was presented at the 2010 ACG meeting. In these studies, mucosal healing was measured using the Mayo endoscopic subscore classification (0=normal, 1=mild disease, 2=moderate disease, and 3=severe disease), and the analysis was limited to patients in either study who were assigned to infliximab and did not receive a colectomy or discontinue treatment prior to Week 8.

Among the 466 evaluable, infliximab-treated patients, the endoscopy score at Week 8 was 0 in 26% of patients, 1 in 38%, 2 in 24%, and 3 in 12%. Week 8 endoscopy scores were significantly associated with a risk of colectomy; the likelihood of remaining colectomy-free at Week 54 decreased from 95% among patients with scores of 0 and 1, to 87% among patients with a score of 2, to 80% among patients with a score of 3 ($P=.0004$). Week 8 endoscopy scores were also associated with symptomatic remission (defined as a stool frequency score of 0 or 1 and a rectal bleeding score of 1) and the need for corticosteroids; at Week 30, symptomatic remission rates ranged from 71% among patients with a score of 0 to 51%, 23%, and 10% among those with scores of 1, 2, and 3, respectively ($P<.0001$). The proportions of patients remaining corticosteroid-free were 62%, 46%, 20%, and 10% among patients with scores of 0, 1, 2, and 3, respectively ($P<.0001$).

Predictors of Response to Infliximab Include Smoking, Fibrostenotic Disease, and Localization of Disease to the Small Bowel Only

In addition to its use in the treatment of UC, infliximab is also commonly used to induce and main-

tain remission in CD. However, some patients either fail to respond to infliximab or they lose response over time. Therefore, a study presented by Dr. Ira Shafraan and Patricia Burgunder at the 2010 Advances in IBD meeting aimed to identify factors that affect response to infliximab among CD patients in a single-center community practice.

In this retrospective chart review, 125 CD patients who had received at least 1 infliximab infusion between January 1, 1998 and August 12, 2010 were identified at a single IBD treatment center; the standard dosing schedule for infliximab was 5 mg/kg at Weeks 0, 2, and 6. Patients were classified as responders (patients who responded to infliximab after 3 infusions; N=87), primary nonresponders (patients who did not respond after 3 infusions; N=25), or secondary nonresponders (patients who responded to initial therapy but lost response during the maintenance period; N=36).

There were few differences in gender among responders (56% female vs 44% male) and primary nonresponders (44% female vs 56% male); however, secondary nonresponders were mostly female (72% female vs 28% male). Patients in the primary nonresponder group were more likely to have fibrostenotic disease than those in the responder or secondary nonresponder groups (68% vs 38% and 53%, respectively). Smoking was more prevalent among primary and secondary nonresponders compared to responders (36% and 28% vs 23%, respectively), but narcotic use was similar in all 3 groups (12%, 11%, and 12%, respectively). More primary nonresponders had disease restricted to the small bowel compared to responders and secondary nonresponders (40% vs 26% and 25%, respectively), while responders had a higher likelihood of disease restricted to the colon compared to primary and secondary nonresponders (26% vs 12% and 17%, respectively). Although this study was limited by its lack of statistical analysis, the investigators concluded that several characteristics may be predictive of primary nonresponse to infliximab: smoking, fibrostenotic disease, and localization of disease to the small bowel only.

Presentations in Endoscopy

Colonoscopy Using a Water-Infusion Method Improves Adenoma Detection Rate in the Proximal Colon

Despite the importance of screening colonoscopy for the overall prevention of colorectal cancer, several reports have shown that traditional colonoscopy fails to reduce the incidence and mortality of colorectal cancer arising in the proximal colon. In an abstract presented at the 2010 ACG meeting, Dr. Felix Leung and colleagues presented an analysis of 2 randomized controlled trials that evaluated whether a water infusion method could increase the adenoma detection rate in the proximal colon. The water method is performed by turning off the air pump prior to insertion of the colonoscope; first, residual air is suctioned, then warm water is infused and residual fecal matter is aspirated, and, finally, additional clean warm water is infused.

Leung and colleagues found that the water method achieved a significantly higher adenoma detection rate in the proximal colon than the air method traditionally used for screening colonoscopy (29% vs 14%; $P=.0196$). A higher overall adenoma detection rate was also observed with the water method compared to the air method, but these results did not achieve statistical significance (38% vs 28%).

