

# The Best in the News on HCV, HBV and HIV/HCV Coinfection from October 15th 2002 thru November 15th 2002

Alan Franciscus  
Editor-in-Chief



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October 16<sup>th</sup>, 2002

## **FDA Approves Pegasys<sup>®</sup> (peginterferon alfa-2a) For the Treatment of Hepatitis C. Roche sample program to provide first 12 weeks of Pegasys at no cost for up to 15,000 patients**

Roche announced today that the U.S. Food and Drug Administration (FDA) has approved Pegasys<sup>®</sup> (peginterferon alfa-2a) for the treatment of adults with chronic hepatitis C who have compensated liver disease and have not previously been treated with interferon alpha. Patients in whom efficacy was demonstrated included patients with compensated cirrhosis.

Pegasys is a pegylated interferon that remains active in the bloodstream longer and at a more constant level than interferon alpha. Currently, 2.7 million Americans are chronically infected with hepatitis C.

“The approval of Pegasys is an important milestone for the hepatitis C patients in the United States who are waiting for treatment,” said George B. Abercrombie, President and Chief Executive Officer, Hoffmann-La Roche Inc. “Roche has supported Pegasys with the most extensive development program ever undertaken for a hepatitis C treatment. The result is that patients and physicians have an important new option for treatment.”

Pegasys was granted approval based on the results of three pivotal Phase III clinical trials that demonstrated it is an effective treatment for patients with chronic hepatitis C, including cirrhotic patients with compensated liver disease, versus treatment with Roferon-A<sup>®</sup> (interferon alfa-2a). Two of these pivotal trials were published in *The New England Journal of Medicine*.

The sustained virological response rate in the Pegasys treated patients was as high as 38 percent in the overall population versus 19 percent in the interferon alfa-2a group. The sustained virological response in patients with cirrhosis treated with Pegasys was as high as 30 percent versus 8 percent in the interferon alfa-2a group. Higher sustained virological response results were also found in patients with genotype 1, on Pegasys treatment (23 percent) versus interferon alfa-2a (6 percent), the most common type in the U.S. and most difficult to treat. Sustained virological response was defined as undetectable serum hepatitis C RNA levels post-treatment (on or after study week 68).

Clinical trials of Pegasys have shown that patients can determine at 12 weeks if they are unlikely to attain a sustained virological response with Pegasys.

Pegasys investigator, Donald Jensen, MD, director of Hepatology at Rush-Presbyterian-St. Luke's Medical Center, Chicago said, “With Pegasys, we can determine at week 12 of therapy those patients who are unlikely to achieve a sustained virological response to treatment. This reduces the cost and burden of taking therapy for patients who are unlikely to respond to therapy. This may help patients adhere to therapy that can be difficult on them, particularly during the first few months.”

### **12-Week Sample Program for Up to 15,000 Patients**

*As part of Roche's commitment to treating patients with hepatitis C, Roche will be providing physicians with samples of Pegasys for the first 12 weeks of therapy. These samples will be provided at the request of a physician for the first 15,000 patients who are started on Pegasys therapy prior to December 31, 2002. Twelve weeks was selected because at that point physicians can predict those patients who will not respond to Pegasys therapy. Samples are available to all physicians. Pegasys, available as a premixed solution, is expected to be in pharmacies within two weeks. Pegasys is dosed at 180 µg as a subcutaneous injection once a week for a recommended duration of 48 weeks.*

Pegasys is supported by the most extensive development program ever undertaken for a hepatitis C treatment. The FDA has granted Pegasys in combination with Copegus<sup>®</sup> (Roche ribavirin) priority review

status, and a decision is expected by the end of 2002. The FDA grants priority review status to products that, if approved, are expected to offer a significant improvement over existing therapies in the safety or effectiveness of the treatment, diagnosis or prevention of a serious or life-threatening disease.

### **About Pegasys**

*Pegasys has been studied in a variety of patient populations, including those with the most difficult to treat form of the disease – patients with genotype 1 and with cirrhosis (scarring of the liver).*

*Pegasys is made when interferon alfa-2a undergoes the process of pegylation in which one or more chains of polyethylene glycol, also known as PEG, are attached to another molecule.*

*In Pegasys, a large, branched, mobile PEG is bound to the interferon alfa-2a molecule and provides a selectively protective barrier. Pharmacokinetic behavior of the end product depends on the length of the PEG and the nature of the link between the PEG and the protein. The high molecular weight (40 kilodalton) branched PEG in Pegasys has been shown to provide sustained pegylated interferon alfa-2a exposure at clinically effective levels over the one-week dosing period.*

*In contrast, interferons with smaller PEGs are excreted more rapidly by the kidneys, requiring more frequent dosing, according to earlier Roche studies, using smaller PEGs developed by the company.*

*Pegasys has been approved for use in 50 countries, including all European Union countries.*

### **Pegasys Adverse Events**

*Alpha interferons, including Pegasys, may cause or aggravate fatal or life-threatening neuropsychiatric, autoimmune, ischemic, and infectious disorders. Patients should be monitored closely with periodic clinical and laboratory evaluations. Patients with persistently severe or worsening signs or symptoms of these conditions should be withdrawn from therapy. In many, but not all cases, these disorders resolve after stopping Pegasys therapy.*

*Pegasys is contraindicated in patients with hypersensitivity to Pegasys or any of its components, autoimmune hepatitis, and decompensated hepatic disease prior to or during treatment with Pegasys. Pegasys is also contraindicated in neonates and infants because it contains benzyl alcohol. Benzyl alcohol has been reported to be associated with an increased incidence of neurological and other complications in neonates and infants which are sometimes fatal.*

*The most common adverse events reported for Pegasys, observed in clinical studies to date, were headache, fatigue, myalgia, pyrexia, rigors, arthralgia, nausea, alopecia, injection-site reaction, neutropenia, insomnia, depression, anorexia, and irritability.*

*Other serious adverse events include bone marrow toxicity, cardiovascular disorders, hypersensitivity, endocrine disorders, pulmonary disorders, colitis, pancreatitis, and ophthalmologic disorders.*

### **About Hepatitis C**

*Hepatitis C, a blood-borne infectious disease of the liver, the leading cause of cirrhosis and liver cancer and the number one reason for liver transplants in the U.S., is transmitted through body fluids, primarily blood or blood products, and by sharing needles. In many patients, the mode of transmission is unknown. Unfortunately, most people infected with hepatitis C are unaware of it because it may take years for symptoms to develop. Hepatitis C chronically infects an estimated 170 million people worldwide (three percent of the world's population), with as many as 180,000 new cases occurring each year. It is estimated that less than 30 percent of all cases are diagnosed. If left untreated, hepatitis C can be fatal for some patients.*

### **About Roche**

*Hoffmann-La Roche Inc. (Roche), based in Nutley, N.J., is the U.S. prescription drug unit of the Roche Group, a leading research-based health care enterprise that ranks among the world's leaders in pharmaceuticals, diagnostics and vitamins. Roche discovers, develops, manufactures and markets numerous important prescription drugs that enhance people's health, well-being and quality of life. Among the company's areas of therapeutic interest are: dermatology; genitourinary disease; infectious diseases, including influenza; inflammation, including arthritis and osteoporosis; metabolic diseases, including obesity and diabetes; neurology; oncology; transplantation; vascular diseases; and virology, including HIV/AIDS and hepatitis C.*

October 21<sup>st</sup>, 2002

## **THE-PINK-SHEET: Roche Pegasys Has \$291 WAC; Launch Includes 12 Weeks of Free Samples**

Roche's Pegasys has a wholesale acquisition cost of \$291 for one week of the hepatitis C therapy.

FDA approved Pegasys (peginterferon alfa-2a) Oct. 16 for the treatment of adults with chronic hepatitis C who have compensated liver disease and have not previously been treated with interferon alpha.

Roche expects Pegasys to be available in pharmacies within two weeks at a comparable price to Schering-Plough's PEG-Intron (peginterferon alfa-2b).

Peg-Intron is available in four different vial sizes with an average wholesale price ranging from \$309.20 to \$357.95. PEG-Intron is used in combination with Rebetol (ribavirin). The average total cost of the combination therapy is \$25,000 annually, Schering said.

Roche expects to have a sufficient supply of Pegasys to meet demand.

Schering is now meeting patient demand for its product as well. The company has increased production capacity at its Brinny, Ireland facility and cleared its patient waiting list for PEG-Intron/Rebetol in September. The patient registry program was put in place in January due to strong demand ("The Pink Sheet" Jan. 28, p. 32).

Pegasys monotherapy is being launched before approval of the combination alfa-2a/ribavirin product. The application for Pegasys combination therapy with ribavirin is pending and will be reviewed by FDA's Antiviral Drugs Advisory Committee Nov. 14 ("The Pink Sheet" Oct. 7, In Brief). Roche's ribavirin will be sold under the name Copegus.

Roche expects approval of the Pegasys/ribavirin combo by the end of the year. Ribapharm, which owns patents on ribavirin capsules, filed a patent infringement suit against Roche Aug. 26 in Los Angeles federal court. Roche said the lawsuit will not keep the combination off the market.

The company anticipates that the monotherapy launch will help prepare the market for the combo therapy ("The Pink Sheet" Aug. 19, p. 7).

A Pegasys sampling program will provide the product for 12 weeks free of charge for up to 15,000 patients.

Under the program, physicians can request samples of Pegasys by registering their patients with specialty pharmacy and distribution company Priority Healthcare.

"Samples will be provided at the request of a physician for the first 15,000 patients who are started on Pegasys therapy prior to Dec. 31, 2002," Roche said.

Roche will provide Pegasys to Priority Healthcare, which will distribute the drug to physicians. Roche says it will not have access to any patient information.

The 12-week duration for the sample program was selected because at 12 weeks, physicians can predict whether a patient will respond to Pegasys therapy, Roche said.

In clinical studies, "of patients who did not demonstrate by 12 weeks of Pegasys 180 mcg therapy, either

undetectable HCV RNA or at least a 2-log drop in HCV RNA titer from baseline, 2% (3/156) achieved a sustained virological response" with continued therapy, labeling states.

Approval for Pegasys was based on the results from three Phase III open-label, active-controlled trials in 1,425 patients. In the first two studies, 20% of patients had cirrhosis or transition to cirrhosis and the third study enrolled patients with a histological diagnosis of cirrhosis or transition to cirrhosis.

"In all three studies, treatment with Pegasys 180 mcg resulted in significantly more responding patients compared to treatment with [Roche's] Roferon-A" (interferon alfa-2a), labeling states.

The sustained virologic response at week 72 for Pegasys in the first study was 23% compared to 9% for Roferon-A. The response rate for Pegasys was 31% in the second study and 28% in the third study.

"Averaged over study 1, study 2, and study 3, response rates to Pegasys were 23% among patients with viral genotype 1 and 48% in patients with other viral genotypes," labeling states.

The labeled indication states that "patients in whom efficacy was demonstrated included patients with compensated cirrhosis."

The recommended dose for Pegasys is 180 mcg once weekly for 48 weeks by subcutaneous administration in the abdomen or thigh.

Pegasys was approved with fixed dosing, as opposed to the weight-based dosing for Schering's PEG-Intron.

PEG-Intron was approved in August 2001 at a recommended dose of 1.5 mcg/kg once weekly in conjunction with Rebetol capsules dosed at 800 mg/day for one year ("The Pink Sheet" Aug. 20, 2001, p. 24). PEG-Intron was approved in January 2001 as monotherapy.

Pegasys is available as a pre-mixed solution for subcutaneous injection. PEG-Intron must be reconstituted with the supplied diluent prior to use.

The most common adverse events in clinical trials for Pegasys compared to Roferon-A were psychiatric reactions, including depression (18% Pegasys vs. 19% Roferon-A), irritability (13% vs. 17%), anxiety (6% vs. 5%), and flu-like symptoms, such as fatigue (50% vs. 50%), pyrexia (36% vs. 41%), myalgia (37% vs. 38%), headache (54% vs. 58%) and rigors (32% vs. 42%).

"The most common reason for dose modification or withdrawal from studies was hematologic abnormalities," labeling says.

Roche will submit data to FDA on three ongoing studies and a new study as part of its postmarketing commitments.

The final report on a trial evaluating the safety and pharmacokinetics of peginterferon alfa-2a in pediatric patients aged two to eight is due to the agency by September 2003. Roche is also comparing Pegasys in African-American and Caucasian genotype 1 patients; the study report is due March 2003.

Roche will submit data on an ongoing study to evaluate the pharmacokinetics and pharmacodynamics of Pegasys in patients receiving methadone.

Roche will also submit a protocol to FDA by February 2003 to evaluate immunogenicity screening assays for detecting binding and neutralizing antibodies using Pegasys as the target molecule. The Phase IV trial will enroll 300 patients. An interim report will be submitted in May 2004 and the final report is due by August 2004.

The Pegasys BLA (1039640) was filed May 22, 2000; FDA sent a "complete response" letter April 10, 2001.

## Peg-interferon price war in the US?

The US approval of Roche's pegylated alpha-interferon product, Pegasys (peginterferon alfa-2a), for chronic hepatitis C could trigger an interferon price war with Schering-Plough, analysts suggest.

