

A January 15th 2002 thru February 15th 2002 Review of HCV and HIV/HCV Coinfection Related News and Highlights

Alan Franciscus
Editor-in-Chief

The last month has provided some exciting news in HCV and HIV/HCV coinfection. It has also been a very difficult month for Schering Plough, manufacturer of Intron A, Rebetron, Rebetol and Peg Intron due to ongoing scrutiny regarding the Patient Assurance Program as well as the wait list that has had to be developed for Peg Intron due to manufacturing problems that the company is experiencing. On the positive side for the pharmaceutical industry, InterMune announced that they are re-launching Infergen as well as announced exciting advances in the development of gamma interferon for the prevention of fibrosis progression in advanced liver disease plus Roche announced that they will be launching Pegasys (pegylated interferon alpha 2a) in the second half of 2002. The following is a compilation of the news and covers the following topics:

1. Schering Plough – the optimism as well as the problems they are facing
2. Prevalence of hepatitis B and hepatitis C infections among ethnic minorities living in Thailand
3. NIH and AHRQ are to collaborate on evidence used to create consensus reports
4. Brazil wages war on hepatitis C drug pricing
5. Schering Plough announces the need for a wait list for Peg Intron due to insufficient supplies
6. NATAP articles
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18. Roche Holding AG announced that the company will launch Pegasys in the second half of 2002
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29. Phlebotomy may delay progression of liver fibrosis in chronic hepatitis C patients
30. ViroLogic announces agreement with Achillion Pharmaceuticals to evaluate novel next generation anti-hepatitis and HIV agents
31. Deaths from hepatocellular carcinoma have increased over the past 30 years in the United

States

32. InterMune announces fourth quarter and year end financial results – product revenue growth exceeds 250%
33. Interferon-gamma improves response to interferon alpha in hepatitis C
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1. On January 15th, 2002 the following article was posted by the New York Times:
“At Schering, Optimism and Problems”.

Pharmacies nationwide are stocked with Clarinex, the company's new allergy drug. Schering-Plough is optimistic that Clarinex will be as big a blockbuster as Claritin, its existing allergy medication and by far its most important product. And the company is near an agreement with regulators to resolve longstanding problems manufacturing the medicines it sells.

Schering-Plough's chief executive, Richard Jay Kogan, predicted last month that "2001 will be seen as a watershed year, when this company undertook important changes to remake itself." But to many others, Schering-Plough's prospects are less certain. The company is facing a possible record government fine for quality control problems in its factories. Many drug industry experts are not convinced that Clarinex is a better drug than Claritin, which it is supposed to replace. And with its stock roughly 30 percent lower than it was a year ago, Schering-Plough is periodically mentioned as a takeover candidate. This year "will be a challenging year for Schering-Plough, and 2003 could be even more so," said Hemant K. Shah, an independent drug industry analyst in Warren, N.J. Schering-Plough's troubles began in 1998, although at the time, few investors knew. The company's sales of Claritin were soaring as it spent \$137 million to advertise the drug, according to Competitive Media Reporting — more than any other company was spending on a single medicine. Schering-Plough's Claritin ads, among the first to take advantage of the loosening of restrictions on pharmaceutical advertising, became ubiquitous, showing up on television, in magazines, subway cars and even paper bags from pharmacies. But federal regulators issued three warning letters to Schering-Plough that year, detailing widespread problems in factories in New Jersey, Puerto Rico and Ireland. During the next three years, the company received two more warning letters about similar manufacturing problems, recalled several defective medicines, and was told by consultants it hired, according to an internal report later made public, that some parts of its factory in Kenilworth, N.J., were "out of control." Over the last several years, hundreds of consumers, according to federal documents, have complained that the company's bottles of Nasonex, a nasal spray, did not work. And a Food and Drug Administration official said in an interview last summer that the agency was investigating whether patients might have died after Schering-Plough shipped asthma inhalers that contained little or none of the medicine that would have helped them breathe during an attack. The company says there is no evidence that ties any deaths to its products and that it has done nothing wrong. After holding up approval of Clarinex because of the factory problems, the F.D.A. approved the drug late last month — but at a high price. The company said it expected to pay a fine of up to \$500 million to the government for its protracted manufacturing problems, five times the highest penalty a drug company has paid for such violations. Apart from the fine, Schering-Plough has spent more than \$60 million to clean up its manufacturing problems, and is adding about 500 employees to its factory payrolls, many of them specializing in quality control. Schering-Plough needs to keep sales increasing to pay for the manufacturing problems, particularly since it has not reserved money to pay the possible fines. But the company is more dependent on a single product — Claritin — than almost any other major drug manufacturer. Sales of all forms of Claritin accounted for 49 percent of Schering-Plough's retail pharmaceutical sales in the United States in the twelve months ended last November, according to Scott-Levin, a consulting firm, and 34 percent of total worldwide sales in the first nine months of 2001, according to the company. The company now needs to switch patients from Claritin to Clarinex before the main patent on Claritin expires at the end of year, which will allow other companies to sell generic versions. Late last month, in an attempt to stimulate sales of Clarinex, the company said the price of the new drug would be 18 percent below Claritin's. But there have been no studies so far comparing Clarinex and Claritin, and few drug industry experts say that Clarinex offers significant advantages over the older medicine. "Claritin is already a very safe and effective drug," Mr. Shah said. "Not all drugs can be improved. Unless you can tell the consumer that this is a better drug, it will be difficult to get them to switch." Mr. Shah expects Clarinex to sell well this year, perhaps reaching \$700 million in sales. But he expects sales of both Clarinex and Claritin to then fall sharply

when the Claritin patent expires, he said. Profits would follow suit, particularly if Schering-Plough finds that it has to cut prices sharply to compete with the new generics. Mr. Shah and other Wall Street analysts say the company's stock — down more than 30 percent from a year ago — could fall even further. Several investment bankers said that some of their clients had already looked at Schering-Plough as a possible takeover target, but the bankers were not aware of active merger discussions. Top executives at Schering-Plough, which has its headquarters in Kenilworth, declined requests for interviews. But William O'Donnell, a Schering-Plough spokesman, said the company believed that it would be able "to establish Clarinex as an important new therapy." The company's clinical trials have shown, Mr. O'Donnell said, that patients' allergy symptoms were reduced 24 hours after taking Clarinex. "We believe this means patients can wake up and enjoy 24 hours of non-drowsy seasonal allergy relief," he said. Advertisements for Claritin, however, also promote it as a "once a day" drug. Mr. O'Donnell said Schering-Plough expected its earnings to grow this year by the "low double-digits." Schering-Plough is working closely with the F.D.A. to resolve the manufacturing issues, he said, although the final terms of the settlement agreement with the government are still unclear. The company does not talk, Mr. O'Donnell said, about merger or takeover speculations. Schering-Plough is determined not to let its sales slip away. Mr. Kogan told analysts last summer that the company would "be very aggressive" in marketing Clarinex, once it was approved. Mr. Kogan also said at the time that the company did not plan to let generic companies start selling Claritin when the product's main patent expires in December. The company has secondary patents on Claritin that extend beyond 2002, Mr. Kogan said. "We will defend our patents vigorously," he added. The company has spent millions of dollars lobbying in Washington in recent years, trying to get lawmakers to pass legislation that would extend the expiration date of Claritin's patent because they say the drug's approval was held up for too long at the F.D.A. But so far, those attempts have failed. Dr. Leonard S. Yaffe, an industry analyst for Banc of America Securities, said he was expecting a generic version of Claritin to hit pharmacy shelves in December, when the first patent on the drug expires. And he expects the decline of Claritin and Clarinex sales to be very sharp, similar to the decline in sales of the antidepressant Prozac, which lost its patent protection last summer. Eli Lilly's sales of that drug fell more than 70 percent within three months after Barr Laboratories, a maker of generic drugs, began selling a lower-priced version of the drug.

Schering-Plough has been an aggressive marketer of many of its drugs. Last year, the Federal Trade Commission charged Schering-Plough with paying two generic drug makers not to sell cheap versions of K-Dur 20, a potassium chloride supplement made by Schering-Plough. The company is vigorously contesting the government's allegations. In addition, in the last couple of years, many patients with hepatitis C have complained about Schering-Plough's marketing of two expensive treatments. The company bundled the two drugs together, charging about \$18,000 for the needed year's worth of treatment and refusing to sell one without the other. Schering-Plough argued that for safety reasons, the drugs should only be taken together, but patients who had wanted to take one of the drugs in combination with another company's drug disagreed. "They have coerced patients into buying both products," said Brian D. Klein, co-founder of the Hepatitis C Action and Advocacy Coalition, a patient group. "They have not made many friends through their marketing tactics."

Schering-Plough has several promising drugs in its research pipeline, which could eventually help offset a decline in Claritin sales. Asmanex, a promising new asthma drug, could be approved by the F.D.A. this year. Dr. Yaffe said maximum annual sales of Asmanex could reach more than \$1 billion. Schering-Plough and Merck ([news/quote](#)) also recently teamed up to file for approval of Zetia, a new type of cholesterol drug. But the new drugs, Dr. Yaffe said, will not begin lifting revenue significantly until 2004.

2. Also on January 15th, 2002 the following article was written by an Editor from Hepatitis Weekly: "Epidemiologists have produced one of the first studies to examine the prevalence of hepatitis B and C virus (HBV, HCV) infections among ethnic minorities living in Thailand."

The high rate of HBV infections among those groups suggests public health policies addressing vaccination practices may be warranted. T. Ishida, University of Tokyo, Japan, headed the epidemiological investigation. Ishida and colleagues identified 658 people representing 7 ethnic groups who lived in northern Thailand for study participation. Researchers listed the individuals as being of Lahu, Lisu, Shan, Red Karen, White Karen, Hmong, and Akha ethnicities. Each person was tested for three viral markers in their serum that would

indicate current or previous infection: hepatitis B virus surface antigen (HBsAg), antibody to hepatitis B surface antigen (anti-HBs), and antibody to HCV (anti-HCV). "An overall prevalence of HBsAg, anti-HBs and anti-HCV in the 7 groups was 10.3, 33.0, and 3.8%, respectively," said Ishida and coworkers. "The positivity rate of HBV and HCV infection in each tribe ranged from 4.7% (Akha) - 22.6% (Lahu) and 2.0% (Hmong and Akha) - 8.1% (Shan), respectively," researchers added.

Although there were no differences with respect to gender in the case of HBV prevalence, there were more men than women infected with HCV. Overall, HBV prevalence was higher than HCV prevalence (Prevalence of hepatitis B and C virus infection in rural ethnic populations of northern Thailand, *Journal of Clinical Virology*, February 2002;24(1- 2):31-35).