Given these findings, the water method may allow improved adenoma detection in difficult-to-assess areas such as the proximal colon. However, the investigators note that the water method is awkward and cumbersome. Thus, future study is needed to determine whether the water method can improve screening colonoscopy and reduce the rate of colorectal cancer and its associated mortality.

Right Colon Retroflexion Improves Detection of Polyps in the Proximal Colon

Another study that focused on improving the miss rate of small adenomas in the proximal colon was presented by Dr. Douglas Rex and colleagues at the 2010 ACG meeting. In this study, retroflexion of the proximal colon was prospectively assessed for its ability to reduce the miss rate of lesions located on the proximal side of folds and flexures.

A total of 1,000 patients undergoing colonoscopy were included in this study (median age=59 years, range 16–90 years). Patients first underwent standard

colonoscopy, during which primary inspection for polyps occurred upon withdrawal. All visualized polyps were removed. After initial clearing of the proximal colon, the cecum was reintubated and retroflexion was performed, with instrument withdrawal to the hepatic flexure. Polyps were again removed.

The retroflexion procedure was successfully performed in 94.5% of patients (98.4% with an adult colonoscope and 88.1% with a pediatric colonoscope). Polyps obtained during standard and retroflexion procedures were sent for separate histologic analyses. In the majority of cases in which the retroflexion procedure was not successful, failure was due to a loop in the instrument. Patients in whom the retroflexion procedure failed were statistically more likely to be female ($P=.002$) and older ($P=.03$).

Initial forward examination of the cecum and ascending colon found 500 polyps in 287 patients (29%). However, an additional 68 polyps in 58 patients were revealed upon retroflexion. The median size of polyps identified during forward versus retroflexion examination was similar (4 mm). Of the 68 polyps identified using retroflexion, 55 were adenomas (1–25 mm) and 10 were hyperplastic/serrated lesions (2–15 mm). Of the 58 patients in whom polyps were identified during the retroflexion examination, 41% had been found to be negative during the forward examination. For forward-only inspection, the polyp miss rate was 13.6%. After adjusting for age, sex, and indication, patients in whom a polyp was identified on forward examination were 3 times more likely to have a polyp identified during the retroflexion examination (OR 3.0; 95% CI: 1.7–5.2; $P<.001$). Both age ($P=.02$) and gender ($P=.01$) were significantly predictive of polyp detection during the retroflexion examination following a negative forward examination.

Video Capsule Endoscopy in Patients with Obscure Gastrointestinal Bleeding

Video capsule endoscopy is a standard method for imaging the small bowel and is commonly used to investigate cases of obscure gastrointestinal bleeding. In an abstract presented at the 2010 ACG meeting, Dr. Dhavan Parikh and colleagues compared the outcomes of video capsule endoscopy in patients treated with chronic anticoagulation therapy versus patients not on chronic anticoagulation therapy.

A retrospective screening of consecutive patients who underwent video capsule endoscopy at a single institution was performed (N=250, age >40 years); of these 250 cases, only patients referred for obscure gastrointestinal bleeding (N=150) were included in this analysis. Of this subset, 33% of patients were on chronic anticoagulation therapy (including warfarin, clopidogrel, 81 mg aspirin, or 325 mg aspirin) and 67% of patients were not receiving anticoagulation therapy. A similar proportion of patients in the on- and off-treatment groups had an incomplete video capsule endoscopy (16% and 15%, respectively).

Patients receiving chronic anticoagulation therapy achieved a significantly higher diagnostic yield with video capsule endoscopy compared to patients who were not receiving chronic therapy (42% vs 24%; $P=.04$; OR 2.34; 95% CI: 1.12–4.90). In addition, patients in the chronically treated group were 2.5 times more likely to have angioectasias identified as a result of the procedure (22% vs 9%; $P=.04$). However, the ability of video capsule endoscopy to guide further clinical interventions was similar in both the anticoagulant-treated and untreated groups (36% vs 26%; $P=.25$). There was no difference between the 2 treatment groups in terms of either gastric transit time or transit time through the small bowel.