Roche is trying to compensate for Pegasys's much later arrival on the US market than Schering-Plough's rival product, PegINTRON (peginterferon alfa-2b), by providing the first three months of therapy free to the first 15,000 patients. This, Bernstein Research analysts say, amounts to a discount which Schering-Plough cannot afford to ignore.

Launch of Pegasys through this free-sample program and prescriptions is due in the next few weeks. It will be priced comparably with the Schering-Plough product, with a wholesale acquisition cost of \$291 for one week's monotherapy. This lies between the prices of the two most commonly prescribed vial sizes for PegINTRON.

Pegasys - which has been given the go-ahead for use as a monotherapy in patients with compensated liver disease who have not previously been treated with alpha-interferon - is already approved in more than 50 markets. However it was held up in the US after modifications were made to the manufacturing process to scale up production capacity and the FDA required data on the process change.

This has given Schering-Plough a significant head start for PegINTRON, which has been available in the US since early 2001 as a monotherapy, and was approved for use in combination with Rebetol (ribavirin; licensed from ICN) in August that year (Scrip No 2668, p 20). Combination therapy with either pegylated interferon plus the antiviral has become the standard of care in hepatitis C.

Approval for use of Pegasys in combination with ribavirin (Roche's version, Copegus), is not expected in the US until the end of the year. But in the meantime, there is nothing to prevent US doctors from prescribing the product as they see fit and Roche is providing samples of Pegasys for the first 12 weeks of therapy for the first 15,000 patients started on Pegasys therapy before December 31st.

Bernstein analyst Richard Evans says this is effectively a discount of 25% over the one-year treatment course and that Roche's claim that it will end next year "sounds more innocent than it really is. If it is worth 25% of sales to buy share, it's worth 25% to defend share," he commented, and he expects Schering-Plough to respond with a similar type of offer. "Schering-Plough can't afford to let this move work," he said.

Despite the significant hurdles of its later arrival onto the US market, Pegasys is seen as a superior product. No head-to-head data have been reported, but Pegasys has the advantage of fewer injection site reactions and seems to have a better side-effect profile, particularly in depression. It also has simpler standard dosing (rather than being dose by weight as with PegINTRON).

Mr. Evans says that given its inferior marketing machine in the US, Roche has to act on price, and as these therapies are expensive, payers will approach Schering-Plough and ask what it will do to compensate. "Faced with a product which is marginally superior, Schering-Plough has little choice but to cut."

This scenario is made more likely by the fact that in any ensuing price war, Schering-Plough will have the upper hand, at least to begin with. Until (and if) Roche gets approval for its version of ribavirin (which is the subject of patent disputes), Pegasys will have to be prescribed alongside Schering-Plough's ribavirin product, Rebetol (licensed from ICN). Since ribavirin accounts for 52% of the total combination cost, Schering-Plough can meet Roche's cost of therapy by lowering its combined price by just 12%, Mr. Evans points out. This will give Schering-Plough more room to maneuver.

Schering-Plough will not comment on questions concerning its marketing and pricing strategies and so had no statement to make on the speculation. The company simply stressed that PegINTRON has been on the market in the US for more than one year and that the combination was "well established". COPYRIGHT 2002

## **Merck Gave Up Schering-Plough Buyout Offer**

**By Peter Landers**

A newly disclosed agreement reveals that Merck & Co. has given up the right to make a buyout offer for Schering-Plough Corp., the drug maker that has been the subject of speculation about a possible merger or acquisition. The agreement also says Merck can take full control of Schering-Plough's most promising drug if a third company buys Schering-Plough, which seems to reduce the chance that any third company would make a buyout offer.

The disclosures come in an agreement dated May 22, 2000, and filed by the two companies with the Securities and Exchange Commission last week. The SEC made the document public yesterday.

The agreement fills in the background of a deal that Schering-Plough, Kenilworth, N.J., and Merck, Whitehouse Station, N.J., announced in May 2000. That deal created a joint venture to cooperate in developing and marketing a new anticholesterol drug called Zetia. The two companies say the combination of Zetia and one of the popular anticholesterol drugs known as statins could someday become the standard treatment for high cholesterol. If so Zetia's sales could be several billion dollars a year or more.

The companies have filed for approval of Zetia with the Food and Drug Administration, and the FDA is expected to decide by the end of this year.

Given the importance of Zetia, observers have long wondered what side agreements Merck and Schering-Plough might have made in forming their alliance. The new disclosure mostly answers that question. In the document, Merck promises that it won't try to buy Schering-Plough "unless specifically requested in writing in advance by the board of directors." The only other exception comes if the Schering-Plough board entertains offers from a third company, in which case Merck has the right to make an offer of its own.

Should a third company end up buying Schering-Plough, Merck also included a protection clause in the agreement giving Merck the right to buy out Schering-Plough's half of the Zetia joint venture. The price would be determined by two investment banks without ties to the companies.

The upshot of the agreement is that a takeover of Schering-Plough seems less likely than some had speculated. Merck is forbidden from making the first move, and if another big pharmaceutical company wanted to buy Schering-Plough it would probably lose control to Merck of Schering-Plough's best hope for future profits. However, Barbara Ryan, an analyst at Deutsche Securities, said a third company might still be interested in Schering-Plough's other drugs and its consumer lineup including Dr. Scholl's foot-care products.

*October 23<sup>rd</sup>, 2002*

## **Virus Weekly: New combination treatment reported more beneficial than standard therapy**

The *New England Journal of Medicine* (2002;347(13):975-982) carried the first published report showing that a combination treatment with peginterferon alfa-2a (Pegasys) - a new long-acting interferon drug - and antiviral medication is more beneficial than the standard combination therapy for people with the most-difficult-to-treat and most common strain of hepatitis C.

The large international study, headed by researchers at the University of North Carolina at Chapel Hill, is also the first published one to show that treatment with the investigational drug peginterferon alfa-2a in combination with the oral antiviral medication, ribavirin, is linked to a lower rate of troublesome side effects - such as depression and flu-like symptoms (chills, headache and fever) - than the standard interferon (Rebetron) and ribavirin.

"Sixty-five percent of patients in the study were infected with hepatitis C genotype 1, the most prevalent genotype we see here in the United States, and typically the least responsive to therapy," said study coauthor Dr. Michael W. Fried, associate professor of medicine and director of clinical hepatology at the UNC School of Medicine.

"With this research, we've found the most significant evidence to date suggesting these patients might benefit by taking peginterferon alfa-2a in combination with ribavirin." According to Fried, side effects of therapy can be very challenging for patients. "The study shows an approach that can offer patients superior efficacy without increases in some of the most common and difficult-to-tolerate adverse events associated with hepatitis C therapy."

Of the six strains, or genotypes, of hepatitis C, approximately 70% of people in North America are infected with genotype 1.

The study was funded by Hoffmann-La Roche, the maker of Pegasys, and was conducted at 81 clinical sites in 18 countries. More than 1100 patients were involved in 1 of 3 study arms: 453 were treated with peginterferon alfa-2a plus oral ribavirin, 224 with peginterferon alfa-2a plus placebo and 444 with interferon alfa-2b plus ribavirin. Patients were treated for 48 weeks and then monitored for an additional 24 weeks.

A key variable measured by the study was sustained viral response, defined as undetectable serum hepatitis C RNA after the treatment-free follow-up period.

Overall, patients treated with the peginterferon alfa-2a plus ribavirin combination achieved a 56% sustained response rate as compared with patients taking Rebetron (44%). Patients with genotype 1 had a sustained response rate of 46%, compared with patients on Rebetron (36%) and those on Pegasys plus placebo (21%).

A retrospective analysis of the data showed that response to PEG interferon alpha-2a plus ribavirin is predictable. At week 12, 86% of patients treated with PEG interferon demonstrated an early viral response; of these, 65% attained a sustained viral response. However, 97% of patients who did not respond by week 12 failed to achieve a sustained response.

"This means that physicians can create an alternate treatment plan for patients who do not show any response by week 12," said Fried. "And for those who do respond, it can be a motivation to continue to adhere to their treatment regimens."

Fried added that these treatment decisions must be individualized for each patient.

While many patients with the hepatitis C virus will not develop complications from their liver disease, chronic hepatitis C is still a leading cause of cirrhosis and liver cancer and is the major indication for liver transplants in this country.

This article was prepared by Virus Weekly editors from staff and other reports.

*October 24<sup>th</sup>, 2002*

## **Higher costs, sales slump cut Schering-Plough profits**

**By Linda A. Johnson**

Drug maker Schering-Plough Corp. said third-quarter profit plunged 29 percent due to higher costs for manufacturing, research and other items and nearly flat revenues as sales of its key allergy drug fell by half.

The Kenilworth-based maker of allergy, respiratory and hepatitis drugs on Thursday reported net income of

\$429 million, or 29 cents per share, for the July-September period, down from \$601 million, or 41 cents per share, a year ago.

The latest results beat by a penny a share the revised consensus forecast of analysts surveyed by Thomson First Call. Analysts had slashed their forecast twice after Schering warned it couldn't make their targets because of slumping sales of its once-a-day, non-sedating allergy drug, Claritin. Analysts initially forecast earnings of 42 cents per share, then cut back to 35 cents and finally 28 cents after the last warning on Oct. 2.

Revenues increased 2 percent to \$2.42 billion from \$2.38 billion, boosted by favorable exchange rates.

Sales of Claritin, which traditionally brought in one-third of company revenues, dropped to \$402 million from \$828 million in 2001's third quarter. That plunge was anticipated because Schering will soon launch an over-the-counter (OTC) version of Claritin and wholesalers have been reducing inventories.

Meanwhile, Clarinex, a successor drug launched in January that treats "indoor allergies" as well as seasonal allergies from pollen, had third-quarter sales of \$164 million. Schering-Plough has been advertising Clarinex heavily to induce Claritin users to switch to the new prescription drug, rather than the less-profitable OTC version.

"It's hard to predict the timing" of when nonprescription Claritin will go on sale, said Schering spokeswoman Denise Foy. The U.S. Food and Drug Administration could act on the company's marketing application in late November.

David Moskowitz, senior pharmaceuticals analyst at Friedman, Billings, Ramsey, said he was concerned that Clarinex sales fell from \$173 million in the second quarter.

"You'd start to think that the product would see traction" in the summer allergy season, he said.

Richard J. Kogan, Schering's chairman and chief executive, said he expects flat earnings per share for all of 2002. Last year, the company earned \$1.58 per share.

Kogan reiterated the company expects earnings per share between \$1 and \$1.15 for 2003, about 20 percent higher than that for 2004 and accelerated growth for 2005, due to a strengthening drug pipeline.

"I don't have a huge amount of confidence in the absolute number," analyst Steve O'Neil of Hilliard Lyons said, referring to the 2004 increase. "I think the direction is right."

Combined third-quarter sales for the Intron family of drugs - Intron A injections for certain cancers and viruses, Intron A combined with Rebetol capsules for hepatitis C, and Peg-Intron, a long-acting form of Intron A for hepatitis C - jumped 134 percent to \$703 million from \$301 million last year.

"The one improvement that impressed us was the hepatitis C franchise," Moskowitz said.

But he said competitor Roche could soon win U.S. approval for its own combination hepatitis C treatment, Copegus, and then would battle Schering-Plough for the entire market.

Kogan said the company is looking forward to getting U.S. approval to sell Zetia, a drug that inhibits cholesterol absorption developed under the company's joint venture with Merck & Co. The venture got its first drug approval, clearance to sell Zetia in Germany, on Wednesday.

"A lot of what the company is banking on (for future earnings) is the new cholesterol drug," Moskowitz said.

Schering-Plough shares rose 2.3 percent, or 43 cents a share, to close at \$19.12 in trading on the New York Stock Exchange.

Moskowitz said "given the dim prospects," it's a mystery why Schering stock is trading at an 11 percent

premium to the rest of the U.S. pharmaceutical industry, with a price-to-earnings ratio of 18.

For the first nine months, Schering-Plough's net income was down 8 percent, to \$1.66 billion or \$1.13 per share, from \$1.8 billion or \$1.22 per share, a year ago. Revenues for the first three quarters totaled \$7.81 billion, down 7 percent from \$7.3 billion in 2001.

October 30<sup>th</sup>, 2002

## Hepatitis C's Steady Response Improvements

Continuous improvement is a process more often associated with Japanese carmakers and software companies than pharmaceutical firms. But one area where stepwise improvements over a number of years are having an impact on the development of therapeutic agents is hepatitis C.

This is not a trivial disease. By 2012, it is expected that more people worldwide will be infected with hepatitis C than with HIV, underlining the importance of finding effective treatments for the infection, which in a proportion of patients progresses to liver cirrhosis and hepatocellular carcinoma. Although infection rates have declined dramatically since blood tests for the virus became available, new infections are still occurring, particularly from body piercing, tattooing and via accidents such as needlestick injuries in healthcare workers.

Schering-Plough and Roche are both developing new therapies for hepatitis C, and each has developed pegylated versions of alpha-interferon. In a recent interview with Scrip, the president of Schering-Plough International, Dr Roch Doliveux, highlighted the ability of steady improvements in hepatitis C products to translate into notable benefits for patients.