In addition, there were HBV but not HCV prevalence differences among the various ethnic minority groups.

Given the high rates of hepatitis infections, particularly HBV infections, among the ethnic minority groups of northern Thailand, Ishida and coauthors recommended that a nationwide, community-based survey of hepatitis virus epidemiology be performed in order to develop a strategic plan for prevention and treatment.

The corresponding author for this study is T. Ishida, Unit of Human Biology and Genetics, Department of Biological Sciences, School of Science, University of Tokyo, Hongo, Bunkyo-ku, 1130033, Tokyo, Japan.

Key points reported in this study include:

HBV prevalence among ethnic minority groups in northern Thailand is high and higher in some groups more than in others

- HCV infections are more prevalent among men than among women in the ethnic minority groups of northern Thailand
- A nationwide, community-based survey of HBV and HCV prevalence in Thailand needs to be conducted so as to produce a strategic plan for prevention and treatment

3. Additionally on January 15th, 2002 the press announced that the NIH and AHRQ are to Collaborate on Evidence used to Create Consensus Reports.

The National Institutes of Health (NIH) has asked the Agency for Healthcare Research and Quality (AHRQ) to help bring more evidence — and a better assessment of that evidence — to the table for the creation of consensus statements.

Each year, the NIH convenes many panels of experts to assess, translate and disseminate results of the latest research on a particular disease or condition. The panels deliberate over several days and issue consensus statements at the end, which are used by insurers, health practitioners, and the general public.

Now, the AHRQ's 12 evidence-based practice centers in the U.S. and Canada will contribute their expertise, submitting formal reports based on their review of all available, relevant scientific literature.

With AHRQ's participation, "each panel will have a strong, already heavily-scrutinized body of evidence before them," Kelli Marciel, communications director for the NIH's Office of Medical Applications of Research told Reuters Health. "It provides them good information on not just what evidence is out there, but also the quality of that evidence," she said, noting that in the past, trials may have been presented to the panels without deep analysis of the methods used.

The AHRQ centers are contributing to the next four NIH conferences, starting with a meeting being held January 14-16 on the use of endoscopic retrograde cholangiopancreatography (ERCP) for diagnosis and therapy.

Upcoming meetings will cover management of the clinically in apparent adrenal mass (February 4-6), management of hepatitis C (June 10-12), and symptom management in cancer (July 15-17).

4. *More news from January 15th, 2002. The press released an article titled "Brazil Wages War on Hepatitis C Drug Pricing."*

Brazil's Health Ministry, emboldened by its successful fight for cheaper AIDS (news - web sites) medicines, is telling makers of a hepatitis C drug to slash prices or face having their patents broken.

Brazil wants pharmaceutical giants Schering-Plough Corp. and Roche Holding AG to reduce the price of the hepatitis C drug pegylated interferon, allowing Latin America's largest country to cure more people with the disease at a much lower cost.

The drug, sold by Schering-Plough as PegIntron and by Roche as Pegasys, is up to 27.5 times more expensive than the standard interferon now used by Brazil's public health service.

Using the drugs could increase the number of Brazilians cured of the illness to 45 percent from 36 percent, the Health Ministry said.

At current prices, the drugs would cost Brazil 200 million reais (\$83 million) per month to treat 7,000 hepatitis C sufferers, compared with 15 million reais (\$6.3 million) it currently spends monthly, the ministry said.

The ministry will be looking to tap the international clout it won when it strong-armed drug firms to lower AIDS drug prices. Its tough stance on AIDS drugs won acclaim for Brazil and for Health Minister Jose Serra, expected to run for president in October elections.

The ministry took up talks with the companies in December and negotiations are expected to continue this month.

Schering-Plough and Roche in Brazil, the United States and Switzerland declined to comment on negotiations.

Last year, Brazil pressured Switzerland's Roche and the United States' Merck & Co. Inc. to cut prices on their AIDS drugs by 40 percent to 65 percent after threatening to copy them locally.

A 1999 Brazilian decree allows the country to issue a compulsory license to produce medicines locally in cases of a national emergency or out of public interest.

In its fight against AIDS, for which it has been held up as a model for the developing world, Brazil is now challenging Abbott Laboratories Inc. to lower the price on its HIV drug Kaletra or see its patent broken.

Brazil produces eight out of the 12 drugs used in an anti-AIDS drugs cocktail distributed free to patients. But high prices of the remaining drugs raise the cost of treatment.

5. *On January 16th the following was announced. "Schering-Plough Corp., citing insufficient supplies of its PEG-Intron treatment for chronic hepatitis C, said on Tuesday it may resort to a waiting list for patients seeking the drug."*

"The overwhelming response to PEG-Intron and Rebetol combination therapy since its launch has recently led the company to conclude that demand for PEG-Intron would exceed its near-term ability to ensure supply of product in the United States at current new-patient enrollment rates," the company said in a statement.

Schering-Plough said it started what it calls an "access assurance" program in October aimed at tracking

how much drug is needed, and that patients would be granted a continued supply.

The waiting list is expected to start for newly enrolled patients in the next 10 days, the company said. Patients on the waiting list would be expected to begin treatment in about 10 to 12 weeks, the company estimates.

Schering-Plough's biotechnology production facility in Ireland is running at full capacity for PEG-Intron and the company is building another biotechnology facility in Singapore for PEG-Intron and other products.

Schering-Plough spokesman Robert Consalvo said 60,000 patients in the United States are enrolled in the access assurance program, so far. This also includes some patients who were receiving treatment before the access assurance program was started in October. Consalvo said the company is establishing an independent medical board to review urgent requests for PEG-Intron therapy and it is allocating some of its supplies to meet emergencies.

6. On January 17th, 2002 the following articles were posted at <http://www.natap.org>

- a. *"Increased Toxicity in Coinfected Patients Receiving Peg-Intron"* was posted at <http://www.natap.org/2001/aasld2/day35.htm>

This study looks at HCV/HIV coinfecting patients on HAART and receiving IFN or Peg-Intron. The study reports finding after 12 weeks of comparing Peg Intron + ribavirin to standard IFN + ribavirin that more significant or faster declines in platelets & neutrophils in coinfecting patients receiving Peg-Intron. Lactic acidosis was experienced by 1 patient receiving d4T/ddl and required hospitalization within 20 weeks of starting HCV therapy, 3 additional patients experienced elevated lactate within 11-19 weeks on AZT/3TC, d4T/3TC or ddl/d4T. Standard recommendations in HIV are not to test lactate. In this study, baseline lactates were not reported and we are unsure about the lactate testing reliability (lactate is difficult to reliably test). These study results suggest HIV-infected patients should be monitored more frequently, particularly in the early stages after starting therapy for neutrophils and perhaps lactate.

- b. *"Pancreatitis & Interferon/Ribavirin in Coinfected Patients"* was posted to <http://www.natap.org/2001/ICAAC/day30.htm>

At ICAAC in December a research group from Parkland Hospital in Dallas also reported seeing problems associated with patients on d4T/ddl and starting HCV therapy. They looked at 22 patients with normal lipase prior to treatment. 10 of 25 had significantly elevated lipase or amylase during therapy with 5 experiencing clinical pancreatitis. None of the patients were alcohol users. The authors concluded d4T/ddl should be used with caution when giving HCV therapy. Ribavirin increases ddl exposure in vitro.

7. On January 18th, 2002 the press announced the following: *"VA Launches Four Hepatitis C Centers."*

In its continuing efforts to provide care to more than 80,000 veterans infected with hepatitis C, the Department of Veterans Affairs (VA) on Jan. 1, 2002, funded four new centers to evaluate and improve hepatitis C screening, testing, clinical care and education.

"These new centers will enhance VA's ability to respond to a large and growing public health problem," said Dr. Frances Murphy, deputy under secretary for health. "They will spearhead efforts to improve care, educate veterans and health care professionals, and evaluate current programs. Ultimately, these efforts will benefit all Americans affected by hepatitis C."

Each of the centers will receive annual funding of up to \$500,000 for five years, plus start-up costs. The centers are located at Minneapolis, San Francisco, West Haven, Conn., and Seattle, in conjunction with the Portland, Ore. VA medical center.

"VA screens, tests and treats more people with hepatitis C than anyone else in the country," said Dr. Lawrence Deyton, director of the Public Health Strategic Health Care Group (PHSHG), which oversees VA's

hepatitis C program. "Even so, VA continues to explore new ways to improve its programs. These new centers will function as field-based clinical laboratories to evaluate current practices and develop new tools for improving the quality of care."

The new centers build on the success of the previous Centers of Excellence in Hepatitis C program, established by VA in 1999. VA also regularly cooperates in many veteran outreach partnerships, conducts extensive research and sponsors educational conferences.

"VA has been and continues to be a leader in hepatitis C programs in the U.S.," said Dr. Michael Rigsby, Director, HIV and Hepatitis C Programs, PHSHG. "In the past several years, VA has educated providers, including updating and distributing treatment guidelines and clinical protocols, hosting national symposiums, setting up a Web site with information for both clinicians and patients, holding a nationwide teleconference and launching a cooperative study involving 26 medical centers."

"VA is in an extraordinary position to continue to lead the way in this rapidly changing area of health care and the new centers will play a critical role," said Murphy.

To learn more about hepatitis C in VA, see <http://www.va.gov/hepatitisC>

8. January 19th, 2002 it was announced that Boulder Biotech's Trial Drug Gives Hope to Hep C Sufferers.

Randi Wheeler of Parker speaks for many with hepatitis C when she says that a more effective and comfortable treatment for the incurable viral infection couldn't come soon enough. That's why millions like her are looking with hope to Ribozyme Pharmaceuticals Inc. (RPI), a Boulder biotechnology company that is developing Heptazyme, a new drug that promises a completely new kind of approach to attacking the liver disease.

"The concept of Heptazyme is very exciting," said Wheeler, who has had hepatitis C for nearly 30 years and runs a support group for those with the disease. "I am hoping for anything that is not as toxic as interferon and ribavirin."

Interferon and ribavirin are two drugs that, when injected together, help slow down the production of the hepatitis C virus, while boosting the body's immunity to it. At this time, they represent the leading treatment regimen for the disease. But they are not without serious side effects, including fatigue, nausea and vomiting, muscle aches, headaches, weight loss, depression and more. Moreover, they generally work in less than 50 percent of patients.