Pancreatic Duct Stenting for Management of Smoldering Pancreatitis

Smoldering pancreatitis occurs when patients have persistent (>10 days) acute pancreatic inflammation. In an abstract presented at the 2010 ACG meeting, Dr. Haq Nawaz and colleagues described their experience in managing smoldering pancreatitis using pancreatic rest combined with total parenteral nutrition (TPN) or nasojejunal (NJ) tube insertion and pancreatic duct stenting.

In this study, 15 patients with smoldering pancreatitis (mean age=40.4 years, range 12–73 years) were retrospectively identified from a single institution's endoscopic records from 2005 to 2009. Smoldering pancreatitis was determined to be idiopathic in origin in approximately half of the cases (N=8). Of the 15 patients included in this study, 5 patients had a sentinel attack and the remaining 10 patients had a history of recurrent acute pancreatitis. The mean duration of symptoms prior to endoscopic retrograde cholangiopancreatography (ERCP) was longer for patients with recurrent versus sentinel pancreatitis (81 days vs 63 days).

All patients had a discrete episode of acute pancreatitis followed by symptoms of smoldering pancreatitis that persisted for more than 10 days beyond the onset of acute pancreatitis. Smoldering pancreatitis was diagnosed in patients with all of the following signs and symptoms:

abdominal pain requiring daily narcotics, food intolerance associated with weight loss, persistently elevated levels of serum amylase and lipase, and ongoing pancreatic inflammation revealed by computed tomography (CT) scan. Patients with large fluid collections (>5 cm), evidence of pancreatic duct disruptions, pancreatic necrosis, multi-organ failure, and chronic pancreatitis were excluded from the study.

Patients were followed for a mean of 46.5 weeks (range 9–104 weeks). Either TPN or NJ tube insertion was initially performed in 9 patients for a mean duration of 36 days; the mean duration of symptoms prior to either intervention was 22 days. All 15 patients underwent ERCP with insertion of a pancreatic duct stent; 8 patients also underwent a pancreatic sphincterotomy. Pancreatic duct stents remained in place for a median of 25 days (range 1–56 days). Patients with a sentinel attack were more likely than those with a recurrent attack to experience both short-term symptom resolution (80% vs 60%, respectively) and long-term symptom resolution (80% vs 50%, respectively). Over half (60%) of the patients experienced long-term symptom resolution, and no complications of ERCP were reported.

Endoscopic Necrosectomy with Self-Expandable Metal Stent Drainage for Treatment of Walled-Off Pancreatic Necrosis

In another abstract from the 2010 ACG meeting, Dr. Elliot Joo and colleagues reported on a new minimally invasive technique for the treatment of pancreatic necrosis. This new procedure, endoscopic necrosectomy with self-expandable metal stent (SEMS) drainage, was performed in 4 patients (mean age=55 years) with walled-off pancreatic necrosis, either sterile (N=3) or infected (N=1). Patients first underwent cyst-gastrostomy with a SEMS, after which they underwent endoscopic necrosectomy. The walled-off pancreatic necrosis was punctured and a guidewire was advanced under direct visualization. After tract dilation, a fully covered or uncovered SEMS was deployed across the tract and used to aggressively irrigate the necrotic area. Following drainage, the SEMS was removed with a gastroscope, and a CRE balloon (Boston Scientific) was used to dilate the tract. The gastroscope was then used to debride the necroma. Plastic stents or nasobiliary drains were left in place at the conclusion of the procedure. Endoscopic necrosectomy was repeated at the discretion of the endoscopist.

A total of 11 endoscopic necrosectomies were performed in these 4 patients, with the goal being to debride the walls of the necroma until pink granulation tissue was uncovered. The average time from the onset of acute pancreatitis to cyst-gastrostomy was 108 days

(range 24–237 days). The mean size of the walled-off pancreatic necrosis prior to cyst-gastrostomy with SEMs was 13.9 cm.

The initial endoscopic necrosectomy procedure was performed a mean of 26 days (range 10–46 days) following the cyst-gastrostomy with SEMs. All 4 patients achieved a significant improvement in symptoms: complete resolution in 2 patients, near-complete resolution in 1 patient, and partial resolution in 1 patient. Several complications arising from the endoscopic necrosectomy procedure were reported, including prolonged procedure time (N=4), fever (N=1), tachycardia (N=1), and persistent leukocytosis (N=1), but there were no deaths.