The significance of these improvements, such as Schering-Plough's recently introduced pre-filled pens for its peginterferon alfa-2b product, Peg-Intron (ViraferonPeg in the UK and France), is often overlooked by those not familiar with the therapeutic area, Dr Doliveux noted. In hepatitis C patients, where poor compliance with therapy can account for the difference between treatment success and failure, any change that may improve compliance, such as more convenient dosing forms that can be easily used at home, could have a major impact on patients' health, he pointed out.

In the early days, interferon alfa-2b (Schering-Plough's Intron A) monotherapy for hepatitis C was associated with a sustained viral response rate of only around 16%, Dr Doliveux noted. The addition of ribavirin (Rebetol), led to something of a quantum leap in efficacy, with a sustained viral response of around 41%. This was followed by the development of long-acting pegylated interferons such as peginterferon alfa-2b, which is associated with a 54% sustained viral response when used in combination with ribavirin, or up to 61% if weight-based dosing for both peginterferon alfa-2b and ribavirin is used.

A recent analysis by John McHutchison and colleagues (including Schering-Plough researchers), published in *Gastroenterology* (Vol 123, p 1,061) has shown that in compliant patients with at least an 80% adherence to therapy with weight-based peginterferon alfa-2b and weight-based ribavirin, sustained virologic response rates can be obtained in around 72% of patients. A further study (*ibid*, Vol 122, p 1,303) indicated that the progression of liver fibrosis in chronic hepatitis C can be reduced by the combination of peginterferon alfa-2b weight-based ribavirin.

Schering-Plough is continuing to work on optimizing approaches to patient compliance, drug dosing and treatment duration, and on preventing disease progression in patients who do not achieve a sustained response to interferon alfa-2b-based therapies, Dr Doliveux said. For example, it may be that low-dose peginterferon alfa-2b maintenance therapy would reduce disease progression in non-responders, Dr Doliveux speculated.

Pegintron has been available in the US since early 2001, and was approved for use in combination with Rebetol in August, while Roche's pegylated product, Pegasys (peginterferon alfa-2a), has only just been

approved for marketing in the US as a monotherapy; approval for use in combination with ribavirin is expected at the end of this year (Scrip No 2792, p 20). Both products are widely available elsewhere. SCRIP - World Pharmaceutical News FILED 30 October 2002 COPYRIGHT 2002 PJB Publications Ltd

October 31<sup>st</sup>, 2002

## **Inmates Will Get Care for Hepatitis: New Jersey Has Identified 1,170 with the Disease. Until now, such Inmates Have Not Been Treated.**

By Mark Fazlollah and Jennifer Lin

New Jersey, the only major state not currently treating prisoners for hepatitis C, announced yesterday that it would cover costs to treat the potentially deadly disease.

Ralph Siegel, a spokesman for the state Treasury Department, said that beginning tomorrow, the state would assume the costs of expensive hepatitis C treatment under a new agreement with its prison medical provider, Correctional Medical Services.

"The state will pay for medicine, test costs and any necessity for additional staff," Siegel said in announcing the agreement, which also extends CMS' contract with the state until Aug. 31.

The money for hepatitis C care will be in addition to the millions of dollars the state pays CMS for medical care. Siegel said it was unclear how much extra money the state would need to spend.

Other states are finding that it can cost from \$15,000 to \$25,000 an inmate to cover testing, monitoring and treating with the new hepatitis C medicines, according to state corrections departments.

The drugs cure about half the patients to whom they are given, with the hepatitis C virus dropping to undetectable levels and staying that way. The blood-borne virus, which attacks the liver, is the number-one cause of liver transplants.

Last July, The Inquirer reported that New Jersey's prison system was not monitoring the health of infected inmates and was repeatedly denying hepatitis C drugs to sick prisoners. One patient was being treated early this year.

In the case of one inmate, Joe Jude, prison doctors halted his medicine when he went to prison in 2000. Yesterday, a prison spokeswoman said Jude's treatment would be restarted this week.

New Jersey's current CMS contract expires today. The state had received no bids that it considered acceptable for a new contract.

CMS had asked for an increase that would have raised the cost of prison medical care 30 percent to more than \$100 million a year. But CMS said the state would have to pay extra for hepatitis C care. The state, which argued that hepatitis C should have always been covered under the medical contract, rejected the proposal.

Siegel said that under the 10-month extension agreement, CMS will receive a 14.7 percent increase.

Siegel said the new agreement will allow New Jersey to hire other companies to provide 10 medical services now covered by CMS – including dental care, vision coverage, ambulance services and lab work.

"This is a pretty significant change from the way things were being done," Siegel said.

New Jersey and other states are facing epidemic levels of hepatitis C infection among inmates. In Pennsylvania, 23 percent of inmates are infected.

New Jersey, which conducts limited testing for the virus, has identified 1,170 inmates with the disease.

Of the 10 largest states, only New Jersey is currently treating no inmates for the disease.

Deirdre Fedkenheuer, a spokeswoman for the state corrections department, said that with attention now being paid to hepatitis C, the number of inmates receiving treatment is expected to increase. "It is expected that it will mirror what happened with the HIV/AIDS crisis 15 year ago."

CMS spokesman Ken Fields said doctors would decide on a case-by-case basis who gets treated. "It's physicians who make decisions on individual treatment plans," he said.

CMS, a \$500 million-a-year company, is the nation's largest private provider of prison health care.

Cost is the biggest deterrent preventing states from addressing hepatitis C in prisons.

"It looks like doom and gloom in terms of having what we need financially to tackle this problem," said Reginald Wilkinson, director of the Ohio Department of Rehabilitation and Correction. "We need federal assistance. This is not just a prison problem."

Nationally, 20 percent to 30 percent of prisoners are infected with the blood-borne hepatitis C virus, according to state corrections officials.

More states are starting to treat hepatitis C, with Pennsylvania, Georgia, Texas and Virginia leading the way in percentage of prisoners treated.

In Georgia, the annual budget for treating hepatitis C could eventually approach \$5 million, according to Joseph Paris, the state's prison medical director. In the last three years, Georgia has initiated treatment for more than 300 inmates.

Although some states are treating prisoners, others, such as Illinois, do not even test for hepatitis C.

"That is medically less and less tenable over time," Paris said.

*November 1<sup>st</sup>, 2002*

## **Program Helps Hepatitis C Patients Comply with Interferon Therapy Regimen**

A new cognitive behavioral therapy strategy developed by Schering-Plough improves compliance among patients with hepatitis C (HCV) who are receiving the pegylated interferon-based combination therapy Peg-Intron(R) and Rebetol(R) (ribavirin), according to a Northwestern University study.

Steven L. Flamm, M.D., associate professor of medicine and of surgery at The Feinberg School of Medicine and principal investigator of the study, will present his group's findings at the 53rd annual meeting of the American Association for the Study of Liver Diseases (AASLD).

In his oral presentation, Flamm showed that HCV patients enrolled in an aggressive side-effect management program, including the Schering-Plough patient assistance program 'Be In Charge', are less likely to stop taking Peg-Intron and Rebetol combination therapy in the first 12 weeks of therapy than patients who receive only routine supportive care by their physicians.

Study results also indicated that pegylated interferon-based combination therapy significantly improves physical and mental health-related quality of life at weeks 4 and 8 of the regimen.

"The next advancement in treatment may be some years down the road. Right now we need to maximize the current standard of care to get better results for patients," Flamm said. "This study suggests that a proactive support program can actually contribute to the success of therapy and may, therefore, lead to increased cures for this often deadly infection."

'Be In Charge' is designed to assist patients in managing side effects associated with HCV therapy through the use of educational materials and telephone support by nurses. To date, the program has enrolled more than 55,000 HCV patients.

Some 4 million Americans are infected with HCV and approximately 70 percent of infected patients go on to develop chronic liver disease, according to the Centers for Disease Control and Prevention. HCV infection contributes to the deaths of an estimated 8,000 to 10,000 Americans each year and this toll is expected to triple by the year-end of 2010. The CDC has reported that HCV-associated end-stage liver disease is the most frequent indication for liver transplantation among adults.

It is predicted that direct U.S. medical costs to treat HCV-related disease will exceed \$13 billion for the years 2010 through 2019, according to a recent study.

## **VA Offers New Treatment for Veterans with Hepatitis C**

Less than 10 days after a new treatment for hepatitis C was approved by the Food and Drug Administration (FDA), the Department of Veterans Affairs (VA) made it available to enrolled veterans. "We take care of more patients with this debilitating liver disease than any other health system in the country - more than 70,000 a year," said Secretary of Veterans Affairs Anthony J. Principi. "These veterans deserve the best, most responsive care we can offer, including the very latest, approved treatments."

The treatment approved by the FDA Oct. 16 is called "pegylated interferon alfa-2a Pegasys – Roche)." VA has made arrangements with the manufacturer to ship the new drug to VA facilities sooner than any other medical system. "We are getting this drug in the shortest time possible to facilities that have the most need," said Secretary Principi.

Several advances in treating hepatitis C, particularly with the introduction of the "pegylated interferons," include drugs that act against the hepatitis C virus used alone or in combination with other drugs.

Through VA's national hepatitis C program, which has been in place about two years, veterans with hepatitis C receive the most appropriate medical care, including:

- ◆ Counseling for risk factor identification and disease prevention;
- ◆ Systematic screening and testing;
- ◆ Proactive patient and clinician education;
- ◆ Liver transplantation if clinically necessary; and
- ◆ Support services such as substance abuse and mental health care.

VA has screened more than 2.6 million veterans for hepatitis C risk factors since the system-wide policy was established in 1999. To better manage and improve patient care, VA created a national case registry of patients. "We have worked hard to put in place the largest hepatitis C screening and testing program in the world, all to the benefit of the veterans we serve," said Dr. Robert H. Roswell, VA under secretary for health. "VA's approach continues to be a model for how large systems can manage this debilitating disease."

For further information on hepatitis C see [www.va.gov/hepatitisc](http://www.va.gov/hepatitisc)

*November 3<sup>rd</sup>, 2002*

## **Once-A-Week Dose of PegIntron May Not Be Enough**

Study shows hepatitis C drug may require twice weekly dosing to effectively suppress viral load. A study conducted at the University of Vienna shows that the currently prescribed once weekly dosing schedule of peginterferon alfa-2b (Peg-Intron - Schering-Plough) does not provide sustained suppression of the hepatitis C virus (HCV), potentially limiting efficacy. The study found that to achieve continuous drug exposure and to improve viral clearance, patients must receive the drug at least twice weekly. These findings were presented today at the 53rd Annual Meeting of the American Association for the Study of Liver Diseases, in Boston, Massachusetts.

"Peg-Intron was the first pegylated interferon to become available, and pegylation was an important process to improve the availability of the drug, which allowed interferons to be dosed once a week instead of the previous three times a week. However, our study results indicate that Peg-Intron remains in the blood for only three to four days and therefore the virus is not sufficiently suppressed," said Dr. Peter Ferenci, study author and Professor of the Department of Internal Medicine IV, Gastroenterology and Hepatology at the University of Vienna.

The aim of University of Vienna study was to investigate whether twice weekly dosing of Peg-Intron improves viral kinetics.

"In the study, serum concentration of Peg-Intron reached maximum levels the day after the injection and then decreased significantly and no drug remained at the end of the week. At the same time, we saw the hepatitis C virus levels decrease initially but then increase in all patients, starting after the third day," said Dr. Ferenci.

This study was a randomized, open-label study involving 20 previously untreated chronic hepatitis C patients with genotype 1 disease. Patients were randomized to receive either 1.0 mcg/kg Peg-Intron once weekly (Group A) or 1.0 mcg/kg Peg-Intron twice weekly (Group B) for four weeks.

In Group A after once weekly dosing, serum concentrations of Peg-Intron reached maximum levels on the day after injection and then there was a linear decline. In 83% of patients, no drug was detectable at the end of the dosing period before the next administration of drug. Virus levels decreased initially on day 1 and 2 after injection but then increased in all patients in this group. In essence, the virus begins replicating on day 3 or 4 in most patients. This pattern was repeated during the next three weeks of therapy.

In contrast, in Group B with twice-weekly dosing, detectable drug levels were maintained during the second part of the week resulting in a more pronounced reduction in viral load following the second dosing. Viral load was significantly lower in group B throughout the four week study period.

"Based on the findings of the present study, once weekly administration of Peg-Intron is not sufficient to suppress the hepatitis C virus," said Dr. Ferenci. "We see the viral load increases in parallel with the decrease of Peg-Intron in the blood which indicates that the rebound in virus is due to insufficient interferon levels being present in the body. I believe this is due to the pharmacokinetics of this particular medication and the clinical efficacy of Peg-Intron could be improved by twice weekly dosing."

Previous studies have also shown that the once weekly administration of Peg-Intron does not result in the continuous decline in viral load.