RPI, by contrast, wants to challenge the hepatitis C virus directly. Heptazyme, a compound based on chemically synthesized RNA molecules called ribozymes, is designed to act like a pair of molecular scissors and selectively cut the disease-causing proteins in the offending virus to stop it from replicating and infecting the liver. Furthermore, the company anticipates a higher level of efficacy and fewer side effects than current treatment methods yield.

"The concept is unique," said Thelma King Thiel, chief executive officer of the Hepatitis Foundation International in New Jersey. "We're hopeful it will be an improvement (over current treatment methods), but nobody is going to say until it is finished with phase III of its trials."

Before it passes that third phase of clinical trials, which is mandated by the Federal Drug Administration before a company can market a drug, Heptazyme must complete phase II to determine its effectiveness. The company has completed the first phase of clinical trials, which proved that the drug is safe.

Alene Anne Campbell, vice president of corporate development for RPI, said the second phase of trials will run through the end of 2002 and the third phase should be completed a couple of years after that. The second-phase trials are going on at six different sites across the nation, including Denver.

"A lot of people are waiting for these studies, particularly those who haven't responded to interferon," Wheeler said.

Dr. Gregory Everson, director of hepatology (the science of treating the liver) at the University of Colorado Health Sciences Center in Denver and the principal investigator for the second-phase trial, said it's too early to tell whether Heptazyme will be the miracle drug for hepatitis C patients. "Like with any new drug being developed, there is an initial boost of enthusiasm," he said. "The reality is that we just started the trials, and there is no data on effectiveness yet."

The hepatitis C virus, which acts on the liver, can eventually cause cirrhosis and death. The Centers for Disease Control says that 80 percent of people do not show symptoms, which include jaundice, fatigue, abdominal pain and nausea, and may not even realize they have the virus until substantial liver damage has already occurred.

Since hepatitis C is only transmittable via blood-to-blood contact, health professionals encourage testing for the disease to anyone who has shot up drugs, snorted cocaine, gotten tattoos or body piercing with dirty equipment, or received a blood transfusion prior to 1992 (when proper screening was applied to the nation's blood supply).

RPI got its start in 1992 in Cleveland and moved to Boulder a few months later. The company hired 130 employees at its facility on Wilderness Drive in Boulder and has not laid off anyone this year, Campbell said. "We always recruit the very best from around the world," she said, "We have the Russian contingent, the French contingent - the best from around the world."

RPI was created with the mission to commercialize Dr. Thomas Cech's 1981 discovery of ribozymes at CU for use in human therapeutics. Competitive Technologies Inc., a Fairfield, Conn. company that brings to market products that are being developed at universities and in private industry, was the first to acquire the rights to Cech's ribozyme-based technology.

"We introduced the technology to RPI," said Johnny Johnson, a spokesman for Competitive Technologies. "It's now up to Ribozyme (RPI) to say, 'What can we do with this?'"

RPI has used the technology to develop several other ribozyme-based drugs, including Angiozyme and Herzyme, two anti-cancer drugs, and HepBzyme, a drug to treat hepatitis B. "The beauty of this approach is that it could be highly applicable," Everson said. "We're enthusiastic that this is a new era in the treatment of viruses."

Overall, RPI has spent \$139 million on research and development. Though it has no sales so far, the publicly traded company reported total revenues in 2000 of more than \$15 million, all coming from collaborative licensing agreements and joint ventures with other pharmaceutical companies. It recently raised \$9.5 million through a new issue of common stock.

But like many biotech companies in an R&D phase, the company is spending more than it is taking in, reporting a net loss of nearly \$16 million last year. And the recent biotech slump has hit RPI's stock hard. Whereas the company's share price once topped \$70 in early 2000, shares of RPI closed at close to an all-time low of less than \$4 in early December.

Losses continued into 2001 for RPI, with \$3.8 million alone in lost revenue attributable to the termination of its joint venture with pharmaceutical giant Eli Lilly and Co. to develop Heptazyme. Instead, RPI repurchased its rights to the drug.

"Lilly wasn't moving as fast as we wanted them to, and there were some buyback provisions in the contact, and so we bought back our rights to the drug" Campbell said.

Much of RPI's value - it still has a market capitalization of nearly \$70 million - lies in the approximately 300 patents and pending patents it holds and the profits that that intellectual property will bring the company once it completes its clinical trials, gets its government approvals, and brings its products to market.

How much it will charge for Heptazyme to recoup its development costs is unknown, but Thiel, of the Hepatitis Foundation International, hopes the cost is reasonable. She said many patients presently face a price of \$20,000 a year for interferon/ribavirin combination treatment.

"The pricing of the medications is extremely high, and many people can't afford to get treated," she said.

Whatever price RPI eventually sets for Heptazyme, the market is enormous. Approximately 4.5 million Americans, and 175 million people around the world, are infected with hepatitis C, according to the World Health Organization.

"With the number of people with hepatitis C and the ones that are going to get it, it's a huge market," said Johnson of Competitive Technologies.

9. On January 19th, 2002 the following e-mail was sent to Jay Siegel, Director of CBER at the FDA. It was also very widely distributed.

Jay Siegel, Director
OTRR, CBER
U.S. Food And Drug Administration
Woodmont Office Complex 1
1401 Rockville Pike, HFM-500
Rockville MD 20852

Dear Dr. Siegel,

As you may be aware, Schering-Plough has recently announced the start of a wait list for the PEG-Intron Access Assurance registration program. This action is adding to existing patient and provider anxiety and frustration with this controversial program. However, this wait list is deflecting attention from a more serious concern that I believe warrants investigation by CBER as soon as is possible.

We are receiving reports from around the country of HCV patients registered in the Schering PEG-Intron Access Assurance program that are experiencing significant delays in receiving their refills of PEG- Intron and consequently, are missing doses. Patients are dispensed four, weekly PEG-Intron doses per monthly prescription/refill. Patients often are not allowed to renew a prescription with their insurance and pharmacy earlier than 3 weeks into that month; about the time they are administering the fourth medication dose (~day 22). We have received reports of patients not receiving drug for up to 10 days past their next scheduled dose being due to be administered (17 days past this last administered dose). Patients are missing doses of drug, a situation that can lead to viral resistance and treatment failure.

Schering has previously stated that this program was designed to assure access to medication for patients who are registered. These patient reports suggest that the program is failing to achieve this goal.

It is my understanding that FDA had previously decided it did not have regulatory authority over this program, as the agency considered it purely to be a marketing concern. But now we seem to be experiencing production shortages and/or distribution problems for this drug that DIRECTLY affect safety and efficacy for those individuals currently on therapy. This is beyond a marketing issue and is serious.

I ask that CBER investigate this situation as soon as is possible and to work with Schering to quickly find solutions to assure that the company fulfills its responsibility to these patients by providing drug in a timely manner to allow that they do not miss doses due to these company problems.

Please contact me if you have any questions or would like to discuss this situation further.
Thank you for your assistance in this matter.

Sincerely,

Brian D. Klein, MA, LMSW
Co-founder
HAAC-SF
Tel/fax: 415.863.5172

Cc: Richard Klein, Office of Special Health Issues, FDA
Aracelia Vila, Vice President, Public Affairs, Schering-Plough Corporation

10. On January 20th, 2002 the following article titled "Shortage of Organs Leaves Few Options" was released by the press.

The shortage of available organs has forced surgeons to rely on living donors, even though the delicate transplant procedure is still fraught with medical and ethical concerns, doctors said. "No one in their right mind would ever want to do a living-donor transplant," said Dr. James Piper, a surgeon who is the director of a liver-transplantation program at Inova Fairfax Hospital in northern Virginia.

"It's crazy," he said. "But you have to put it in perspective. You have to look at the options." Piper said that in New York alone, the organ-donor shortage has gotten so bad that 20 percent of the people waiting for a liver will die without getting the chance of a transplant.

Adam Hurewitz, 54, a Long Island doctor, could have been among that number was it not for the selfless act of his brother, Mike, who donated about 60 percent of his own liver so that Adam could live. Three days later, Mike Hurewitz, 57, died.

Experts said there are a number of things that can go wrong during or after such a delicate procedure, including an injury to the bile duct. In some cases, dangerous blood clots can develop or heart attacks can occur, doctors said.

Fewer than 10 people out of 1,200 have died nationwide as a result of the operation, some of them because of inexperienced surgeons, doctors said.

"It's not a huge number, but it's certainly too high," said Dr. John Balint, director of the Center for Medical Ethics at Albany Medical College and a member of the ethics committee of the American Association of the Study of Liver Disease.

Doctors began performing living-donor liver transplants in 1989, realizing the organ can regenerate itself in both the donor and recipient.

11. On January 22nd, 2002 the press announced a twelve-week cable television series to focus on hepatitis C in Miami-Dade. The series is being organized by Hep-C Alert and is titled "From The Streets to The Specialist".

Local nonprofit Hep-C ALERT raises awareness of chronic hepatitis C with the 12-week cable TV program "From the Streets to the Specialist." The show will air every Monday 8:00pm, Wednesday 9:00am and Friday 12:00pm, starting February 4, 2002 on Community Channel 36.

Hosting the show is Andi Thomas, Hep-C ALERT's founder and executive director. Joining her are renowned hepatologists Dr. Christopher O'Brien, Associate Professor of Clinical Medicine and Dr. Enrique Molina,

Assistant Professor of Clinical Medicine, University of Miami's Center for Liver Diseases.

Each program will focus on a different aspect of hepatitis C, with lively conversations between the host (the Streets), the doctors (the Specialist) and the show's special guest. Viewers can call Hep-C ALERT's education, counseling and referral hotline after each program to request more information about the show topic. Additionally, the Hep-C ALERT will offer group-training programs and individual counseling sessions at their new facility in North Miami. Free hepatitis C testing is offered for a limited time.

Hep-C ALERT's "From the Streets to the Specialist" is made possible by Cable-TAP, a joint partnership of WLRN, Miami-Dade County Public Schools, and Miami-Dade County government. Special thanks to the University of Miami Center for Liver Diseases and Procure Pharmacy, Inc. for their support.

Often called the Silent Epidemic, infection with the hepatitis C virus rarely causes distinct symptoms and can remain undetected for decades. The virus is transmitted by direct contact with infected blood. Many people with hepatitis C don't know they have it and are at risk for unknowingly spreading the virus to others. It's estimated that 40,000 to 50,000 people in Miami-Dade county (or 1 in about every 50 people) are infected.