Insertion Depth During Double-Balloon Enteroscopy Is Linked to Postprocedure Pancreatitis

Acute pancreatitis is a significant adverse event known to occur in 0.3% of patients following double-balloon enteroscopy. To investigate factors that may influence this complication, Dr. Robert Basseri and colleagues analyzed the incidence and occurrence of acute pancreatitis following double-balloon enteroscopy procedures performed at a single institution. Their results were presented at the 2010 ACG meeting.

In this retrospective analysis, all double-balloon enteroscopy procedures performed at a single institution between 2004 and 2010 were evaluated (N=1,030 procedures in 930 patients; N=691 oral examinations in 600 patients). All procedures were performed by 5 physicians with similar training who were experienced in double-balloon enteroscopy. Both the time of the procedure and the depth of insertion were compared. In the case of oral double-balloon enteroscopy, depth of insertion was quantified using a 1–6 scale: 0=proximal jejunum, 1=mid-jejunum, 2=distal jejunum, 3=proximal ileum, 4=mid-ileum, 5=terminal ileum, and 6=cecum. Pancreatitis was diagnosed when the patient had typical abdominal pain accompanied by hyperamylasemia.

The rate of pancreatitis in all double-balloon enteroscopy procedures was 1.4% (N=14). Interestingly, all 14 pancreatitis cases occurred following oral double-balloon enteroscopy procedures (2.1% of all oral cases). Evidence of hyperamylasemia was seen in blood drawn a mean of 3.7 ± 1.0 hours following the procedure; in the 4 patients who underwent CT imaging, pancreatitis was evident a mean of 2.6 ± 0.9 hours following double-balloon enter-

oscopy. Both the time of the procedure as well as the depth of endoscope insertion differed significantly among the 5 endoscopists ($P < .0001$ and $P < .04$, respectively.) However, only the insertion depth in patients who developed pancreatitis uniformly exceeded the mean overall insertion depth.

Rates of Deep Cannulation and Complications During ERCP Are Not Influenced by Time of Day

Physician fatigue is a potential cause of lower rates of colonoscopy completion and adenoma detection, particularly when colonoscopy is performed later in the workday. Given the highly technical and operator-dependent nature of ERCP, the efficacy of this procedure may also be directly related to physician fatigue. To address this issue, Dr. Paresh Mehta and colleagues compared ERCP outcomes for procedures performed in the morning with those performed in the afternoon; these data were presented at the 2010 ACG meeting.

All ERCP procedures performed over a 2-year period by senior therapeutic endoscopists were included in this retrospective review, except for procedures performed in patients who had prior papillary interventions (ie, a papillotomy or a stent placement). Overall, a total of 296 patients were included in the analysis (mean age=59.1 years). Of these patients, 38.5% underwent AM procedures (prior to 12 PM) and 61.5% underwent PM procedures (after 12 PM). Nearly half (47.0%) of the patients were male.

The overall success rate of deep cannulation was 95.3%, and no difference was observed for AM versus PM procedures (98.3% vs 94.0%; 95% CI: -0.9 to 8.9 ; $P = .08$). Similarly, the rate of complications associated with ERCP (including pancreatitis, cholangitis, hemorrhage, perforation, or death) showed no difference between the morning and afternoon procedures (8.8% vs 7.1%; $P = .61$). A precut was required in 23.7% of AM procedures and 29.1% of PM procedures ($P = .31$), and moderate sedation was required in 41.2% and 50.0% of cases, respectively ($P = .14$). There was no difference in the proportion of procedures in which trainees were involved (49.1% vs 42.3%; $P = .25$). Based on these results, the investigators concluded that the time of day did not significantly affect the success of ERCP, nor did it have an effect on the occurrence of complications associated with the procedure.

SUPREP® BOWEL PREP KIT

(sodium sulfate, potassium
sulfate and magnesium sulfate)

Oral Solution

(17.5g/3.13g/1.6g) per 6 ounces

The bowel prep, reinvented

Low volume and ACG-recommended split-dose regimen



References: 1. DiPalma JA, Rodriguez R, McGowan J, Cleveland MvB. A randomized clinical study evaluating the safety and efficacy of a new, reduced-volume, oral sulfate colon-cleansing preparation for colonoscopy. *Am J Gastroenterol.* 2009;104:2275-2284. 2. SUPREP Bowel Prep Kit [package insert]. Braintree, MA: Braintree Laboratories, Inc; 2010.