*November 4<sup>th</sup>, 2002*

## **Pegasys Helps Hard-to-Treat Hepatitis Patients**

Roche Holding AG's Pegasys hepatitis C drug also helps hard-to-treat patients, the Swiss-based healthcare group said on Monday while presenting results of a dozen clinical studies into its top new drug launch this year.

Findings to be presented at a liver disease conference in the United States include results showing Pegasys in combination with Roche's branded ribavirin Copegus is effective in treating 79 percent of so-called genotype-4 patients normally deemed difficult to treat.

Such combination therapy also aided people who had originally responded to treatment but then had relapses, it said.

Trials suggest Pegasys can also help some patients who have undergone liver transplants, it added in a statement.

U.S. regulators have already approved Pegasys as a standalone therapy for hepatitis C, a viral infection that attacks the liver. More than 170 million people suffer from the disease around the world.

Roche expects crucial U.S. regulatory approval for pegylated interferon drug Pegasys in combination with Copegus next month. Analysts think the drug, which has already been approved in Europe, could have peak annual sales above \$1 billion.

## **American Association for the Study of Liver Diseases/ Liver mortality in patients with HIV infection**

Liver mortality in patients who are co-infected with HIV and hepatitis C (HCV) is known to be high, however, liver mortality in patients who are co-infected with HIV and hepatitis B (HBV) or those with HIV alone has not been well studied. In addition, while highly active antiretroviral therapy (HAART) has been associated in a decline of overall mortality, no data have assessed its impact on hepatic mortality in those co-infected with hepatitis B, C, or both. In this study, liver mortality in patients who are HIV/HBV coinfecting was found to be as high as those who were HIV/HCV co-infected.

Researchers further identified the importance of three factors in determining liver mortality in patients with HIV who are co-infected with one or more hepatitis virus.

Those factors are:

1. CD4 counts less than 200
2. a significant lifetime alcohol use
3. and treatment for HIV prior to 1996.

Patients with all three factors had a 12-fold higher mortality risk compared to patients with none of these factors.

"This is a single-center study from the University of Southern California with 474 patients, but it highlights the need for further investigation into the immune system and the control it has on both hepatitis B and C," says Dr. Maurizio Bonacini, "Clearly, the introduction of HAART in 1996 and maintaining CD4 counts greater than 200 cells/mm<sup>3</sup> are associated with significantly lower hepatic mortality risks. According to Dr. Bonacini, "patients with HIV, even those who are not co-infected with viral hepatitis, need to be concerned with liver health. In particular, the potential liver toxicity of antiretroviral drugs and alcohol must be underscored."

In summary, it appears that both HBV and HCV have deleterious consequences in terms of hepatic mortality in patients with HIV infection. Individuals with co-infection and higher CD4 counts, however, appear to be relatively protected.

These findings may have some bearing in the post-transplant setting, where immunocompromised patients also experience more progressive liver disease, while remaining at risk for rejection. More research is needed to understand mechanisms of allograft rejection and antiviral immunity in the hope of developing future therapeutic strategies.

## **ZADAXIN Adds Benefit to Pegylated Interferon for HCV Non-Responders; Hepatitis C Patients who Failed Prior Therapy Responding to ZADAXIN**

ZADAXIN(R) in combination with pegylated interferon advanced in its effort to be part of the first approved hepatitis C therapy for non-responders. Close to half of all patients fail to respond to initial treatment with currently available therapies and become non-responders.

Today, SciClone Pharmaceuticals, Inc. (Nasdaq:SCLN) reported that ZADAXIN in combination with pegylated interferon alpha increased the early virologic response (EVR) rates up to 36% in hepatitis C patients who had failed prior therapy. Complete data from a twelve week dose ranging study showed that groups of non-responders treated with ZADAXIN combination therapy reported positive dose related EVR rates ranging from 20 to 36%. EVR is suggested to be an early indicator of sustained response, and non-responders seldom have a sustained response to re-treatment.

The results of this dose ranging study were presented today at the annual meeting of the American Association for the Study of Liver Disease (AASLD) by a team lead by Dr. Adrian Di Bisceglie of Saint Louis University School of Medicine. Dr. Di Bisceglie concluded, "These data suggest that ZADAXIN in combination with pegylated interferon may be able to treat a large subset of hepatitis C patients that have been extremely difficult to treat in the past -- non-responders infected with hepatitis C genotype 1. ZADAXIN was well tolerated with no obvious side effects."

Dr. Eduardo Martins, Medical Director of SciClone Pharmaceuticals, commented, "These data add to our belief that ZADAXIN has the potential to offer new, safer and better therapy options for hepatitis C patients. Twelve week EVR data has been proposed by hepatologists to be a predictor of patients that may or may not respond to pegylated interferon therapy. Significantly, the twelve week data from this dose ranging study clearly show ZADAXIN's ability to add to the antiviral effects of pegylated interferon and improve response rates in the treatment of some of the most difficult to treat hepatitis C patients, those who have already failed to respond to prior therapy. Based on these results, we are optimistic about the outcome of the two phase 3 hepatitis C clinical trials we are conducting."

Close to half of all hepatitis C patients fail to respond to the standard therapy of pegylated interferon plus ribavirin. More dramatically, an estimated two million hepatitis C carriers in the U.S. are infected with a high viral load of genotype 1 virus and are the most difficult group of patients to treat. In comparison to the general hepatitis C patient population, 70% of these patients fail to respond to standard therapy.

All 31 hepatitis C patients in the dose ranging study had a high viral load of genotype 1 virus, 27 having failed previous treatment with interferon plus ribavirin and four having failed with interferon alone. Patients were randomized into three groups to receive 180 mcg/week of pegylated interferon alfa-2a plus one of three different bi-weekly doses of ZADAXIN. Observation at the end of 12 weeks of therapy showed that EVR (measured by negative or a greater than 2 log reduction in hepatitis C viral RNA) increased with higher doses of ZADAXIN. The groups receiving 0.8 mg, 1.6 mg and 3.2 mg doses of ZADAXIN in combination therapy reported EVR rates of 20%, 30% and 36%, respectively. Based on extensive previous ZADAXIN clinical data and commercial experience, SciClone's two U.S. phase 3 hepatitis C clinical trials are using the 1.6 mg twice weekly dose.

### ***About SciClone's Phase 3 Hepatitis C Trials***

*SciClone's phase 3 hepatitis C clinical trials are currently enrolling 1,000 non-responders at multiple sites throughout the U.S. During these trials, patients will be randomized to receive either ZADAXIN plus pegylated interferon or placebo plus pegylated interferon for a period of 12 months, followed by a six-month observation period. F. Hoffmann LaRoche has provided Pegasys brand pegylated interferon alfa-2a for these trials. Additional information can be found at [www.sciclone.com](http://www.sciclone.com).*

### ***About SciClone***

*SciClone Pharmaceuticals is a biopharmaceutical company primarily focused on the development of Immune System Enhancers. Its lead product ZADAXIN is in two phase 3 hepatitis C clinical trials in the U.S., a phase*

*3 hepatitis B clinical trial in*

*Japan, a phase 2 malignant melanoma clinical trial in Europe, and two phase 2 liver cancer clinical trials in the U.S.*

*ZADAXIN has been approved for sale by the ministries of health in over 30 countries and is marketed in China and selected other countries outside the U.S. ZADAXIN has been administered to more than 10,000 patients in both clinical and commercial use, alone and in combination with anti-viral and anti-cancer drugs, without producing any reported ZADAXIN related significant side effects or toxicities.*

*SciClone's strategic goal is to become a principal worldwide provider of Immune System Enhancers (ISEs) both as monotherapies and as critical components of combination drug therapies for infectious diseases and cancer. In addition to*

*ZADAXIN, SciClone's drug development opportunities include SCV-07, a potentially orally available ISE, and products to address the protein-based disorder that causes cystic fibrosis.*

## **Viramidine to Advance to Phase II Clinical Trials in Hepatitis C Phase I Clinical Trial Data Presented at the 53rd Annual Meeting of the American Association for the Study of Liver Diseases**

Ribapharm Inc., today announced it will commence phase II clinical trials of viramidine in the treatment of chronic hepatitis C (HCV) by the end of 2002. Data from several preclinical and phase I clinical studies on viramidine were presented at the ongoing 53rd Annual Meeting of the American Association for the Study of Liver Diseases (AASLD) in Boston, MA.

Viramidine is a nucleoside analogue structurally related to ribavirin. Ribavirin is currently approved in the combination treatment with interferon alpha or pegylated interferon alpha in patients with clinically compensated chronic hepatitis C infection. Ribapharm filed an Investigational New Drug application (IND) for viramidine with the U.S. Food and Drug Administration (FDA) in December 2001.

"Biochemical and animal studies showed that viramidine is converted to ribavirin predominately in the liver, the organ infected by hepatitis C," said Jane W.S. Fang, MD, Vice President of Clinical Affairs and Clinical Operations at Ribapharm. "Given the results from the phase I studies, we anticipate initiating phase II studies on the combination use of viramidine and pegylated interferon alpha before the end of 2002."

"A phase I rising multiple-dose study with viramidine dosing from 800 mg per day to 1,600 mg per day for four weeks was conducted. There was no significant decrease in hemoglobin levels even with the highest doses (1,600 mg per day) of viramidine," said Daryl Lau, MD, Assistant Professor of Medicine, University of Texas Medical Branch in Galveston and a study investigator.

Preclinical studies of viramidine were also presented at the AASLD meeting. Studies in monkeys showed that 28 days of viramidine dosing up to 600 mg/kg per day induced no significant change in hemoglobin levels in males and a mild decrease of less than 10% from baseline in females. In the same study, ribavirin at 300 mg/kg per day induced a decrease of hemoglobin of 11-14% in male and 23-25% in female monkeys.

"Preclinical studies provided scientific support for viramidine to proceed to advanced clinical studies," said Chin-chung Lin, PhD, Vice President, Drug Development at Ribapharm.

### **About Hepatitis C**

*Hepatitis C is an inflammatory liver disease, caused by the infection of the hepatitis C virus. Globally, an estimated 170 million persons are chronically infected with hepatitis C and three to four million are newly infected each year. HCV is now four times as widespread as HIV in the U.S.*

*In June 2002, the National Institutes of Health (NIH) convened a Consensus Conference Panel to examine current management and treatment practices for hepatitis C. The panel noted that the hepatitis C virus is the*

*leading cause of chronic liver diseases in the United States, including liver cirrhosis and hepatocellular carcinoma. In a final consensus statement, the NIH panel concluded that the most effective treatment of chronic hepatitis C is with a combination therapy of pegylated interferon alpha and ribavirin.*

### **About Ribapharm**

*Ribapharm is a biopharmaceutical company that seeks to discover, develop, acquire and commercialize innovative products for the treatment of significant unmet medical needs, principally in the antiviral and anticancer areas.*

## **SciClone Pharmaceuticals Reports Third Quarter 2002 Results; New Data Support Clinical Trials; ZADAXIN Sales up 20%**

SciClone Pharmaceuticals, Inc. (Nasdaq:SCLN) today reported results from the third quarter ended September 30, 2002. Revenues from sales of ZADAXIN, the company's lead immune system enhancer drug, were \$4,298,000, a 20% increase over the \$3,580,000 reported during the third quarter of 2001. In addition, the company recognized \$224,000 as contract revenue from the \$2.6 million payment received in January from Sigma-Tau. For the first nine months of 2002, total revenues were \$12,294,000, a 24% increase over the \$9,943,000 reported during the same period of 2001.

Net loss for the quarter ended September 30, 2002 was \$1,672,000, or \$0.05 per share, compared to a net loss of \$173,000, or \$0.01 per share, for the third quarter of 2001. Although revenues increased in 2002, the difference in net loss mainly was attributable to the recognition in the third quarter of 2001 of a lump sum net receipt of \$3,205,000 in full satisfaction of a promissory note. This note previously had been written off as a non-cash charge to earnings in the fourth quarter of 1998.

"Revenue growth has benefited from continued increasing ZADAXIN demand in China, our largest market," said Richard Waldron, SciClone's Chief Financial Officer. "Research and development expenses and cash disbursements will increase over the coming quarters as we progress with our U.S. phase 3 hepatitis C clinical trials and complete our phase 3 hepatitis B clinical trial in Japan."

Cash and short-term investments totaled \$24,506,000 at September 30, 2002, similar to the \$24,400,000 in cash and short-term investments at June 30, 2002. This slight increase was mainly due to a \$1.2 million total decrease in accounts receivable and inventory, and a \$1.1 million increase in accounts payable during the third quarter 2002.

"Our goal is to have ZADAXIN be part of the first approved hepatitis C therapy for non-responders, since close to half of patients fail to respond to currently available therapies," said Donald R. Sellers, SciClone's President and Chief Executive Officer. "Today, we issued a press release regarding data from a 12 week dose ranging study showing that ZADAXIN in combination with pegylated interferon increases early virologic response up to 36% for hepatitis C patients who have failed previous therapy. We are focused on our primary goal of ZADAXIN approvals in the U.S., Europe and Japan, and continue to see positive clinical and scientific data to support this goal. Our late-stage clinical trials for ZADAXIN continue to progress, with patient enrollment underway for our U.S. phase 3 hepatitis C clinical trials and European phase 2 malignant melanoma clinical trial, conducted by Sigma-Tau. Our Japanese phase 3 hepatitis B trial will conclude by the end of this year and we expect final data during the first half of 2003."