Show topics:

1. Hep-C 101
2. Deciphering Lab Tests
3. The Role of Ultrasound and Liver Biopsy
4. Treatments - Now and Beyond
5. Treatment Training and Compliance Tips
6. Employee Health - Aggressive Post- Exposure Management & Treatment
7. HCV/HIV Co-infection
8. Liver Transplant
9. Hep-C 101 (In Spanish)
10. Deciphering Lab Tests (In Spanish)
11. The Role of Ultrasound and Liver Biopsy (In Spanish)
12. Treatment - Now and Beyond (In Spanish)

12. On January 22nd the following was released by the American Liver Foundation. American Liver Foundation Hepatitis Council Issues Advisory Concerning Shortage of PEG-INTRON for Treatment of Hepatitis C

The American Liver Foundation (ALF) and the American Association for the Study of Liver Diseases (AASLD) have been informed that the heavy demand for pegylated interferon alfa-2b (PEG-INTRON) has temporarily exceeded the available supply.

The development of combination therapy (PEG-INTRON with ribavirin) has been an important advance in the treatment of hepatitis C. The manufacturer, Schering-Plough, has reassured us that an adequate supply of this drug is available to ensure that patients currently being treated will be able to complete their required course of therapy. From now on, patients for whom PEG-INTRON is newly prescribed will be placed on a waiting list and the drug provided when it becomes available, some time in the next few months.

The Hepatitis Council of ALF has reviewed the situation in consultation with AASLD and would like to reassure patients with hepatitis C that this temporary shortage will not adversely affect their health. Because of the slowly progressive nature of chronic hepatitis C, a delay in starting treatment of three to six months, or even longer, should not present a problem to most patients. Furthermore, conventional interferon alpha, which may be used in combination with ribavirin, is readily available should patients or physicians desire to start treatment now. Ultimately, individuals with hepatitis C who are considering treatment need to discuss what options are best for them with their physicians.

ALF and AASLD will continue to monitor this situation and keep the public informed of any new developments. ALF appreciates the cooperative effort of Schering-Plough in sharing the current market situation so that we may all work toward our common goal of serving the best interests of patients and physicians.

13. On January 24th the Newark Star Ledger in New Jersey that covers a lot of pharmaceutical industry news released the following article: "FDA looking at Schering's treatment for hepatitis C."

The Food and Drug Administration is exploring concerns raised by patient activists concerning how Schering-Plough Corp. distributes its new medicine for treating the chronic liver disorder hepatitis C.

To prevent shortages, Kenilworth-based Schering-Plough required patients to register and, more recently, warned of potential waiting lists. The treatment consists of weekly injections of Peg-Intron plus capsules called Rebetol.

Activists complain that some patients who have begun the 48-week treatment had to wait up to 10 days to get prescriptions refilled, delays that can disrupt the treatment. Without any of the antiviral Peg-Intron in the body, the hepatitis C virus can rebound.

"Patients are missing doses of drug, a situation that can lead to viral resistance and treatment failure," Brian Klein of the Hepatitis C Action and Advocacy Coalition recently wrote the FDA, calling for an investigation.

Jay Siegel, director of the FDA's office of therapeutics research and review, said the agency is "exploring its options and authorities" and will follow up with the manufacturer of the product in an effort to help address them.

Robert Consalvo, a Schering-Plough spokesman, said the company is unaware of any significant problems in distributing the medicine. More than 90 percent of prescriptions are filled within three days.

In addition, he said delays may be caused by other factors not within Schering-Plough's control. The hepatitis C medicine normally is not stocked by most pharmacies and must be ordered to fill prescriptions.

The company has said about 60,000 patients have signed up for the new hepatitis C treatment.

14. Also on January 24th, 2002 the press released the following information that will be published in the January 26th issue of Lancet. "Race Seems to Affect Outcome After Liver Transplantation"

African Americans and Asians have worse outcomes after orthotopic liver transplantation. The finding, reported in the January 26th issue of The Lancet, adds to earlier research showing that African Americans have poorer long-term survival after renal transplantation.

Using information from the United Network of Organ Sharing transplant registry, Dr. Paul J. Thuluvath, from The Johns Hopkins University School of Medicine, Baltimore, and colleagues collected data on 16,669 liver transplants performed in the US between 1988 and 1996. Of these patients 82% were white, 6% were African American, 9% were Hispanic, and 3% were Asian.

After adjusting for confounders, the investigators found that among African Americans and Asians, 2-year graft survival was significantly lower (68% and 64%, respectively) compared with whites and Hispanics (74% and 72%, respectively).

Two-year survival after transplantation was significantly lower among African Americans (74%) and Asians (69%) compared with whites (83%) and Hispanics (79%). This was also the case for 5-year survival: African Americans 48%, Asians 37%, whites 58% and Hispanics 52%, Dr. Thuluvath's team found.

"Compared with white Americans, African American (hazard ratio 1.36, $p < 0.0001$) and Asian (hazard ratio 1.25, $p = 0.03$) race were independent predictors of poor survival at 2 years," the investigators conclude.

In preliminary research, the researchers found no association between socioeconomic status or education and the difference in outcomes between the groups, Dr. Thuluvath told Reuters Health.

The difference between the groups in outcome may lie in differences in the immune system, he said. "Most drugs used are tested in mostly white populations, but maybe drugs need to be tested in diverse populations to find out if another drug or another dose would be more appropriate for these patients."

Dr. Thuluvath and colleagues conclude that "our study suggests that there is a clear need for prospective studies to examine our observations further. Until then, the reasons for poor survival in African Americans will remain speculative and will probably be dismissed as being due to poor compliance with therapy."

15. Furthermore on January 24th, 2002 InterMune Inc. announced that the Phase II Trial of Actimmune as an Antifibrotic Therapy as been Initiated.

InterMune, Inc., announced that it has begun enrolling patients in its Phase II clinical trial of Actimmune (interferon (gamma)-1b) injection for the treatment of severe liver fibrosis, or cirrhosis, caused by hepatitis C virus (HCV).

The objective of the study, called AEGIS (Antifibrotic Efficacy Gamma Interferon Study), is to evaluate the safety and antifibrotic activity of Actimmune in HCV patients who have failed standard antiviral therapy.

More than 4 million people are affected with HCV in the United States, and current antiviral therapy for HCV infection is effective in only approximately 50% of patients. Because treatment is often not effective, continued HCV infection leads to progressive liver fibrosis or cirrhosis (scarring caused by the accumulation of tough fibrous proteins). These patients are at an increased risk of developing life-threatening complications such as internal bleeding, inability to remove toxins from the blood, progressive liver failure, and death.

"Interferon (gamma) has been shown to inhibit activation, proliferation, and production of extra-cellular proteins associated with fibrosis in the hepatic stellate cells - the key cell type involved in liver fibrosis," said Henry Hsu, MD, InterMune. "Preclinical and clinical data have demonstrated that Interferon gamma may prevent or reverse the development of cirrhosis. Based on these data, we believe the results of this trial, which we expect in early 2004, could represent a major advance in the management of patients with advanced liver disease."

In the Phase II, multicenter, placebo-controlled study, 450 patients will be randomized to receive either placebo, 100 mcg of Actimmune or 200 mcg of Actimmune three times per week via subcutaneous injection. The study is designed to evaluate the proportion of patients showing a reduction of one or more points on the fibrosis staging score (using the Ishak staging system, a standard clinical measurement in this disease) following treatment with Actimmune, compared with placebo, for 48 weeks.

"There is a clear unmet medical need in patients suffering from HCV-related liver fibrosis, as they have few, if any, effective treatment options," said W. Scott Harkonen, MD, InterMune. "Actimmune is a promising therapy against this disease, and if demonstrated safe and effective in this study, could also possibly be used broadly to treat other forms of liver cirrhosis such as those caused by alcoholism, metabolic disorders or the hepatitis B virus."

Actimmune is being investigated as a potential treatment for liver fibrosis based on an emerging body of evidence that demonstrates the importance of interferon gamma as a cytokine that modulates the interaction of a downstream protein, transforming growth factor-(beta) that has been shown to play a critical role in the

pathogenesis of fibrotic diseases. Data from in vitro studies, studies in animal models of liver fibrosis and studies in humans with HCV infections and idiopathic pulmonary fibrosis support a potential therapeutic role for interferon (gamma) in the inhibition of fibrosis in the liver and other organs. This article was prepared by Hepatitis Weekly editors from staff and other reports.

16. Additionally on January 24th, 2002 an article was published by editors of Hepatitis Weekly in response to an article published in the January 2002 issue of the Journal of Viral Hepatitis titled "Hepatitis C Genotypes Among the French Changes Because of Drug Use."

A French study suggests hepatitis C virus (HCV) genotypes in that country have changed over the past several years because of a rise in intravenous drug use.

Intravenous drug use is a risk factor for HCV infection and transmission. Marc Bourliere and colleagues, Saint Joseph Hospital, France, recently characterized the nature of HCV genotypic transformation among the French population and in intravenous drug users in a new report published in the January 2002 issue of the Journal of Viral Hepatitis.

"The prevalence of genotype 1b decreased from 47% before 1978 to 18.8% in the 1990s while the prevalence of genotype 1a and 3a increased during the same period from 18% and 15.3% to 28.8% and 26.3%, respectively," Bourliere and coworkers said.

Statistical analysis suggested that genotype 1a was more likely to associate with intravenous drug use whereas genotype 1b was less likely to be associated with that activity. The genotype became more common after 1990 (Epidemiological changes in hepatitis C virus genotypes in France: Evidence in intravenous drug users, J Viral Hepat, January 2002;9(1):62-70).

Genotype 3a, also highly likely to be identified in injection drug users, was also significantly associated with tattooing. Prevalence of HCV genotype 3a was particularly high between 1979 and 1990, according to Bourliere's group.

Investigators attributed much of the genotypic transformation to an increase in the number of people in France using illicit drugs.

"Our results show a modification of HCV genotypes distribution over the last four decades due to an increase of intravenous drug use contamination and an evolution of HCV genotypes distribution only in the intravenous drug use population characterized by a decrease of genotype 1b, an increase of genotype 2a from 1970 to 1990, and a higher increase of genotype 1a, which is currently the predominant genotype in our population," the authors said.

The corresponding author for this study is Marc Bourliere, Hepato-Gastroenterology Service, Saint Joseph Hospital, 26 Boulevard de Louvain 13008, France. E-mail: mbourliere@hopital-saint-joseph.fr.

Key points reported in this study include:

- Intravenous drug use has increased in the French population
- The increase of intravenous drug use has changed the nature of HCV genotype distribution in France
- HCV genotypes 1a and 3a are now the most common genotypes in France

17. On January 25th, 2002 it was announced that Lilly, Vertex will Team Up for Hepatitis Therapy

ELI LILLY and Company has selected Vertex Pharmaceuticals Inc.'s LY570310 (VX-950), a small molecule protease inhibitor for treating hepatitis C virus (HCV) infection as a development candidate. The companies formed a drug pact in 1997. Phase I clinical trials are expected to begin in 2003.