BRIEF SUMMARY: Before prescribing, please see full Prescribing Information and Medication Guide for SUPREP® Bowel Prep Kit. **INDICATIONS AND USAGE:** An osmotic laxative indicated for cleansing of the colon as a preparation for colonoscopy in adults. **CONTRAINDICATIONS:** Use is contraindicated in the following conditions: gastrointestinal (GI) obstruction, bowel perforation, toxic colitis and toxic megacolon, gastric retention, ileus, known allergies to components of the kit. **WARNINGS AND PRECAUTIONS:** SUPREP Bowel Prep Kit is an osmotic laxative indicated for cleansing of the colon as a preparation for colonoscopy in adults. Use is contraindicated in the following conditions: gastrointestinal (GI) obstruction, bowel perforation, toxic colitis and toxic megacolon, gastric retention, ileus, known allergies to components of the kit. Use caution when prescribing for patients with a history of seizures, arrhythmias, impaired gag reflex, regurgitation or aspiration, severe active ulcerative colitis, impaired renal function or patients taking medications that may affect renal function or electrolytes. Pre-dose and post-colonoscopy ECG's should be considered in patients at increased risk of serious cardiac arrhythmias. Use can cause temporary elevations in uric acid. Uric acid fluctuations in patients with gout may precipitate an acute flare. Administration of osmotic laxative products may produce mucosal aphthous ulcerations, and there have been reports of more serious cases of ischemic colitis requiring hospitalization. Patients with impaired water handling who experience severe vomiting should be closely monitored including measurement of electrolytes. Advise all patients to hydrate adequately before, during, and after use. Each bottle must be diluted with water to a final volume of 16 ounces and ingestion of additional water as recommended is important to patient tolerance. **Pregnancy:** Pregnancy Category C. Animal reproduction studies have not been conducted. It is not known whether this product can cause fetal harm or can affect reproductive capacity. **Pediatric Use:** Safety and effectiveness in pediatric patients has not been established. **Geriatric Use:** Of the 375 patients who took SUPREP Bowel Prep Kit in clinical trials, 94 (25%) were 65 years of age or older, while 25 (7%) were 75 years of age or older. No overall differences in safety or effectiveness of SUPREP Bowel Prep Kit administered as a split-dose (2-day) regimen were observed between geriatric patients and younger patients. **DRUG INTERACTIONS:** Oral medication administered within one hour of the start of administration of SUPREP may not be absorbed completely. **ADVERSE REACTIONS:** Most common adverse reactions (>2%) are overall discomfort, abdominal distention, abdominal pain, nausea, vomiting and headache. **Oral Administration: Split-Dose (Two-Day) Regimen: Early in the evening prior to the colonoscopy:** Pour the contents of one bottle of SUPREP Bowel Prep Kit into the mixing container provided. Fill the container with water to the 16 ounce fill line, and drink the entire amount. Drink two additional containers filled to the 16 ounce line with water over the next hour. Consume only a light breakfast or have only clear liquids on the day before colonoscopy. **Day of Colonoscopy (10 to 12 hours after the evening dose):** Pour the contents of the second SUPREP Bowel Prep Kit into the mixing container provided. Fill the container with water to the 16 ounce fill line, and drink the entire amount. Drink two additional containers filled to the 16 ounce line with water over the next hour. Complete all SUPREP Bowel Prep Kit and required water at least one hour prior to colonoscopy. Consume only clear liquids until after the colonoscopy. **STORAGE:** Store at 20°-25°C (68°-77°F). Excursions permitted between 15°-30°C (59°-86°F). **Rx only.** Distributed by Braintree Laboratories, Inc. Braintree, MA 02185

For additional information, please call 1-800-874-6756 or visit www.suprekit.com

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SUPREP The bowel prep, reinvented

- Effective bowel cleansing^{1,2}
- No sodium phosphate
- Low volume
- ACG-recommended split-dose regimen



Important Safety Information

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Please see brief summary of Prescribing Information on adjacent page.

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