### **Recent developments at SciClone include:**

*A phase 2 dose ranging study for ZADAXIN in combination with pegylated interferon showed early virologic response (EVR) rates ranging from 20 to 36% in hepatitis C patients who had failed prior therapy. The complete data from this 12 week dose ranging study were presented today at the annual meeting of the American Association for the Study of Liver Disease (AASLD) by a team lead by Dr. Adrian Di Bisceglie of Saint Louis University School of Medicine. SciClone's goal is for ZADAXIN in combination with pegylated interferon to be part of the first U.S. FDA approved hepatitis C therapy for non-responders, the close to half of hepatitis C patients who fail currently available therapies.*

*A phase 2 clinical trial for ZADAXIN as a treatment for malignant melanoma has begun enrolling patients in Europe. SciClone's European Union (EU) marketing and development partner, Sigma-Tau S.p.A., is conducting and funding a 300 patient, multicenter phase 2 clinical trial using ZADAXIN in combination with chemotherapy to treat malignant melanoma. This trial is part of a phase 2-3 oncology program pursuing European regulatory approval for ZADAXIN.*

*Phase 2 clinical trials for SCV-07 as a treatment for tuberculosis (TB) yielded positive results which were presented at the Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC). These trials demonstrated that 80% of TB patients treated with SCV-07 (for five days) combined with standard anti-TB chemotherapy for 3 months were no longer contagious, compared to 37% of patients whose anti-TB therapy did not include SCV-07.*

*Positive data from a ZADAXIN colorectal cancer cell study were presented at the 30th Meeting of the International Society for Oncodevelopmental Biology and Medicine. An in vitro study showed that after treatment with ZADAXIN, the percent of cancer cells with a colorectal cancer-specific protein on their surface increased to 90%, compared to a normal range of 10 to 20%. This effect was also seen in an in vivo study of colorectal cancer induced animals that were treated with ZADAXIN.*

*Positive data from ZADAXIN hepatitis B virus (HBV) and human immunodeficiency virus (HIV) cell studies were presented at the Therapies for Viral Hepatitis Conference in Boston. In vitro studies showed that ZADAXIN, in addition to previously observed immunological effects, for the first time has shown direct antiviral effects on cells infected with HBV and HIV. This mechanism of action supports the exploration of ZADAXIN in the therapy of patients coinfecting with HBV and HIV.*

*ZADAXIN was granted orphan drug status for the treatment of hepatocellular carcinoma (HCC) by the European Medicines Evaluation Agency (EMA). Orphan drug status provides for EU marketing exclusivity for 10 years upon marketing approval. This status is granted by the EMA to medicines intended for rare and serious or life threatening diseases affecting fewer than 5 in 10,000 people in the EU. In March 2000, the U.S. FDA granted orphan drug status to ZADAXIN for the treatment of HCC.*

### **About SciClone**

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*ZADAXIN has been approved for sale by the ministries of health in over 30 countries and is marketed in China and selected other countries outside the U.S. ZADAXIN has been administered to more than 10,000 patients in both clinical and commercial use, alone and in combination with anti-viral and anti-cancer drugs, without producing any reported ZADAXIN related significant side effects or toxicities.*

*SciClone's strategic goal is to become a principal worldwide provider of Immune System Enhancers (ISEs) both as monotherapies and as critical components of combination drug therapies for infectious diseases and cancer. In addition to ZADAXIN, SciClone's drug development opportunities include SCV-07, a potentially orally available ISE, and products to address the protein-based disorder that causes cystic fibrosis.*

## **Schering-Plough Reports Results of Clinical Studies of PEG-INTRON(R) and REBETOL(R) Combination Therapy for Hepatitis C at American Association for the Study of Liver Diseases Meeting: Studies Evaluate Clinical Benefits in Diverse Treatment Populations**

Schering-Plough Corporation (NYSE: SGP) today reported results of several investigator-initiated clinical studies presented here at the 53rd Annual Meeting of the American Association for the Study of Liver Diseases (AASLD) evaluating new treatment strategies for patients with hepatitis C involving PEG-INTRON (R) (peginterferon alfa-2b) Powder for Injection in combination with REBETOL(R) (ribavirin, USP) Capsules. In all, 40 studies with PEG-INTRON were presented by clinical investigators.

PEG-INTRON and REBETOL is the first and only pegylated interferon-based combination therapy approved in the United States and is indicated for the treatment of chronic hepatitis C in patients with compensated liver disease who have not been previously treated with interferon alpha and are at least 18 years of age. To date, more than 150,000 patients worldwide have received this combination therapy.

"Schering-Plough's ongoing commitment to developing improved treatments for patients with hepatitis C is evidenced by the numerous clinical studies with PEG-INTRON, INTRON A and REBETOL reported by investigators at this year's AASLD meeting," said Robert J. Spiegel, M.D., senior vice president of medical affairs and chief medical officer, Schering-Plough Research Institute. "Schering-Plough is currently supporting a comprehensive independent clinical study program with PEG-INTRON and REBETOL involving more than 10,000 patients that is designed to maximize treatment benefits and improve outcomes for a variety of patient populations."

In an oral presentation at AASLD, investigators reviewed data demonstrating that patients chronically infected with the hepatitis C virus (HCV) who participated in a new cognitive behavioral therapy strategy in addition to Schering-Plough's Be In Charge patient-support program, had a lower drop-out rate in the first 12 weeks of therapy than patients who participated in Be In Charge alone and/or received routine supportive care by their physicians. In this study, patients in the active intervention arm received patient education, aggressive side-effect management and supportive nursing intervention with cognitive behavioral therapy by telephone utilizing the Be In Charge patient-support program.

Schering-Plough's Be In Charge program is available free of charge to all patients treated with the company's HCV products, including PEG-INTRON and REBETOL combination therapy. The program has enrolled more than 55,000 HCV patients since its inception in 1997, with more than 25,000 patients enrolling in 2002 alone.

"As clinicians, we strive to maximize the potential of combination therapy for our patients with hepatitis C," said Steven L. Flamm, M.D., associate professor of medicine, Northwestern University Medical School, Chicago, and the lead investigator of the study. "These data demonstrate the importance of active intervention and supportive care in helping HCV patients benefit from their treatment."

PEG-INTRON Studies Presented at AASLD Researchers also presented interim data from ongoing investigator-initiated clinical studies examining how best to optimize treatment with PEG-INTRON and REBETOL combination therapy in difficult-to-treat patient populations. Ongoing studies supported by Schering-Plough include defining the optimal dose and duration of PEG-INTRON and REBETOL combination therapy in all HCV virus genotypes; the effectiveness of combination therapy in African-American patients, patients on methadone and HIV/HCV co-infected patients; the effect of treatment on liver cirrhosis; and long-term maintenance therapy in patients who are non-responders to previous combination therapy.

Interim data from the ongoing WIN-R Trial, the largest prospective hepatitis C study undertaken to date, which has enrolled more than 4,000 U.S. patients, including more than 400 African Americans with hepatitis C, showed no racial differences linked to toxicity or side effects of PEG-INTRON with or without REBETOL that would account for the higher rates of dose reduction or treatment dropout typically seen among African American patients.

Investigators suggested that, although virologic data remain blinded, any differences observed in response rate by race or ethnicity cannot be explained by differences in hematologic toxicity or dose modification or discontinuation.

"These preliminary results provide another important piece to helping us understand how to more effectively treat African American patients with HCV," said Robert Brown, M.D., M.P.H., medical director, the Center for Liver Disease and Transplantation, Columbia University College of Physicians and Surgeons, New York. "These data show that we need to look beyond problems with dose reduction and discontinuation or side effects when examining how the virus responds to treatment in the African American population."

In another presentation based on data from the ongoing WIN-R Trial, researchers looked at the relationship

between HCV genotype and viral load on other clinical aspects of the disease, such as fibrosis and steatosis (fatty liver). For this study, enrollment data were analyzed for 4,657 patients, of whom 68% have genotype 1 infection, 18% genotype 2, 13% genotype 3, 1% genotype 4, and less than 1% have other genotypes. Researchers found no association of advanced fibrosis with any particular genotype. Study data reinforce recent evidence that genotype 3 is associated with hepatic steatosis (seen in 50% of these patients). As seen in this analysis, viral load is higher in patients with genotype 1, and high viral load is as common in patients with mild fibrosis as in patients with bridging fibrosis or cirrhosis.

Schering-Plough HCV Products PEG-INTRON, which is approved for dosing according to patient body weight, is a longer-acting form of INTRON(R) A (interferon alfa-2b, recombinant) Injection that uses proprietary PEG technology developed by Enzon, Inc. (Nasdaq: ENZN) of Piscataway, N.J. PEG-INTRON, recombinant interferon alfa-2b linked to a 12,000 dalton polyethylene glycol (PEG) molecule, is a once-weekly therapy. Schering-Plough holds an exclusive worldwide license to PEG-INTRON.

INTRON A is a recombinant version of naturally occurring alpha interferon, which has been shown to exert both antiviral and immunomodulatory effects. Schering-Plough markets INTRON A for 16 major antiviral and anticancer indications worldwide.

REBETOL is an oral formulation of ribavirin, a synthetic nucleoside analog. Schering-Plough has exclusive worldwide rights to market oral ribavirin for hepatitis C through a licensing agreement with Ribapharm Inc. (NYSE: RNA) of Costa Mesa, Calif.

#### **WARNING**

*REBETOL monotherapy is not effective for the treatment of chronic hepatitis C virus infection and should not be used alone for this indication. (See WARNINGS.) The primary toxicity of ribavirin is hemolytic anemia. The anemia associated with REBETOL therapy may result in worsening of cardiac disease that has led to fatal and nonfatal myocardial infarctions. Patients with a history of significant or unstable cardiac disease should not be treated with REBETOL. (See WARNINGS, ADVERSE REACTIONS, and DOSAGE AND ADMINISTRATION.)*

*Significant teratogenic and/or embryocidal effects have been demonstrated in all animal species exposed to ribavirin. In addition, ribavirin has a multiple-dose half-life of 12 days, and so it may persist in nonplasma compartments for as long as 6 months. Therefore, REBETOL therapy is contraindicated in women who are pregnant and in the male partners of women who are pregnant. Extreme care must be taken to avoid pregnancy during therapy and for 6 months after completion of treatment in both female patients and in female partners of male patients who are taking REBETOL therapy. At least two reliable forms of effective contraception must be utilized during treatment and during the 6-month post-treatment follow-up period. (See CONTRAINDICATIONS, WARNINGS, PRECAUTION Information for Patients and Pregnancy Category X.)*

*Alpha interferons, including PEG-INTRON and INTRON A, may cause or aggravate fatal or life-threatening neuropsychiatric, autoimmune, ischemic and infectious disorders. Patients should be monitored closely with periodic clinical and laboratory evaluations. Patients with persistently severe or worsening signs or symptoms of these conditions should be withdrawn from therapy. In many but not all cases these disorders resolve after stopping therapy with PEG-INTRON or INTRON A. (See WARNINGS, ADVERSE REACTIONS.)*

#### **PEG-INTRON**

*There are no new adverse events specific to PEG-INTRON as compared to INTRON A, however, the incidence of some (e.g., injection site reactions, fever, rigors, nausea) were higher. The most common adverse events associated with PEG-INTRON were "flu-like" symptoms, occurring in approximately 50% of patients, which may decrease in severity as treatment continues. Application site disorders were common (47%), but all were mild (44%) or moderate (4%) and no patient discontinued, and included injection site inflammation and reaction (i.e., bruise, itchiness, irritation). Injection site pain was reported in 2% of patient receiving PEG-INTRON. Alopecia (thinning of the hair) is also often associated with alpha interferons including PEG-INTRON.*

*Psychiatric adverse events, which include insomnia, were common (57%) with PEG-INTRON, but similar to INTRON A (58%). Depression was most common at 29%. Suicidal behavior including ideation, suicidal attempts, and completed suicides occurred in 1% of patients during or shortly after completing treatment with PEG-INTRON. PEG-INTRON is contraindicated in patients with autoimmune hepatitis and decompensated liver disease.*

*The following serious or clinically significant adverse events have been reported at a frequency < or = 1% with PEG-INTRON or interferon alpha: Severe decreases in neutrophil or platelet counts, hypothyroidism, hyperglycemia, hypotension, arrhythmia, ulcerative and hemorrhagic colitis, development or exacerbation of autoimmune disorders including thyroiditis, RA, systemic lupus erythematosus, psoriasis, pulmonary disorders (dyspnea pulmonary infiltrates, pneumonitis and pneumonia, some resulting in patient deaths), urticaria, angioedema, bronchoconstriction, anaphylaxis, retinal hemorrhages and cotton wool spots.*

*Renal failure patients should be closely monitored for signs and symptoms of interferon toxicity and PEG-INTRON should be used with caution in patients with creatinine clearance <50 mL/min. Patients on PEG-INTRON therapy should have hematology and blood chemistry testing before the start of treatment and then periodically thereafter.*

*INTRON A All patients receiving INTRON A therapy experienced mild-to-moderate side effects. Some patients experienced more severe side effects, including neutropenia, fatigue, myalgia, headache, fever, chills and increased SGOT. Other frequently occurring side effects were nausea, vomiting, depression, alopecia, diarrhea and thrombocytopenia. Depression and suicidal behavior, including suicidal ideation, suicidal attempts, and completed suicides, have been reported in association with treatment with alfa interferons, including Intron a therapy.*

*Schering-Plough is a research-based company engaged in the discovery, development, manufacturing and marketing of pharmaceutical products worldwide.*

## **Human Genome Sci/Albuferon: To Increase Test Dosages**

Human Genome said that no patient has yet developed an immune response to Albuferon, and some patients have experienced a reduced viral load.