The compound is in a new class of antiviral drugs being studied to inhibit hepatitis C NS3-4A protease, an enzyme considered essential for HCV viral replication. "HCV protease has proved to be a challenging target for drug discovery, but Vertex and Lilly have successfully identified a potent, oral inhibitor," says John Thomson, vice president of research for Vertex.

Competing therapies may include pegylated interferons being developed by Hoffmann-La Roche Inc. and Schering-Plough Corp., and Albuferon by Human Genome Sciences Inc. Albuferon is a new protein created by fusing the gene for the human protein, alpha interferon, to the gene of another human protein, albumin. ICN Pharmaceuticals Inc. filed an investigational new drug application to begin clinical testing of its nucleoside analog viramidine for combination treatment with interferon alpha in patients with chronic hepatitis C.

18. On January 29th, 2002 Roche Holding AG announced that the company will launch Pegasys in the second half of 2002

Roche Holding AG said it will have new data on its Pegasys (pegylated interferon alfa-2a) hepatitis C drug by early March, enabling the company to launch Pegasys in the second half of this year.

The Food and Drug Administration had requested bioequivalence data on the drug prior to granting approval for launch.

19. January 31st, 2002 Idun Pharmaceuticals' Announced that their Potential Liver Disease Drug, IDN-6556, Demonstrates Safety in Phase I Trial and Opens the Door To Treat Multiple Liver Diseases.

Idun Pharmaceuticals, Inc. today announced the results of its Phase 1 clinical trial of IDN-6556. The drug was safe and well tolerated in a clinical study involving 50 normal adults. Evaluation of patients with mild hepatic impairment is ongoing. In the Phase 1 study, IDN-6556 was administered in both single doses and for a week of therapy with various doses. The drug was well tolerated in all groups of subjects.

"We are excited to have completed this Phase 1 stage of the drug's development," said Dr. David Shapiro, Chief Medical Officer and Executive Vice President at Idun. "This drug may prove to be useful in multiple liver diseases and we will shortly start Phase 2 studies to evaluate its effects on different groups of hepatic patients. We will conduct Phase 2 trials of individuals with hepatitis C virus (HCV) infections, alcoholic liver disease and, subsequently, additional trials of individuals experiencing acute alcoholic hepatitis. HCV affects about 4 million Americans and another 200 million people worldwide. Acute alcoholic hepatitis is an often-lethal condition that affects about 85,000 people in the U.S. alone and for which there is no effective treatment. We believe that IDN-6556 can play an important role in the standard care for people with HCV, acute alcoholic hepatitis, and many other liver diseases."

"There are literally more than a half-billion people in the world suffering with liver diseases that may benefit from this drug," added Dr. Steve Mento, Idun's President and CEO. "The success of the Phase 1 trial of our caspase inhibitor is the first clinical step to a new and important therapy for patients with liver disease. It also validates Idun's approach to small molecule drug development and the role that apoptosis modulators can play in the treatment of a number of diseases. We've always believed that caspase inhibitors would be effective drugs for a number of diseases. IDN-6556 is the first broad-spectrum caspase inhibitor to be studied in humans.

"This is just the beginning of many exciting new opportunities that can come from Idun's technology. We have programs in earlier stages of development in cardiovascular disease, inflammation, central nervous system diseases, and cancer with just as much potential."

Idun Pharmaceuticals, Inc. is a biopharmaceutical company located in San Diego, CA, creating innovative human therapeutics with a primary focus on controlling apoptosis, or programmed cell death. Apoptosis is a genetically controlled normal physiological process mediated by a cascade of intra-cellular proteins. Too much, inappropriate, or too little apoptosis is believed to play a role in many important human diseases. Idun believes that controlling the cell death process will have utility in treating cancer, neurodegenerative diseases, ischemic disorders and cardiovascular disease. The company has adopted a commercialization strategy encompassing strategic collaborations with major pharmaceutical companies; internal, independent development of selected small molecule therapeutics; and out-licensing of diagnostics, gene therapies, and bioproduction technologies. Idun has an extensive patent portfolio covering the fundamental and core technologies involved in the regulation of cell death.

20. On January 31st, 2002 it was announced that InterMune is Relaunching Infergen for Hepatitis C Infections.

InterMune, Inc. of Brisbane, California announced today that the Company has relaunched Infergen(R) (Interferon alfacon-1) for the treatment of chronic hepatitis C infections. Effective immediately, InterMune's recently expanded sales force will focus on hepatologists and support them in the safe and appropriate use of Infergen in the treatment of hepatitis C. Hepatitis C virus (HCV) infection is known as the "silent epidemic," affecting nearly four million people in the United States.

Infergen, also known as consensus interferon (CIFN), is a bioengineered type I interferon alfa is FDA approved for the treatment of patients with chronic hepatitis C infections.

"Infergen provides hepatologists with another treatment option for the nearly 50 percent of HCV patients who will either fail or relapse from initial therapy," said W. Scott Harkonen, M.D., President and Chief Executive Officer of InterMune. "The continued unmet medical need for effective, advanced HCV treatments will be a key driver of the near-term revenue growth of Infergen. At the same time, we are also aggressively developing a pegylated form of Infergen that we believe will enable us to capture a significant portion of the maximum \$3 billion U.S. market opportunity for HCV, once that product becomes available in 2005."

Recently, the Company reported positive interim results from a Phase IV clinical trial comparing the use of Infergen plus ribavirin to the use of interferon alfa-2b plus ribavirin (Rebetron(TM)) for the treatment of chronic hepatitis C infections. Patients treated with Infergen in combination with ribavirin achieved a sustained virology response (SVR) of 56% compared with an SVR of 31% in patients treated with Rebetron. Results of the study were presented in November 2001 at the 52nd Annual Meeting of the American Association for the Study of Liver Diseases.

Physicians and patients can obtain additional information about Infergen by visiting <http://www.infergen.com/>.

21. Also on January 31st, 2002 the following article was posted in the Daily Health Reporter "Incidence of Hepatitis C Increasing, Officials Say: Condition Dormant for Years; Better Tracking Needed."

Public health officials report that hepatitis C is on the rise, both around the globe and in West Virginia.

Diagnosis can be a problem because the symptoms aren't discernable at first. When the nausea, fatigue, muscle and joint pain and tender liver become evident, sometimes 20 or 30 years after contact with another's infected blood, the liver may already be scarred, a condition called cirrhosis.

"Yes, we are diagnosing more," said Dr. Fred Kerns, a Charleston infectious disease specialist. Pat White, executive director of West Virginia Health Right, agreed.

Health Right sponsors a treatment program for those with the virus. Currently, 50 patients are taking the expensive medicines, White said.

The Kanawha/Charleston Health Department just submitted a grant application requesting funds to improve

its effort at tracking hepatitis C, said Dr. James Felsen, medical director.

Earlier this month, Mercer County health officials reported that incidence of the virus had increased dramatically in the county.

So what is hepatitis C and why does it trouble the public health community?

An estimated 3 percent of the world's population now carries the mysterious virus, the Mayo Clinic reported last week. That's more than 170 million people.

A relative newcomer to medical sleuths, hepatitis C wasn't discovered and reported until 1989. The first blood test to diagnose it was developed in May 1990. While blood transfusions and organ transplants before 1992 could be a source, the virus also can be transmitted by anyone who ever snorted cocaine. Tiny droplets of blood can be dislodged when a cocktail straw or rolled up dollar bill bumps delicate capillaries in the nose.

About half of cases are linked to intravenous drugs, according to the Centers for Disease Control and Prevention. Also at risk are health care workers exposed to blood, dialysis patients, those who received body piercing or tattoos from unsanitary parlors and people who shared toothbrushes or razors.

Only in rare cases is the infection transmitted sexually.

Some practitioners call hepatitis C a disease of old hippies who shared intravenous drugs during their youths.

But Health Right physicians are noticing it in younger people, many of whom deny injecting drugs, Felsen said.

One of six identified hepatitis viruses, C is considered to be among the most serious, with 20 percent of those infected developing cirrhosis. But up to one-third of people who acquire the infection will clear it up on their own, Felsen said. As many as half of cases can be treated - as long as the patient also gives up alcohol, drugs and other high-risk behaviors for the virus.

One such patient is a young woman with small children, White said. Because she couldn't afford the medicine, a doctor told her she just had to wait until she needed a liver transplant. But once she got into Health Right's free program and spent eight months on combination drugs, her liver began to function normally, White said.

"She'll have to be monitored the rest of her life, but she's out of danger," White said.

Felsen said medications could cost up to \$10,000 a month, posing an economic challenge to public health officials. And they can cause flu-like side effects that sometimes are worse than the disease.

Further, acute hepatitis C is a reportable disease, meaning the state keeps track of its incidence. But chronic hepatitis C doesn't need to be reported. So no one is sure how big the problem really is, Kerns said.

The latest treatment, approved in January by the federal Food and Drug Administration, combines two drugs - pegylated interferon alfa 2-b and ribavirin. Studies are showing that the combination may be twice as effective as regular interferon, according to the Baylor College of Medicine.

"Some preliminary German studies show that if the infection is diagnosed in its early stages, the virus can be cleared within a month of treatment," Felsen said. "However, the problem is that often we have no real way of identifying those recently infected since there is no wide-scale screening and the infection is often asymptomatic."

Felsen said public health officials need to better educate physicians and nurse practitioners about hepatitis

C, improve screening and reporting and clear up the difference between what is considered acute infection and chronic disease.

22. February 1st, 2002 the editors from *Immunotherapy Weekly* published an article "Reason for Enzyme Level Elevation During Interferon Therapy Still Mystery" based upon data that was published in the January 2002 issues of the *Journal of Gastroenterology*.

Doctors still can't explain why levels of the liver enzyme alanine aminotransferase (ALT) may rise in some chronic hepatitis C patients on interferon (IFN)-(beta) therapy despite reduced viremia.

A research team in Japan recently attempted to answer that question by analyzing several patients given standard regimens of IFN-(beta), but their analysis left many questions unanswered.

In the study, 109 chronic hepatitis C patients received 6 MU doses of IFN-(beta) daily for up to 12 weeks. "When serum ALT levels during the therapy were higher than three times the level before the therapy, liver biopsy was performed," said Kenji Fujimori and colleagues, Saitama Medical School, Japan. All of the patients had undergone liver biopsies before therapy was started.