The company has amended its study and will begin to test higher doses at up to five times the highest amount, or until it reaches the maximum tolerated dose.

Human Genome said current treatments on the market can be taken as a pegylated interferon once a week in combination with ribavirin, or as an alpha-interferon three times a week.

Schering-Plough Corp. (SGP) currently markets Peg-Intron and Rebetrol, the only U.S.-approved pegylated interferon and ribavirin combination. Peg-Intron's side effect warnings include a 29% incidence of depression, including possible suicide, and a 50% incidence of flu-like systems.

Roche Holding AG (Z.ROC) markets a competing once-a-week hepatitis-C treatment called Pegasys, which is an alpha interferon that includes possible neuropsychiatric, autoimmune and ischemic side effects.

Like Schering-Plough's Peg-Intron, Pegasys is a long-acting form of interferon that makes it easier for patients to keep up with their doses. Before the long-acting forms won FDA approval, patients had to inject interferon three times per week. Both Pegasys and Peg-Intron are pegylated forms of interferon, meaning a molecule was added to the interferon to prevent the body from breaking it down quickly, thus cutting down on the number of doses needed.

Human Genome's shares recently traded at \$9.69, up 60 cents, or 6.6%, on Nasdaq market composite volume of 2.1 million shares. Average daily volume is 2.4 million shares.

*November 5th, 2002*

## **Ribapharm Reports Third-Quarter Earnings**

Ribapharm Reports Strong Growth in Third Quarter Revenue and Earnings; Research and Development Programs Continue to Advance on Schedule

Ribapharm Inc. (NYSE: RNA) today announced third quarter 2002 net income of \$28.9 million, compared to

\$8.1 million for the same period in 2001. The company also reported earnings per share of 19 cents, compared to five cents per share for the third quarter last year.

Third quarter royalty revenues of \$63.4 million were derived from sales of ribavirin, an antiviral drug licensed to and marketed by Schering-Plough. Revenues were reduced by approximately \$6.0 million for changes in estimated rebates incurred by Schering-Plough related to sales of ribavirin in prior periods. Revenue during the same period in 2001 totaled \$21.5 million. Ribavirin is marketed in combination with Schering-Plough's interferon alfa-2b (REBETRON(TM)) and with Schering-Plough's pegylated interferon alfa-2b (PEG-INTRON (R) - REBETOL(R)) for the treatment of chronic hepatitis C.

Operating income in the third quarter was \$47.0 million, versus \$13.7 million for the same period in 2001. Research and development expenses were \$13.5 million and general and administrative costs were \$2.9 million this quarter compared with \$5.6 million and \$2.2 million last year, respectively.

In the nine-month period ending September 30, 2002, royalty revenues were \$186.4 million as compared to \$89.0 million for the same period in 2001. Net income for this period was \$90.0 million versus \$42.2 million in 2001, and earnings per share were 60 cents compared to 28 cents last year.

"Our strong revenue growth allows us to aggressively advance our highly-focused research and development programs in antiviral and anticancer therapies," said Johnson Y.N. Lau, M.D., President and CEO of Ribapharm.

In October, 2002, Ribapharm submitted an Investigational New Drug (IND) application with the U.S. Food and Drug Administration (FDA) to initiate phase I clinical studies for Hepavir B in patients with chronic hepatitis B infection.

In addition, Ribapharm presented data this week on phase I studies of viramidine in the treatment of chronic hepatitis C at the 53rd Annual Meeting of the American Association for the Study of Liver Diseases in Boston. Based on the results from these studies, it is expected that viramidine will advance to phase II clinical trials in combination with pegylated interferon alfa by year's end, in which initial efficacy and additional safety data will be obtained from patients with chronic hepatitis C patients enrolled in the study.

"The outstanding efforts of our preclinical, clinical development and regulatory colleagues, as well as our partners, have enabled us to meet our company objectives so far this year, driving our research and development pipeline forward as planned and on schedule," said Dr. Lau. "I am extremely pleased with their dedication and commitment."

#### **About Hepatitis B**

*Hepatitis B is a viral infection of the liver caused by the hepatitis B virus, or HBV. The World Health Organization (WHO) estimates that more than 350 million people worldwide are chronically infected with HBV. In the United States, the Centers for Disease Control and Prevention (CDC) estimate that 1.25 million people are chronically infected with HBV, with 5,000 deaths occurring annually from chronic liver disease and other complications associated with the virus.*

#### **About Hepatitis C**

*Hepatitis C is a disease of the liver caused by the hepatitis C virus, or HCV. The WHO estimates that more than 170 million people worldwide are chronically infected with HCV. In the United States, the CDC estimates that 2.7 million people are chronically infected with HCV, with 10,000 deaths occurring annually from chronic liver disease and other complications associated with the virus.*

#### **About Ribapharm**

*Ribapharm is a biopharmaceutical company that seeks to discover, develop, acquire and commercialize innovative products for the treatment of significant unmet medical needs, principally in the antiviral and anticancer areas.*

## **InterMune Announces Infergen Study Results: InterMune Announces Phase IV Study Shows Infergen Combination Therapy More Effective than Rebetron for Hepatitis C. Infergen plus Ribavirin Produces Higher Sustained Viral Response Rates at 72 Weeks than Rebetron(R)**

InterMune, Inc. (Nasdaq: ITMN) today announced that positive preliminary results of an investigator initiated, prospective randomized Phase IV clinical trial comparing the use of Infergen(R) (interferon alfacon-1) plus ribavirin versus interferon alfa-2b plus ribavirin (Rebetron(R)) for the treatment of chronic hepatitis C infections were presented at the 53rd Annual Meeting of the American Association for the Study of Liver Diseases (AASLD) in Boston. Patients treated with Infergen in combination with ribavirin achieved a higher sustained virologic response (SVR), the study's primary endpoint, compared to those patients treated with Rebetron.

"These data suggest that the combination of consensus interferon plus ribavirin is more efficacious than Rebetron therapy," said Maria H. Sjogren, M.D., M.P.H., Chief, Department of Clinical Investigations, Walter Reed Army Medical Center in Washington, D.C. and lead investigator of the Phase IV trial.

"The sustained response we observed in this trial with the Infergen combination could set a new treatment threshold for this difficult to treat U.S. patient population. As a matter of fact, the SVR is consistent to that reported for the pegylated interferons plus ribavirin but with less hematologic toxicity. These data help to provide clinical confirmation of the in vitro biologic potency of Infergen. Infergen in combination with ribavirin appears to be a viable treatment alternative. Further study comparing the use of Infergen to other treatment regimens is warranted."

In data analyzed and reported by a group at Walter Reed Army Medical Center and Kaiser Permanente Mid-Atlantic Region, 127 patients with chronic hepatitis C (128 patients randomized; one patient data point pending) were randomized to receive Infergen (15 mcg, TIW) plus ribavirin (1 g/day) or interferon alfa-2b (3MU, equivalent to 15 mcg, TIW) plus ribavirin (1g/ day) for up to 48 weeks with an additional 24 weeks of observational follow-up. Patients who were still HCV RNA positive following 24 weeks of therapy stopped treatment and were considered treatment failures. Analysis of the 127 patients who reached week 72 or who discontinued early for any reason, revealed an overall SVR rate of 57% in the Infergen plus ribavirin-treated group compared to 39% in the interferon alfa-2b plus ribavirin group ( $p = 0.04$ ).

Dr. Sjogren and colleagues reported that all patients in the study received the same dose of ribavirin. However, a retrospective analysis demonstrated those patients who received the appropriate dose of ribavirin based on their weight (i.e., greater than 10.6 mg/kg per day) achieved a higher sustained viral response rate in both treatment arms: 75% SVR for the Infergen/ribavirin treated patients and an SVR rate of 52% for the Rebetron arm of the study. According to Dr. Sjogren, the side effects associated with Infergen plus ribavirin were similar to those seen with Rebetron and included flu-like symptoms, fatigue, headache, nausea, cough and mood disorders such as depressed mood, anxiety, irritability and insomnia.

"There remains a great medical need for effective therapies for the treatment of hepatitis C because approximately 50% of patients currently fail best available therapy," said Scott Harkonen, InterMune's President and CEO. "This study, which suggests that Infergen plus ribavirin makes a compelling treatment option for HCV patients, will play an important role in our efforts to broaden this drug's use in managing chronic hepatitis."

### ***About Infergen for Hepatitis C***

*Infergen is a bioengineered type I interferon alfa indicated for treatment of adult patients with chronic hepatitis C infections, including therapy for patients who have never been treated with interferons and for patients following relapse or non-response to treatment with certain previous treatments. Physicians and patients can obtain additional information about Infergen by visiting <http://www.infergen.com>.*

*Hepatitis C is a liver disease caused by the hepatitis C virus that is found in the blood of people with this*

disease. It is the most common form of hepatitis infection in North America and Europe. According to the National Center for Infectious Diseases, there are an estimated 3.9 million (1.8%) Americans who have been infected with hepatitis C, of whom 2.7 million are chronically infected. If not detected and treated, hepatitis C may lead to chronic liver disease, including liver cancer, and ranks second to alcoholism as a cause of cirrhosis. Hepatitis C causes an estimated 8,000 to 10,000 deaths annually in the United States.

#### **About InterMune**

*InterMune is a commercially driven biopharmaceutical company focused on the marketing, development and applied research of life-saving therapies for pulmonary disease, infectious disease and cancer. For additional information about InterMune, please visit [www.intermune.com](http://www.intermune.com).*

## **New Phase II Data Confirm ISIS 14803 Produces Significant Viral Level Reductions in Patients With Drug-Resistant Hepatitis C. Clinical Investigators Report Data From Two Clinical Trials**

Isis Pharmaceuticals, Inc., (Nasdaq: ISIS) announced today that its antisense drug ISIS 14803 demonstrated promising antiviral activity by producing up to 3.8 log reductions in plasma virus levels in patients with chronic hepatitis C virus (HCV), in an ongoing Phase II clinical trial. The majority of patients participating in the three month study are HCV genotype 1, the most common and difficult to treat form of HCV, and all but two had been treated previously with interferon. Clinical investigators presented results from this study as well as final data from a previous Phase I/II trial at the 53rd Annual Meeting of The American Association for the Study of Liver Diseases (AASLD) in Boston, Massachusetts.

"The results from this Phase II trial are encouraging. ISIS 14803 reduces viral burden in patients with chronic HCV, many of whom had received prior treatment. We observed significant viral load reductions in patients that had extremely high viral levels and were genotype 1. These two key factors are important as they represent our most difficult clinical challenge," said Stuart C. Gordon, M.D., of William Beaumont Hospital, Royal Oak, Michigan, and first author of the Phase II study.

### **Results from the Three Month Phase II Clinical Trial**

In the study, two doses and two treatment schedules of ISIS 14803 are being evaluated. A total of 43 patients were enrolled in the trial. All patients initially received 2.5 mg/kg of ISIS 14803 three times a week for two weeks. Patients then received 4 mg/kg or 6 mg/kg of ISIS 14803 either once weekly or twice weekly for 10 weeks. The drug was administered by intravenous infusion. At the time of reporting these data, the majority of patients in the once weekly treatment arm are still early in their treatment courses. Thus, data for these patients are not yet available.

Clinical investigators reported that six of 17 patients receiving 6 mg/kg of ISIS 14803 twice a week experienced viral titer reductions of 1.0 - 3.8 logs, with three of these patients experiencing a greater than 3.0 log reduction. Consistent with data reported from a previous clinical trial, this study suggests that elevated levels of liver function tests, including alanine aminotransferase (ALT), may correlate with antiviral activity of ISIS 14803. In the trial, decreases in viral titers were accompanied by asymptomatic transient increases in ALT levels. The ALT flares resolved while dosing with ISIS 14803 continued.

"In addition to the responses observed in this trial to date, ISIS 14803 treatment has also been well tolerated," said Bruce R. Bacon, M.D., James F. King MD Endowed Chair in Gastroenterology, Professor of Internal Medicine, Director, Division of Gastroenterology and Hepatology, Saint Louis University, Saint Louis. "There are no treatment options for drug resistant HCV patients, so we are encouraged by the data from this Phase II trial of ISIS 14803. We look forward to continuing to evaluate whether ISIS 14803 can be a valuable new addition to the HCV treatment armamentarium."

### **Final Results from the One Month Phase I/II Trial**

ISIS 14803 clinical investigators also presented final results of an initial one month Phase I/II study of the antisense drug in patients with chronic HCV. Twenty-eight patients were enrolled in the study, which was designed to evaluate escalating doses of ISIS 14803 administered three times a week for one month by either intravenous infusion or subcutaneous injection. In the trial, five of 28 patients had meaningful viral reductions. Three of 10 patients that received 2 mg/kg of ISIS 14803 experienced 1.3-2.2 log reductions in viral levels. Reductions in viral titers were maintained for more than 40 days. The majority of patients in this study were genotype 1 and all but three patients had failed previous interferon-based therapy. ISIS 14803 was well tolerated in the Phase I/II clinical trial. Adverse events reported were minor. Isis previously reported preliminary data from this trial in June 2001.

"Data reported from the three month Phase II trial confirm and enhance the results of our earlier clinical experience. We are very encouraged by the activity of ISIS 14803 in drug resistant patients and the safety profile of the drug," said F. Andrew Dorr, M.D., Isis' Vice President and Chief Medical Officer. "We believe that ISIS 14803 is the only agent in development to produce viral titer reductions of this magnitude in this patient group."

Hepatitis C causes chronic inflammation of the liver that can go undetected for months or years but is frequently progressive, resulting in life-threatening impairment of liver function. Persistent liver inflammation causes ongoing injury to the cells of the liver. If left untreated, it can lead to liver scarring called cirrhosis, liver failure, possibly liver cancer and death due to the complications of these hepatic insults. Liver complications of chronic HCV infections are the most frequent indication for liver transplantation.

According to the National Institute of Diabetes, Digestive and Kidney Diseases (NIDDK), HCV is one of the most important causes of chronic liver disease in the U. S. It accounts for approximately 20 percent of acute viral hepatitis, 60 to 70 percent of chronic hepatitis, and 30 percent of cirrhosis, end-stage liver disease, and liver cancer. Nearly four million Americans, or 1.8 percent of the U.S. population, have antibody to HCV (anti-HCV), indicating ongoing or previous infection with the virus. There are at least six major genotypes and more than 50 subtypes of HCV. Genotypes 1a and 1b are the most common in the U.S. Genotypes 2 and 3 are present in approximately 30 percent of patients. There is little difference in the severity of disease or outcome of patients infected with different genotypes. However, patients with genotypes 2 and 3 are more likely to respond to interferon and ribavirin. HCV causes an estimated 8,000 to 10,000 deaths annually in the U.S.

Isis Pharmaceuticals, Inc. is exploiting its expertise in RNA to discover and develop novel human therapeutic drugs. The company has commercialized its first product, Vitravene(R) (formivirsen), to treat CMV-induced retinitis in AIDS patients. In addition, Isis has 13 antisense products in its development pipeline, with two in late-stage development and six in Phase II human clinical trials. Affinitac(TM) (formerly called LY900003 and ISIS 3521), an inhibitor of PKC-alpha, is in Phase III trials for non-small cell lung cancer, and alicaforsen (ISIS 2302), an ICAM-1 inhibitor, is in Phase III human clinical trials for Crohn's disease. Isis has a broad patent estate, as the owner or exclusive licensee of more than 1000 issued patents worldwide. Isis' GeneTrove(TM) division uses antisense to assist pharmaceutical industry partners in validating and prioritizing potential gene targets through customized services. Isis Therapeutics(TM) is a division focused on the discovery of small molecule drugs that bind to RNA. Additional information about Isis is available at [www.isispharm.com](http://www.isispharm.com).

## **HCV Nonresponders Get Second Chance with Daily Consensus Interferon**

**Medscape Medical News 2002. © 2002 Medscape, Neil Osterweil**

A daily rather than three-times-weekly (TIW) regimen of high-dose consensus interferon followed by combination therapy with interferon (IFN) and ribavirin (RBV) reduced hepatitis C viral loads to undetectable levels in 72% of patients. All of these patients had previously been labeled as nonresponders to combination IFN/RBV therapy, and the majority of whom were infected with the hepatitis C virus (HCV) genotype 1, the most refractory form of the virus, reported Stephan Kaiser, MD, and colleagues from the University of Tubingen, Germany, at the 53rd annual meeting of the American Association for the Study of Liver Diseases.

"This is a remarkable study because it really backdates history", comments Elizabeth Fagan, MD, who has been researching interferon-based therapies for the past two decades and is professor of pediatrics and internal medicine at Rush Children's Hospital and Rush-Presbyterian St. Luke's Medical Center in Chicago, Illinois. "These patients would be discriminated against for being poor responders: they're mostly male, at least a quarter of the study patients had cirrhosis, they're mostly genotype 1, they're the wrong age group - these are patients who are doomed to failure on the current regimes that are being talked about", Dr. Fagan told Medscape.

In several previous studies, retreatment of patients who failed to respond to conventional therapy with IFN-alpha and RBV yields sustained virologic response rates of only about 7%, Dr. Kaiser and colleagues noted in a poster session at the meeting. However, recent studies have shown improved response rates using consensus IFN (interferon alfacon-1, CIFN) even as monotherapy in previous combination therapy nonresponders.

They conducted a study of the efficacy of a CIFN induction therapy followed by a CIFN/ribavirin combination treatment in 120 patients who previously had been determined to be nonresponders to standard combination therapy. By all clinical measures, the odds appear to have been stacked against this group from the beginning: the patients had a mean age of 46 years, 79% were men, all had elevated alanine aminotransferase (ALT) values, and all were viremic. In all, 91% of the patients were found to have HCV genotype 1, which is associated with poor prognosis. In addition, 28% of the patients had evidence of either bridging fibrosis or cirrhosis.

The patients were treated with either CIFN 18 µg daily for 4 weeks followed by 9 µg daily for 8 weeks, or with CIFN 27 µg daily for 4 weeks, followed by 8 weeks of CIFN 18 µg daily. After 12 weeks, treatment in all groups was continued with CIFN 9 µg daily and RBV 10 to 15 mg/kg/day for another 36 weeks.

After the first six weeks, 42% of patients in the 18-µg CIFN group and 57% of those in the 27-µg group had serum HCV RNA levels that were undetectable on assay. After 24 weeks of combined therapy, 64% of those in the 18-µg group and 72% of the patients in the 27-µg group were seronegative on polymerase chain reaction assay.

The treatment was generally well tolerated, with dose reductions required in only 9% to 18% of patients in the 18-µg and 27-µg groups, respectively, and only 6% to 10% required discontinuation of therapy. The most common reasons for withdrawal from treatment were significant reductions in white blood cell and platelet counts, especially in the 27-µg CIFN group. The researchers did not use erythropoietin in this study.

"I think there are two major points to this study", Dr. Kaiser, who is head of the liver outpatient department and lecturer in hepatology at the University of Tübingen, told Medscape. "One is that we continue to keep the patients on daily dosing, and we've performed studies on [treatment-] naive patients where we clearly saw that daily dosing has a significant effect on inhibiting viral replication and getting the virus down, vs TIW dosing, and I think that's especially important for the nonresponder population. I don't think it makes any sense to use TIW dosing in nonresponders, because you have very high likelihood of breakthrough," Dr. Kaiser said.

"The other point is that we start with a considerably higher dose of interferon, based on viral kinetics studies in the naive patients, where we observed a better effect for genotype 1, high-viral-load patients. If you calculate that the observations for the naive populations are also to a certain extent true for the nonresponder populations, then I think it makes sense to use 27-µg doses," Dr. Kaiser told Medscape.

"These data are as good as the current data on patients with genotypes other than 1, the people who have all the good prognostic indicators," Dr. Fagan commented.

## **Roche Stirs Anger over Drug Price**

By Ed Silverman, Star-Ledger Staff

Hoffmann-La Roche Inc. is under fire from a prominent group of AIDS activists over the pricing of its new treatment for hepatitis C.

In a Nov. 4 letter to company executives, the activists criticized the Nutley drug maker for charging nearly \$14,000 a year for the treatment. That is \$850 more than a rival product from Schering-Plough Corp., which has been widely criticized for its own pricing.

The activists described this as an act of "betrayal," because they held numerous meetings with Roche over the past two years to provide patient input about various treatment issues, especially pricing, according to the activists.

Charles Alfaro, a company spokesman, said Roche had not received the letter and could not comment. But when asked about pricing, he said the product was priced competitively.

Among the groups that signed the letter were Project Inform; Hepatitis C Action & Advocacy Coalition; AIDS Treatment Data Network, and Treatment Action Group. AIDS activists are involved in the effort because many AIDS patients also have hepatitis C.

The letter, which accused Roche of "greed and opportunism," could create a public relations quandary for the company, which is counting on the Pegasys treatment to restore its financial fortunes. In recent years, the drug maker has suffered recalls, disappointing sales of key drugs and controversy over other medicines.

Moreover, Roche may find itself further enmeshed in the nationwide debate over the high cost of prescription medicines. In their letter, the activists threatened to raise the issue with Congress and the media as part of their protests over Roche's pricing.

There is no debate that hepatitis C is a big opportunity for Roche. Four million Americans are estimated to have the disease, which is the leading cause of liver transplants.

Until Roche's Pegasys was approved by regulators last month, Schering-Plough had little competition. Last year, Schering-Plough's hepatitis C treatment generated about \$1 billion in worldwide sales.

The real rivalry may not begin until next month, when Roche hopes to receive regulatory approval to sell Pegasys with another drug as part of a combination therapy, which it claims is more effective than a similar Schering-Plough package.

By courting activists with large patient networks, Roche hoped to get an edge in the upcoming battle with Schering-Plough. It also was in Roche's favor that many of these same activists successfully generated bad press about Schering-Plough's pricing.

*November 11<sup>th</sup>, 2002*

## **ALT Doesn't Reveal the Entire Truth about Liver Fibrosis in Hepatitis C**

News Rx, Hepatitis Weekly, by Sonia Nichols, senior medical writer

Liver enzyme levels may not reveal the full picture of liver fibrosis in some patients with chronic hepatitis C.

A collaborative multicenter study of chronic hepatitis C patients in Europe indicates alanine aminotransferase (ALT) values, used as indicators for liver biopsy, may be insufficient for depicting the true extent of a patient's liver disease.

In a study sponsored by Schering-Plough International, Pierre Pradat, of the University of Padova in Italy, joined colleagues from Spain, Sweden, and France to evaluate the predictive value of ALT in relation to liver histology. The retrospective study included 864 patients who were positive for HCV RNA.

"ALT values were obtained at the time of biopsy (before treatment), and normal ALT values were defined as normal values obtained at serial evaluations during a 6-month period," said Pradat and colleagues.

Based on METAVIR scoring for histology, nearly all patients with high ALT levels scored F1, with 88% of those individuals scoring above A1F1, according to study data.

"Among patients with persistently normal ALT values, 65% had a score of at least F1 (negative predictive value, 35%) and 26% had a score greater than A1F1," Pradat and coauthors stated.

Although ALT values were expectantly high among those with liver fibrosis, others with persistently normal ALT values also had fibrosis, which in most instances was mild. However, some individuals with normal ALT values sometimes exhibited marked fibrosis, with some even showing signs of cirrhosis. This data is being published in an article titled "Predictive value of ALT levels for histologic findings in chronic hepatitis C": A European collaborative study. *Hepatology*, 2002;36(4):973-977).

"In this subset of patients, the indication of liver biopsy and the potential benefit of therapy need to be further evaluated," said Pradat and associates. "These results suggest the need to revisit the algorithm for liver biopsy practice."

Key points reported in this study include:

- ◆ Alanine aminotransferase (ALT) values are used for assessing liver functioning in patients with chronic hepatitis C
- ◆ Some patients with persistently normal ALT values will have fibrosis, with others showing signs of cirrhosis.
- ◆ Though valuable, ALT values cannot be used as the only indicator for whether liver biopsy is warranted in patients with chronic hepatitis C.

November 12<sup>th</sup>, 2002

## **Schering-Plough gets subpoenas for sales practices**

Schering-Plough Corp. said on Tuesday it received two additional grand jury subpoenas from federal authorities regarding its sales and marketing practices under a probe into its relationship with insurers and doctors.

The drugmaker said that it received the subpoenas this month from the U.S. Attorney for the District of Massachusetts, which has been investigating certain sales and marketing practices at Schering-Plough in a previously disclosed probe.

Schering-Plough said federal prosecutors are seeking a "broad range" of information related to its Intron A and Rebetron line of hepatitis C products, and oral chemotherapy agent Temodar for brain tumors. They also seek information regarding its marketing contacts with health insurers and doctors.

The company said the U.S. Attorney's office is also seeking information on grants, honorariums or other items of value Schering-Plough gave to insurance companies, doctors and educational institutions.

"It is not possible to predict the outcome of the investigation, which could include commencement of civil or criminal proceedings involving the imposition of fines, penalties," the company said in a release.

Schering-Plough said it is cooperating with the investigation.

A spokeswoman for Schering-Plough declined to elaborate on the nature of the company's relationship with doctors and insurers or the difference between the newest subpoenas and older ones.