ALT levels rose in 19 patients after therapy began, according to the researchers. "Autoimmune hepatitis was not contributory in any of these 19 patients because serum antinuclear antigen was negative and immunoglobulin (Ig)G levels were not increased," they said.

Fujimori and coworkers also said that evaluations of liver tissues from 10 of the 19 patients showed liver appearance was better than before therapy in 2 patients, and in the other 8 patients, hepatitis grade was the same, "but vacuole formation and apoptotic nuclei in hepatocytes were found in 2 patients, and centrilobular necrotic areas in 1 patient."

Increased hepatitis activity could not explain higher ALT levels during therapy, the researchers indicated. However, degenerative processes within the liver cells resulting from the therapy itself might have been the reason, they said (Possible mechanisms of elevation of serum transaminase levels during interferon-beta therapy in chronic hepatitis C patients, *Journal of Gastroenterology*, January 2002;37(1):40-46).

Even so, a majority of patients did not exhibit such changes, "suggesting that decisions on the discontinuation of IFN-(beta) therapy must be made in accordance with liver histology findings," they recommended.

The corresponding author for this study is Kenji Fujimori, Third Department of Internal Medicine, Saitama Medical School, 38 Morohongo, Moroyama-cho, Iruma-gun, Saitama 350-0495, Japan.

Key points reported in this study include:

- Chronic hepatitis C patients can experience elevated enzyme levels while taking interferon-(beta), despite exhibiting virus eradication
- Several patients in the study demonstrated degenerative liver cell changes but no increases in hepatitis activity
- Interferon-(beta) cytotoxicity may be one of several reasons for elevated ALT in patients undergoing therapy for chronic hepatitis C

23. On February 1st, 2002 XTL Bipharmaceutical Ltd. Announced Positive Phase 1a Clinical Trial Results for Xtl-002

XTL Biopharmaceuticals, Ltd., announced positive clinical data on the antiviral activity and safety of XTL-002,

being developed for the treatment of hepatitis C virus (HCV) infections.

Results of the Phase Ia study, which included 15 chronic HCV patients, indicated that HCV viral RNA levels were reduced in over half the patients following a single dose. No serious adverse events were reported.

The single-center study, under the regulation of the United States Food and Drug Administration (FDA) and Ministry of Health, Israel, was designed to test safety, tolerability and efficacy of a single-dose of XTL-002 in chronic HCV patients. The 15 patients were divided into 5 groups, with each group receiving 0.25, 1.0, 2.5, 10, or 40 mg of XTL-002 in a single intravenous infusion. HCV viral RNA levels were measured pre-infusion and at multiple time intervals following infusion of XTL-002.

In 8 out of 15 patients, significant reduction of HCV viral RNA, ranging from 2- to 100-fold, was demonstrated following XTL-002 administration.

XTL-002 is a fully human high-affinity monoclonal antibody which was shown to reduce viral levels of the HCV virus in XTL's proprietary in vivo model, the HCV TrimeraxTL model. This model is being used in conjunction with a variety of corporate and academic partners to screen and evaluate novel compounds to treat HCV. A peer reviewed scientific article on XTL's HCV TrimeraxTL model was recently published in the Journal of Infectious Disease.

Professor Eithan Galun, director, Goldyne Savad Institute of Gene Therapy, Hadassah University Hospital and a principal investigator in the study, commented: "XTL-002 is a promising new therapeutic modality for treating chronic HCV patients. In addition, XTL-002 could be employed to prevent HCV reinfection in HCV-associated liver transplant patients, where no drug currently exists."

Martin Becker, PhD, XTL, said: "XTL is the first company to initiate clinical trials with a monoclonal antibody against HCV. We are pleased that the clinical results with XTL-002, though early stage, suggest that XTL-002 is active against the HCV virus. XTL-002 is the most advanced drug in our broad HCV program, which includes multiple drug candidates that are either fully owned by XTL or co-developed with corporate partners."

Hepatitis C is a major public health concern. The World Health Organization estimates that 170 million people worldwide are chronic carriers of the hepatitis C virus, with 4 million carriers in the United States alone. It is estimated that 25-35% of these chronic disease patients will develop progressive liver disease including cirrhosis and liver cancer. Hepatitis C is the leading cause of liver transplantation. This article was prepared by Drug Week editors from staff and other reports.

24. On February 1st, 2002 the editors from Gene Therapy Weekly, based upon an article to be published in the March 2002 issue of the Journal of Medical Virology, wrote the following: "Hepatitis C Vaccine Enhanced by Gm-Csf Gene Therapy"

A group studying hepatitis C virus DNA vaccines has found granulocyte macrophage-colony stimulating factor (GM-CSF) gene therapy increases their effectiveness in inoculated mice.

The group, lead by P. Ou-Yang, works in the College of Medicine at National Taiwan University of Taipei. According to their data, immune response was heightened in mice immunized with both agents.

"In this study, female Balb/c mice immunized with HCV core plasmid DNA with or without adjuvant GM-CSF cytokine gene could induce both cellular immune response and HCV core-specific antibody titers after injection," Ou-Yang and colleagues said.

More analysis revealed that in mice given both the DNA vaccine and the gene therapy, antibody titer, as well as cytotoxic T-cell activity, was greater.

Investigators believed the local lymph nodes of the inoculated mice played a key role in immune response activity because reporter protein, expressed after animals were treated with specially designed constructs containing reporter gene and cytokine gene plasmid, could be detected within inguinal nodes within a day of gene therapy administration, "especially in mice immunized with HCV/core plasmid plus GM-CSF." They also detected the protein in muscle tissues, and in some dendritic cells located within the lymph nodes (Co-delivery of GM-CSF gene enhances the immune responses of hepatitis C viral core protein-expressing DNA vaccine: Role of dendritic cells, *Journal of Medical Virology*, March 2002;66(3):320-328).

Ou-Yang and coauthors suggested that GM-CSF could augment HCV DNA vaccine effectiveness and those dendritic cells, particularly in relation to local lymph nodes, may influence immune response activity after DNA vaccines are administered.

The corresponding author for this study is P. Ou-yang, Graduate Institute of Immunology, College of Medicine, National Taiwan University, Taipei, Taiwan.

Key points reported in this study include:

- GM-CSF gene therapy improved antibody titer and cytotoxic T-cell activity in mice vaccinated with HCV DNA vaccine
- Reporter gene could be detected around the injection site and in local lymph nodes after mice were administered DNA vaccine and gene therapy
- Dendritic cells appear to play an important role in stimulating immune response activity after HCV DNA vaccination and GM-CSF gene therapy

25. On February 1st, 2002 editors from *Hepatitis Weekly* published an article titled "Picture of Hepatitis B and C in Drug Users Needs Fine-Tuning" based upon data published in the medical journal, *Addiction*, in 2001.

Epidemiologists using data collected from injection drug users who attend treatment centers may be getting an incomplete picture about viral hepatitis infection rates in the injection drug use population at large.

More specifically, information about hepatitis B and C virus (HBV, HCV) infection rates cannot be extended from information gathered at treatment centers to wider population groups when looking at injection drug users, according to P.A. Cook and colleagues of Liverpool John Moores University School of Health and Human Sciences in England.

Cook and associates conducted a cross-sectional survey of HBV and HCV risk factors among 360 injection drugs users who either were or were not in contact with treatment or needle exchange programs in two major cities in England, administering questionnaires and tests for HBV and HCV to all participants.

"HBV prevalence differed between groups, from 19% of those not in contact to 41% of those presenting to request a test," Cook and coworkers said. "Prevalence of hepatitis C ranged from 48% (needle exchange programs) to 62% among those presenting for a test," they added.

Risk factors for HCV infection included duration of injection drug use, doing time in prison, injecting more than one kind of drug, and being female, and risk factors for HBV infection included having been in prison and longer duration of injection drug use (Predictors of hepatitis B and C infection in injecting drug users both in and out of drug treatment, *Addiction*, 2001;96(12):1787-1797).

Of those participating in the study, nearly 40% had practiced needle sharing in the past four weeks. "People recently starting injecting were more likely to share, and sharing was more likely to occur when injecting with

only one other user rather than in large groups," Cook and associates stated.

Interestingly, study group participants who had been tested for HCV before were not as likely to share injecting equipment, regardless of whether or not they were negative or positive for infection.

"When assessing prevalence of hepatitis B and C, our results suggest that figures cannot be extrapolated from those in service contact to those in the wider drug-use population," Cook coauthors said.

The corresponding author for this study is P.A. Cook, Liverpool John Moores University, School of Health and Human Sciences, Public Health Sector, 70 Great Crosshall Street, Liverpool L3 2AB, Merseyside, UK.

Key points reported in this study include:

- Common risk factors for HBV and HCV infection among injection drug users included length of time using injection drugs and having been in prison
- Injection drug users who had been previously tested for HCV were less likely to share injection drug equipment, regardless of infection status
- Data obtained from injection drug users who attend treatment centers is not necessarily representative of HCV and HBV infection rates among the entire injection drug use community in a given population

26. Additionally on February 1st, 2002 the press announced that Hepatotoxicity has been Seen with Serzone Use in Patients with Liver Disease

Pharmaceutical Care Network (PCN), a leading pharmacy benefit manager (PBM), is alerting physicians of the new black box warning for Serzone (nefazodone), a medication commonly used for the treatment of depression.

Cases of life-threatening hepatic failure resulting in transplantations or deaths have been reported in patients treated with Serzone at a reported rate of 1 case per 250,000 to 300,000 patient-years of Serzone treatment. The U.S. Food and Drug Administration (FDA) have advised that treatment with Serzone should not be initiated in individuals with active liver disease or with elevated baseline serum transaminases. Patients who develop evidence of hepatocellular injury, such as increased serum AST or serum ALT levels three times or greater than the upper limit of normal while on Serzone should be withdrawn from the drug.

Upon receiving notification of Serzone's new black box warning, PCN immediately incorporated the information into its December 2001 issue of the Drug Therapy Council Newsletter focusing on the pharmacologic treatment of depression. The DTC Newsletter is distributed to health care professionals, including physicians and pharmacists, and is accessible at the PCN website www.pharmcarenet.com/publications_dtc.asp.

Additionally, PCN used its new, web-enabled version of MedIntelligence Analytical Guide Pro, proprietary PCN data warehouse query software to comprehensively identify all patients in PCN administered programs currently receiving Serzone. To ensure patient safety, PCN alerted those patients' physicians of Serzone's potential hepatotoxicity through notifications/alerts using PCN's MedIntelligence Case Management Support. This article was prepared by Hepatitis Weekly editors from staff and other reports.