The company said in earlier filings with the Securities and Exchange Commission that the U.S. Attorney's Office in Massachusetts was probing whether the average wholesale price declared by pharmaceutical companies for certain drugs improperly exceeds the actual prices, therefore unlawfully inflating certain government reimbursements for drugs.

In March 2001, the company received a subpoena from the Massachusetts Attorney General's office seeking documents concerning the use of average wholesale price and other pricing practices.

The U.S. Attorney's Office in Massachusetts has also investigated sales and marketing practices by other drugmakers, including Bristol Myers-Squibb Co. Eli Lilly and Co. and TAP Pharmaceutical Products, a joint venture between Abbott Laboratories Inc. and Takeda Chemical Industries Ltd.

The Schering-Plough spokeswoman would not say whether the subpoenas into the company were related to the probes into the other firms.

Schering-Plough's image was tarnished last month after a three-day 20-percent fall in its stock price. The company's chief executive officer, Richard Kogan, met with select analysts and investors during that time but the company did not issue any public comment about its falling shares.

Then, at about 10:45 p.m. EST on the third day of the stock fall, Schering-Plough issued earnings expectations for this year and next year that were well below Wall Street's expectations. The Securities and Exchange Commission is investigating the company's disclosure policies.

*November 13<sup>th</sup>, 2002*

## **Nation's First Health Care Center Targeted to Injection Drug Users Opens in New York City. Injection Drug Users Account for 30 Percent of All New HIV/AIDS Cases in the U.S.**

Positive Health Project, a New York City syringe exchange program, and Diversified Health Systems Management, Inc., today announced the opening of Positive Health Care, the nation's first comprehensive health care center targeting high-risk clients, including current and former injection drug users (IDUs). The center aims to minimize the risk of infection with HIV and hepatitis C within this population and to maintain the health of those who already have contracted these diseases.

Positive Health Care provides primary medical care, dentistry, and HIV/AIDS testing and counseling services. The health care center's patient base includes clients from syringe exchange programs such as Positive Health Project and other organizations throughout the city.

"Positive Health Care provides medical services in a respectful, compassionate manner," said Dr. Richard Gold, medical director of Positive Health Care. "It is our hope that by offering them access to high quality and non-discriminatory health care, they will begin to realize their self-worth and make lifestyle changes that can reduce their health risks."

Many injection drug users and other high-risk populations are homeless and therefore have limited access to medical services. Moreover, this population often avoids medical services for fear of legal repercussions and discrimination associated with drug addiction.

Although New York City encompasses only three percent of the U.S. population, the city claims sixteen percent of all AIDS cases in the nation. Of the 4,000 - 6,000 new HIV/AIDS cases reported in New York City in 2000, 39 percent of those infections are attributable to injection drug use.

Independent research studies have shown that Positive Health Project and other needle exchange programs have significantly reduced the risk of HIV infection in New York City among IDUs. According to the Office of Drug Control and Policy, New York City continues to be the most significant heroin destination and distribution center in the U.S.

#### **About Positive Health Care**

*Positive Health Care is a health care center targeted to injection drug users, and founded on the basic principles of harm reduction. The health care center currently includes five exam rooms, one treatment room for medical procedures and three dental suites. Supporting hospital services for Positive Health Care are provided by St. Vincent's Medical Center.*

#### **About Positive Health Project**

*Positive Health Project, Inc. is a HIV prevention and syringe exchange program that targets injection drug users and other substance users, sex workers, transgender individuals and their partners. Positive Health Project's services include syringe exchange, street outreach, support groups, case management, mental health services, HIV/HCV treatment advocacy, HIV/HCV educational workshops, women's services and transgender advocacy.*

November 14<sup>th</sup>, 2002

## **FDA Advisory Committee Unanimously Recommends Approval of Pegasys<sup>®</sup> (peginterferon alfa-2a) in Combination with Copegus<sup>™</sup> (Ribavirin) for Treatment of Hepatitis C**

Roche announced today that the U.S. Food and Drug Administration (FDA) Anti-Viral Drugs Advisory Committee (AVDAC) unanimously voted to recommend marketing approval of Pegasys<sup>®</sup> (peginterferon alfa-2a) in combination with Copegus<sup>™</sup> (ribavirin) for the treatment of chronic hepatitis C.

AVDAC's vote to recommend approval was made after Roche presented results of two pivotal Phase III clinical trials that demonstrate combination therapy with Pegasys and Copegus is a more effective treatment for patients with chronic hepatitis C than treatment with interferon alfa-2b and ribavirin or Pegasys monotherapy.

Pegasys, in combination with Copegus, was granted six-month Priority Review Status in July of this year and Roche anticipates action on the file by the end of the year. This designation is granted to biologics and drugs that if approved, address unmet medical needs, offering a significant improvement in the safety or effectiveness of the treatment, diagnosis or prevention of a serious or life-threatening disease, according to FDA policies and procedures.

"We are delighted with the committee's recommendation and we commend the committee on its thorough analysis of Roche's extensive clinical development program," said Georges Gemayel, Vice President, National Specialty Care Business Operations at Roche. "Our studies were designed to reduce the duration and dose of therapy for certain patient groups while not compromising efficacy. This can lead to improved safety and a reduction in cost."

Pegasys monotherapy was approved by the FDA on October 16, 2002 as a simple, fixed dose of 180 mcg for the treatment of adults with chronic hepatitis C who have compensated liver disease and have not previously been treated with interferon alfa. Patients in whom efficacy was demonstrated included patients with compensated cirrhosis. Clinical trials of Pegasys have shown that patients can determine at 12 weeks if they are unlikely to obtain a sustained virological response with Pegasys monotherapy.

## **About Pegasys**

*Pegasys is supported by the most extensive development program ever undertaken for a hepatitis C treatment. Pegasys has been studied in a variety of patient populations, including those with the most difficult to treat form of the disease – patients with genotype 1 and with cirrhosis (scarring of the liver).*

*Pegasys is made when interferon alfa-2a undergoes the process of pegylation in which one or more chains of polyethylene glycol, also known as PEG, are attached to another molecule.*

*In Pegasys, a large, branched, mobile PEG is bound to the interferon alfa-2a molecule and provides a selectively protective barrier. Pharmacokinetic behavior of the end product depends on the length of the PEG and the nature of the link between the PEG and the protein. The high molecular weight (40 kilodalton) branched PEG in Pegasys has been shown to provide sustained pegylated interferon alfa-2a exposure at clinically effective levels over the one-week dosing period.*

*In contrast, interferons with smaller PEGs are excreted more rapidly by the kidneys, requiring more frequent dosing, according to earlier Roche studies, using smaller PEGs developed by the company.*

*Pegasys has been approved for use in more than 50 countries, including all European Union countries.*

## **Pegasys Adverse Events**

*Alfa interferons, including Pegasys, may cause or aggravate fatal or life-threatening neuropsychiatric, autoimmune, ischemic, and infectious disorders. Patients should be monitored closely with periodic clinical and laboratory evaluations. Patients with persistently severe or worsening signs or symptoms of these conditions should be withdrawn from therapy. In many, but not all cases, these disorders resolve after stopping Pegasys therapy.]*

*Pegasys is contraindicated in patients with hypersensitivity to Pegasys or any of its components, autoimmune hepatitis, and decompensated hepatic disease prior to or during treatment with Pegasys. Pegasys is also contraindicated in neonates and infants because it contains benzyl alcohol. Benzyl alcohol has been reported to be associated with an increased incidence of neurological and other complications in neonates and infants,*

*The most common adverse events reported for Pegasys, observed in clinical studies to date (n=559), were headache (54%), fatigue (50%), myalgia (37%), pyrexia (36%), rigors (32%), arthralgia (28%), nausea (23%), alopecia (23%), injection-site reaction (22%), neutropenia (21%), insomnia (19%), depression (18%), anorexia (17%), diarrhea (16%), dizziness (16%) and irritability (13%).*

*Serious adverse events include neuropsychiatric disorders (suicidal ideation and suicide attempt), bone marrow toxicity (cytopenia and rarely, aplastic anemia), cardiovascular disorders (hypertension, arrhythmias and myocardial infarction), hypersensitivity (including anaphylaxis), endocrine disorders (including thyroid disorders and diabetes mellitus), autoimmune disorders (including psoriasis and lupus), pulmonary disorders (dyspnea, pneumonia, bronchiolitis obliterans, interstitial pneumonitis and sarcoidosis), colitis, (hemorrhagic/ischemic colitis), pancreatitis, and ophthalmologic disorders (decrease or loss of vision, retinopathy including macular edema and retinal thrombosis/hemorrhages, optic neuritis and papilledema).*

*In addition, ribavirin has its own adverse events, the most serious of which are birth defects. For this reason, ribavirin and interferon with ribavirin must not be used by women or male partners of women who intend to become pregnant during therapy or within six months of therapy. Ribavirin has been shown to cause anemia in some patients, which may exacerbate previous coronary heart disease, or deteriorate heart function.*

## **About Roche**

*Hoffmann-La Roche Inc. (Roche), based in Nutley, N.J., is the U.S. prescription drug unit of the Roche Group, a leading research-based health care enterprise that ranks among the world's leaders in pharmaceuticals, diagnostics and vitamins. Roche discovers, develops, manufactures and markets numerous important prescription drugs that enhance people's health, well-being and quality of life. Among the company's areas of therapeutic interest are: dermatology; genitourinary disease; infectious diseases, including influenza; inflammation, including arthritis and osteoporosis; metabolic diseases, including obesity and diabetes; neurology; oncology; transplantation; vascular diseases; and virology, including HIV/AIDS and hepatitis C.*

*For more information on the Roche pharmaceuticals business in the United States, visit the company's*

November 15<sup>th</sup>, 2002

## **Hematologic Toxicity to Interferon/Ribavirin Does Not Vary by Race**

The largest study of antiviral therapy for hepatitis C in African Americans to date shows that, despite reports to the contrary, hematologic toxicity is not greater in that race compared with Caucasians.

"Reports indicate that African Americans respond less well to antiviral therapy than Caucasians," Dr. Robert Brown of Columbia University College of Physicians and Surgeons in New York told attendees of the 53rd annual meeting of the American Association for the Study of Liver Diseases.

Results of a study of more than 3000 treatment-naïve patients with hepatitis C indicate otherwise, Dr. Brown reported in a preliminary presentation of 12- to 24-week data from the ongoing trial.

Patients were randomized to 800 mg ribavirin qd or to weight-based dosing of the drug, with doses ranging from 800 mg to 1400 mg qd. All patients received pegylated interferon alpha 2b at 1.5 micrograms/kg once a week.

The patient population consisted of 81% Caucasians, 9.3% African Americans, 5.4% Hispanics and 2.5% Asians. In this early phase of study, the investigators have analyzed the rate of adverse events, primarily the hematologic effects.

"Though African Americans started with a lower white blood count at baseline, the drop [across races] was similar," Dr. Brown told Reuters Health in an interview during the meeting. Neither did the incidence of anemia differ by race, he added.

Rates of dose reductions were also similar among the ethnic groups. Investigators are still blinded as to virologic response in the study population.

"We have not yet broken down the incidence of other side effects by race," he said, "but it seems unlikely that the difference [in antiviral response] is due to toxicity."

Dr. Brown suspects that the difference in response may be due to drug adherence. "We need to strive toward making drugs better, but in the meantime we need to promote adherence," he said.

## **HCV Particle Densities Differ in Immunocompetent and Immunodeficient Patients**

The finding that hepatitis C virus (HCV) particle density patterns are different in chronically infected immunocompetent and immunodeficient patients may be a key to understanding the mechanisms by which the virus persists, researchers report in the November issue of the *Journal of Medical Virology* (J Med Virol 2002;68:335-342).

Dr. G. L. Toms from the Medical School, Newcastle upon Tyne, UK, and colleagues studied blood samples from patients with hepatitis C who were immunocompetent and immunodeficient. The blood samples were fractionated by ultracentrifuge into low density (< 1.063 g/mL), intermediate density (1.063g/mL to 1.21 g/mL) and high density (> 1.21 g/mL) fractions, and HCV RNA measured in each.

The researchers found that the low-density lipoproteins co-fractionated with low-density viral particles, while the high-density lipoproteins co-fractionated with intermediate-density particles. Immunoglobulins were found only in high-density fractions, they add.

Among patients who had congenital immunodeficiencies, the mean titers of HCV RNA were the same in each fraction.

In contrast, in immunocompetent patients who were antibody-positive, virus titers were absent or reduced in both the high- and low-density fractions, the researchers found. This suggests that they are subject to antibody-mediated clearance.

Patients in both groups had approximately the same amount of intermediate-density virus particles, which indicates that humoral immune responses do not clear these particles, Dr. Tom's team notes.

The results of immunoprecipitation experiments found that intermediate-density HCV particles did not complex with high-density lipoprotein or with immunoglobulins, they add.

"These virus particles remain enigmatic," Dr. Toms and colleagues write. "Increased knowledge of their heterogeneity, their origins and their interactions with other blood proteins may be fundamental to our understanding of the mechanisms of persistence, and thus the pathogenicity, of the virus."