27. On February 6th, 2002 the press published an article titled "TIPS versus drug therapy in preventing variceal rebleeding in advanced cirrhosis". The full publication will be included in the February issue of Hepatology.

TIPS should not be used as a first-line treatment for the prevention of variceal rebleeding in advanced

cirrhosis, but as a rescue for failures of medical and endoscopic treatments, claims a team from Barcelona and Madrid, Spain.

The researchers compared the efficacy, safety, and cost of transjugular intrahepatic portosystemic shunt (TIPS) versus pharmacologic therapy in preventing variceal rebleeding in patients with advanced cirrhosis.

A total of 91 Child-Pugh class B/C cirrhotic patients, surviving their first episode of variceal bleeding, were included in the trial.

The patients were randomized to receive TIPS (n = 47) or drug therapy (propranolol and isosorbide-5-mononitrate, n = 44) to prevent variceal re-bleeding.

After a mean follow-up of 15 months, re-bleeding occurred in 6 (13%) TIPS-treated patients versus 17 (39%) drug-treated patients.

The 2-year rebleeding probability was 13% versus 49%, respectively.

2-year rebleeding probability:

TIPS: 13%

Drug therapy: 49%

A similar number of reinterventions were required in the two groups. These were mainly angioplasty with or without restenting in the TIPS group (90/98), and endoscopic therapy for rebleeding in the medical group (45/62).

The researchers found that encephalopathy was more frequent in TIPS than in drug treated patients (38% vs. 14%).

In addition, Child-Pugh class improved more frequently in drug-treated than in TIPS treated patients (72% vs. 45%).

The 2-year survival probability was identical (72%) for the two groups.

The identified cost of therapy was found to be double for TIPS-treated patients.

Àngels Escorsell said on behalf of fellow authors, "Medical therapy was less effective than TIPS in preventing rebleeding. However, it caused less encephalopathy, identical survival, and more frequent improvement in Child-Pugh class with lower costs, than TIPS in high-risk cirrhotic patients. This suggests that TIPS should not be used as a first-line treatment, but as a rescue for failures of medical and endoscopic treatments," it was concluded.

28. On February 5th, 2001 Health Canada advises against kava

Health Canada is advising consumers not to use kava-kava (commonly called kava) or kava-containing products until it has completed a safety review this herb. Kava and its extracts are commonly used to treat the following conditions:

- anxiety
- nervousness
- difficulty falling asleep
- pain relief
- muscle tension

Health Canada has issued this advisory because of reports of severe liver damage among kava users in Germany and Switzerland. In those countries, there have been at least 25 cases of adverse effects possibly

related to kava usage. At least one person has required a liver transplant. It is noteworthy that in at least 18 of the 25 cases, kava users were also taking prescription and non-prescription medication with the potential to cause liver damage.

The situation elsewhere is as follows:

- UK - the British Medicines Control Agency has asked stores in that country to temporarily stop selling kava
- Germany- kava-containing products have been withdrawn from sale and the government is considering making kava available only by subscription
- United States - the Food and Drug Administration is currently investigating whether the use of kava is associated with liver problems

Kava has had a relatively good safety profile in Canada with no cases of liver toxicity being reported in this country. Health Canada advises consumers to consult with their health care practitioner if they have experienced any adverse effects from taking products containing kava. The following signs/symptoms may be associated with liver problems:

- jaundice (yellowing of the skin or whites of the eyes)
- brown urine
- nausea
- vomiting
- unusual tiredness
- weakness
- stomach or abdominal pain
- loss of appetite

Health care practitioners are being asked to report to regulatory authorities any cases of liver toxicity in association with kava-containing products, at the following toll-free numbers:

* Canada 1.866.234.2345

* United States 1.800.332.1088

29. Also on February 6th, 2002 the press released an article titled "Phlebotomy May Delay Progression of Liver Fibrosis in Chronic Hepatitis C Patients" based upon an article that was published in the January issue of The American Journal of Gastroenterology.

The use of phlebotomy to reduce iron levels in patients with chronic hepatitis C appears to delay the progression of liver fibrosis, according to a recent report by Japanese investigators.

The accumulation of iron in the liver that is observed in patients with chronic hepatitis C has been associated with elevated serum aminotransferase (ALT) levels and liver fibrosis.

Although phlebotomy to reduce iron levels in these patients leads to decreased serum ALT, it is unclear if phlebotomy produces long-term beneficial effects.

Dr. Motoyoshi Yano, from Nagoya University, and colleagues assessed the outcomes of 25 chronic hepatitis C patients who underwent phlebotomy to achieve and maintain iron levels of 10 ng/mL or less over a 5-year period.

Thirteen additional patients who were virologic nonresponders to interferon therapy alone and had underwent liver biopsies served as a histologic control group.

The initial phlebotomy session produced a significant reduction in serum ALT levels and these levels were maintained with subsequent sessions ($p < 0.05$), the investigators note in the January issue of *The American Journal of Gastroenterology*.

At 5-year follow-up, histologic grading scores had improved significantly in the phlebotomy group, but were unchanged in the control group ($p < 0.05$). Staging scores worsened in the control group, but remained stable in the phlebotomy group ($p < 0.005$).

Furthermore, disease progression was significantly slower in the phlebotomy group ($p < 0.05$).

The current findings suggest that "maintenance of the iron-deficient state has beneficial effects in preventing disease progression in chronic hepatitis C patients," the authors state. Such therapy may be particularly useful in patients with elevated viral levels despite treatment with interferon alone or in combination with ribavirin. However, a prospective controlled study is needed to confirm the present results.

30. On February 7th, 2002 ViroLogic Announced Agreement With Achillion Pharmaceuticals to Evaluate Novel Next-Generation Anti-Hepatitis And HIV Agents.

ViroLogic, Inc. (Nasdaq: VLGC) on South San Francisco today announced an agreement with Achillion Pharmaceuticals, a privately held pharmaceutical company, to utilize ViroLogic's drug resistance assays to evaluate Achillion's lead product candidate, ACH-126,443 (Beta-L-Fd4C), an L-nucleoside in clinical development for the treatment of hepatitis B (HBV) and HIV.

Under the terms of the agreement, Achillion can utilize ViroLogic's assays to evaluate its pipeline of investigational antiviral agents. Achillion is currently evaluating Beta-L-Fd4C in chronically-infected HBV patients in a Phase Ib/II clinical trial. Additional Phase II studies are planned for 2002 to evaluate the drug in both chronic HBV and HIV patients. Financial terms of the agreement were not disclosed.

"This collaboration represents ViroLogic's first service agreement covering hepatitis B, and reflects how leading companies in this area are recognizing the critical role our technology can play in support of their drug development efforts," said Bill Young, ViroLogic's Chairman and Chief Executive Officer. "Our technology can be used by Achillion to enhance the development of novel, differentiated new agents for serious viral diseases."

"Achillion is focused on developing new therapeutic agents that address the challenge of drug resistance in infectious diseases," said William G. Rice, Chief Executive Officer of Achillion. "Our goal is to deliver innovative drugs that meet current and emerging needs in the marketplace, and we look forward to applying ViroLogic's leading technology and expertise to aid in the rapid evaluation of our anti-viral agents."

31. Additionally on February 7th, 2002 the press printed an article titled "Deaths from hepatocellular carcinoma have increased over past 30 years in USA". The entire article is published in the January issue of the Journal of Gastroenterology

There has been a marked increase in deaths from hepatocellular carcinoma over the past 3 decades in a region of the USA, especially among men and white Americans, finds a study published in January's *American Journal of Gastroenterology*.

Researchers from Baltimore, Maryland, USA, determined the epidemiologic trends in mortality from hepatocellular carcinoma (HCC) and biliary cancers (BCs) in Maryland during the last three decades.

The number of deaths due to HCC and BCs, from 1970 to 1997, was obtained from the Maryland State Department of Health and Hygiene vital statistics database.

Malignant neoplasms of the gallbladder and intrahepatic and extra hepatic bile ducts were grouped together as biliary cancers.

To determine the trend in mortality, the total time period was divided into seven 4-year periods.

Mortality due to HCC in men increased from 1.34 to 2.7 per 100,000 between 1970 and 1997.

Mortality from HCC increased from 0.94 to 1.84 per 100,000 population (rate ratio = 1.94) and that from BCs increased from 1.28 to 1.7 per 100,000 population (rate ratio = 1.31) over the study period.

Although mortality due to HCC doubled in men (1.34 to 2.7 per 100,000) during this period, only a modest increase was observed among women (0.59 to 1.06 per 100,000).

Due to a marked increase in the number of deaths among white Americans, the difference in HCC-related mortality between white Americans and African Americans decreased considerably during this period.

The team found that mean age at death increased steadily for BCs, from 67 to 73 years, whereas there was no real trend for HCC.

Among African Americans, the death from HCC remained stable. However, there was a 2-fold increase in BC-related death.

Author S. Nair, of the Johns Hopkins University School of Medicine, Baltimore, said on behalf of the group, "There was a marked increase in deaths from HCC over the past 3 decades in Maryland. This increase was more evident among men and white Americans."

"Deaths due to BCs increased modestly during the same period of observation. The marked rise in BC-related deaths among African Americans remains unexplained," it was concluded.

32. On February 13th, 2002 InterMune Announces Fourth Quarter and Year-End Financial Results. Product Revenue Growth Exceeds 250%. Company Advances Commercial Products and Development Pipeline

InterMune, Inc. announced today financial results from operations for the fourth quarter ended December 31, 2001. Total product sales were \$15.1 million for the fourth quarter of 2001 compared to \$4.2 million for the same quarter in 2000, an increase of 256%. Sales of Actimmune® (interferon gamma-1b) for the fourth quarter of 2001 were \$13.8 million, compared to \$4.2 million in the same period in 2000, an increase of 226%.

Total product sales for the year ended December 31, 2001 were \$40.0 million compared to \$11.2 million for the same period in 2000, an increase of 257%. Sales of Actimmune for the year ended December 31, 2001 were \$36.3 million, compared to \$13.0 million in the same period in 2000, an increase of 179%. The Company recognized \$11.2 million of the \$13.0 million of Actimmune sales in 2000 based upon a prior revenue-sharing agreement, which has since been terminated.

"Product revenue growth was very strong in 2001," said W. Scott Harkonen, M.D., President and CEO of InterMune. "We are well-positioned to continue this growth as we target \$100 million in product revenues in 2002, and \$200 million in product revenues in 2003."

InterMune reported a pro forma net loss of \$23.0 million, or \$0.83 per share, in the fourth quarter of 2001, compared to a net loss of \$6.3 million, or \$0.27 per share, for the same period in 2000. The pro forma net loss for the fourth quarter of 2001 excludes a one-time charge of \$51.0 million for acquired in-process research and development costs relating to the acquisition of worldwide rights to oritavancin from Eli Lilly and Company. Including this one-time charge, the net loss for the quarter ended December 31, 2001 was \$74.0 million, or \$2.67 per share.

For the year ended December 31, 2001, InterMune reported a pro forma net loss of \$61.8 million, or \$2.44

per share, compared to a net loss of \$52.3 million, or \$3.05 per share, for the same period in 2000. Including one-time charges, the net loss for the year ended December 31, 2001 was \$118.2 million, or \$4.67 per share.

“InterMune made unprecedented progress in 2001 toward our goal of becoming a leading biopharmaceutical company with rapid growth in our marketed products and progress in the execution of our world class development program,” Dr. Harkonen said. “We have three potential blockbuster opportunities and a rich pipeline with 17 clinical trials underway.”

“Our experienced teams have advanced our efforts over the past year to maximize the potential of life-saving therapies for infectious diseases, pulmonary diseases and cancer,” Dr. Harkonen said. “We are extremely well-positioned with upward revenue momentum driven by our commercial products; a pipeline with significant future market potential; and a focused strategy to augment our current assets through in-licensing, acquisition and our own applied research.”

Research and development expenses were \$50.5 million for the year ended December 31, 2001, compared to \$18.1 million in the same period in 2000. The increase was due primarily to the expansion in the number of clinical programs and product development staff in the Company.

Selling, general and administrative expenses were \$33.6 million and \$12.1 million for the year ended December 31, 2001, and 2000, respectively. This increase was attributable primarily to the expanded number of field specialists and increased corporate staffing. At December 31, 2001, the Company's cash, cash equivalents and available-for-sale securities totaled \$332.1 million.

Background Information on Actimmune:

- *Completed enrollment of the Phase III clinical trial of Actimmune for the treatment of idiopathic pulmonary fibrosis (IPF), a debilitating and usually fatal disease for which there is no effective therapy.*
- *Received recommendation from the Data Safety Monitoring Board for the Phase III clinical trial of Actimmune for IPF to continue the study as originally designed.*
- *Received Fast Track Designation from the U.S. Food and Drug Administration (FDA) for Actimmune for the treatment of IPF.*
- *Initiated a Phase III clinical trial of Actimmune as adjunctive first-line treatment for ovarian cancer.*
- *Initiated a Phase II clinical trial of Actimmune for the treatment of severe liver fibrosis, or cirrhosis, caused by hepatitis C infection.*
- *Initiated a Phase II clinical trial of inhaled Actimmune for the treatment of pulmonary atypical mycobacterial infections.*
- *Reported positive Phase II clinical trial results of Actimmune as adjunctive therapy to conventional anti-fungal treatment of cryptococcal meningitis, a life-threatening fungal infection of the central nervous system.*
- *Received FDA approval to transfer the manufacturing of Actimmune from Genentech, Inc. to Boehringer Ingelheim Austria GmbH in Vienna, Austria.*
- *Filed a New Drug Submission (NDS) with the Therapeutic Products Programme of Health Canada (TPP) to market Actimmune in Canada for chronic granulomatous disease and severe, malignant osteopetrosis, both life-threatening childhood diseases.*

- *Expanded an international strategic partnership with Boehringer Ingelheim International GmbH to include the development and commercialization of interferon gamma-1b for the treatment of ovarian cancer.*
- *Significantly expanded product line beyond Actimmune by acquiring oritavancin from Eli Lilly and Company, licensing Infergen from Amgen Inc., and acquiring worldwide rights to Amphotec from ALZA Corporation.*

Background on Infergen:

- *Relaunched Infergen(R) (Interferon alfacon-1), also known as consensus interferon (CIFN), for the treatment of chronic hepatitis C infections.*
- *Announced positive interim results from a Phase IV clinical trial favorably comparing the use of Infergen plus ribavirin to the use of interferon alfa-2b plus ribavirin (Rebetron(TM)) for the treatment of chronic hepatitis C infections.*

Background of oritavancin:

- *Signed agreement with Abbott Laboratories to manufacture oritavancin, InterMune's second-generation glycopeptide antibiotic for the treatment of Gram-positive bacterial infections.*
- *Announced encouraging Phase III clinical trial results during late-breaker poster session at ICAAC demonstrating that oritavancin cut the treatment time in half for complicated skin and skin-structure infections versus current standard therapy (e.g., vancomycin plus cephalexin).*

Background in Business Progress:

- *Raised \$287 million through public offering of common stock and convertible notes.*
- *Hired pharmaceutical industry veteran James E. Pennington, M.D. to Executive Vice President of Medical and Scientific Affairs.*
- *Appointed several new senior executives to strengthen clinical development team, including: Steven Porter, M.D., Ph.D., to the position of Vice President of Clinical Research; Mack Mabry, M.D., as the position of Senior Director of Clinical Research -- Oncology; Michael Crager, Ph.D., to the position of Senior Director, Biostatistics; and Williamson Bradford, M.D., Ph.D., to the position of Director of Clinical Research -- Pulmonary Medicine.*
- *Nearly doubled the number of field specialists.*

Background on Research Collaboration Progress:

- *Formed collaboration with Maxygen to develop and commercialize novel, next generation interferon*

gamma products.

- *Formed collaboration with MoliChem Medicines, Inc., to jointly develop and commercialize MoliChem's pulmonary molecule Moli1901 (duramycin) for the treatment of a range of pulmonary indications, including cystic fibrosis.*

33. *On February 14th, 2002 in response to an article published in the January issue of Hepatology Research the editors from Immunotherapy Weekly wrote an article "Interferon-(Gamma) Improves Response to Interferon-(Alpha) in Hepatitis C".*

Insufficient T-cell response can leave some patients battling hepatitis C virus (HCV) infection despite extended treatment with interferon (IFN)-(alpha). Doctors in Japan say IFN-(gamma) can improve the efficacy of IFN-(alpha) in some patients with chronic hepatitis C.

Working at Kurume University School of Medicine in Japan, R. Kumashiro and colleagues treated 17 patients infected with HCV genotype 1b with sequential dosing schemes of IFN-(alpha) and IFN-(gamma), prescribing IFN-(alpha) for 24 weeks, and then IFN-(gamma) for 2 additional weeks.

Patients with genotype 1 often respond the poorest to IFN monotherapy; however, in the study described by investigators, three of the four patients who attained normal liver enzyme levels (alanine aminotransferase, ALT) also cleared HCV RNA, representing almost 20% of the study group.

Changes in cytokine and cell factor levels following IFN-(gamma) treatment suggested Th1 responses, lacking before, were enhanced as a result of the additional therapy (Interferon-(gamma) brings additive anti-viral environment when combined with interferon-(alpha) in patients with chronic hepatitis C, Hepatology Research, January 2002;20-26).

"Serum interleukin (IL)-12, CD4 and CD8 remained unchanged with IFN-(alpha) but increased after IFN-(alpha) was replaced by IFN-(gamma)," Kumashiro and coworkers said, "Productions of IL-2, IFN-(gamma) and tumor necrosis factor (TNF)-(alpha) by peripheral blood mononuclear cells did not change by IFN-(alpha) therapy, however, they were enhanced at the end of IFN-(gamma) therapy."

Neither of the interferons changed the expression of IL-10, the researchers noted.

"The results show that some immune parameters become Th1-dominant by additional IFN-(gamma) in patients with chronic hepatitis C," the authors said. They suggested that further evaluation of their findings would be warranted.

The corresponding author for this study is R. Kumashiro, Second Department of Medicine, Kurume University School of Medicine, 67 Asahimachi, Kurume, 830-0011, Fukuoka, Japan.

Key points reported in this study include:

- Interferon-(alpha) monotherapy often fails to induce a sustained response in patients with chronic hepatitis C
- Interferon-(gamma) added to interferon-(alpha) therapy increased Th1 responses in patients treated for chronic hepatitis C
- Interferon-(gamma) may be an important adjunctive agent for interferon-(alpha) therapy in patients with chronic hepatitis C

34. *On February 14th, 2002 Hepatitis Weekly editors released an article titled "Drugs to Prevent Graft Rejection Worsen Liver Disease in Those with Hepatitis C"*

Immunosuppressive drugs designed for extending survival in kidney transplant patients may actually lead to worsened liver disease in transplant recipients also infected with hepatitis C virus (HCV).

A new study of 28 renal transplant patients on immunosuppressive therapy and 28 immunocompetent individuals normal immune system response, all of whom were infected with HCV, has revealed that the therapy can lead to liver damage by suppressing antiviral activity. The study, conducted by researchers at INSERM in Paris, France, was published in the January 2002 edition of *Nephrology, Dialysis, and Transplantation*.

Liver biopsies performed an average of 7 years after transplantation showed that fibrosis and liver scores, indicators for liver injury, increased significantly among patients who received renal grafts but not in controls with intact immune systems, according to H. Zylberberg and colleagues, INSERM.

"The yearly progression rate of activity and fibrosis was significantly higher in the renal transplant group as compared with the immunocompetent group: 0.26 ± 0.41 versus 0.01 ± 0.19 ($p < 0.01$) and 0.26 ± 0.35 versus 0.05 ± 0.21 ($p < 0.03$), respectively," the researchers reported.

In addition to liver activity and fibrosis, researchers observed cirrhosis more often in graft recipients; six of that group developed cirrhosis, whereas one of the controls did (Severe evolution of chronic hepatitis C in renal transplantation: A case control study, *Nephrol Dial Transplant*, January 2002;17(1);129-133).

At least 10% of the HCV-positive patients who received renal grafts died from liver-related ailments while none in the group with healthy immune response did.

"Using conventional immunosuppressive regimens, renal transplantation is associated with a more severe evolution of chronic hepatitis C as compared with HCV-infected immunocompetent subjects," Zylberberg and coauthors cautioned. Antiviral therapy should be considered before such transplants are performed, study organizers recommended.

The corresponding author for this study is H. Zylberberg, INSERM, Paris, France.

Key points reported in this study include:

- Kidney transplant recipients infected with hepatitis C virus experienced more liver disease progression and fibrosis than nontransplanted HCV-positive controls did
- Liver-related death among HCV-positive renal graft recipients was higher than among nontransplanted HCV-positive controls
- Because drugs taken after renal transplantation suppress the immune system, antiviral therapies may be warranted for patients before they undergo surgery