

# HCV ADVOCATE WEEKLY NEWS REVIEW

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*Review of HCV, HBV and HIV/HCV Coinfection Related News and Highlights*

*Alan Franciscus  
Editor-in-Chief*

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Oct 27, 2008

## ***Liver disease blood test***

<http://www.hoinews.com>

By Jen Christensen

### **Hepatitis**

Hepatitis is an inflammation of the liver caused by infection with one of the hepatitis viruses. The infection may be acute (lasting a limited time) or chronic (lasting a long time or a lifetime). General signs of hepatitis may include: jaundice, fatigue, headache, fever, stomach pain, loss of appetite, nausea, vomiting and/or diarrhea. However, not all patients develop symptoms of infection.

Five different hepatitis viruses have been identified, named A, B, C, D and E. In the U.S., hepatitis A, B and C are the most common. Hepatitis A is spread through contact with food or water contaminated with the hepatitis A virus. It's not very common in the U.S. and is more likely to be acquired during travel to other countries. The CDC estimates each year about 32,000 Americans are infected with hepatitis A and roughly 100 people die.

Hepatitis B is spread through contact with contaminated body fluids. The virus can also be passed from a mom to her baby during birth. 46,000 new cases were diagnosed in 2006. About 5 percent of patients develop a chronic infection. The condition causes about 5,000 deaths each year.

Hepatitis C is mostly spread through contact with contaminated blood. The Hepatitis Foundation International estimates 25,000 to 30,000 new hepatitis C infections occur annually in the U.S. About 60 to 85 percent of people who get the virus develop chronic infection. Hepatitis C causes about 8,000 to 10,000 deaths every year.

### **Liver Disease Progression: Fibrosis and Cirrhosis**

In the beginning, liver disease is marked by inflammation. Initially, some people have no signs of a problem. If the body fights off the disease, the liver can heal (a healthy liver can regenerate).

Sometimes inflammation leads to the formation of scars. Scar tissue is tough and fibrous. As more of the scar tissue forms in the liver, it replaces healthy tissue. This stage of liver disease is called fibrosis. Patients may still not have any symptoms. However, blood flow through the liver may be impeded and the healthy areas of the liver must work harder. If the underlying condition is treated, doctors may be able to reverse the effects of fibrosis.

Cirrhosis occurs when a significant amount of healthy liver tissue has been permanently replaced with scar tissue. At this stage, the damage can't be repaired by the body. The liver can't function as it should, causing a patient to bruise or bleed easily, jaundice, accumulation of fluid in the legs or stomach, intense skin itching and a build-up of toxins in the brain. The National Institute of Diabetes and Digestive and Kidney Diseases estimates about 26,000 Americans die of cirrhosis annually. Cirrhosis is also an important cause of liver cancer.

### **Monitoring Liver Disease**

Currently, the only way for doctors to accurately determine the health of a diseased liver is through a biopsy. A small incision is made into the abdomen. Then, a needle is inserted into the liver to retrieve one or more samples of tissue. The biopsy is examined under a microscope for signs of disease and measurement of fibrosis or scarring. A biopsy may also be used to monitor the effectiveness of treatment for liver disease.

A liver biopsy is considered to be minor surgery. But it's not a trivial procedure. There is a very small risk of accidental puncture of the lung or gallbladder, infection or excessive bleeding. After surgery, patients may have significant discomfort and need to lie still for one to two hours. Some patients need to spend the night in the hospital. Those who are discharged the same day need to remain in bed for 8 to 12 hours. Activity levels are restricted for about a week.

### **A New Tool**

Researchers at the Drexel Institute for Biotechnology and Virology Research have developed a new blood test that may help doctors monitor liver disease and reduce the need for a liver biopsy. Drexel Virologist Anand Mehta, D. Phil., says that as liver disease progresses, certain types of bacteria increase in the blood. The antibodies to those bacteria have a different kind of sugar attached to them. The new blood test can measure the levels of the antibody and the amount of sugar on the antibody. Preliminary research shows levels of this antibody correlate with the degree of liver fibrosis and cirrhosis.

Mehta says the blood test requires less than a drop of blood. It currently takes about six hours to process the test. But scientists are working on a way to produce results more rapidly. The goal is to develop a test that takes about five minutes, so doctors can give patients the results during the office visit.

Currently, the liver disease blood test is in research phases. Timothy Block, Ph.D., Virologist with the Hepatitis B Foundation, says the markers are being licensed to several companies that will use them to develop their own diagnostic tests and clinical trials for the tests.

**For information on hepatitis:**

Hepatitis C Advocate, <http://www.hcvadvocate.org>  
Hepatitis Foundation International, <http://www.HepatitisFoundation.org>

**For general information on liver disease:**

American Association for the Study of Liver Diseases, <http://www.aasld.org>  
American Liver Foundation, <http://www.liverfoundation.org>  
National Institute of Diabetes and Digestive and Kidney Diseases, <http://www.niddk.nih.gov>

**Vertex Pharmaceuticals Highlights Progress with Hepatitis C and Cystic Fibrosis Programs and Reports Third Quarter 2008 Results**

<http://www.centredaily.com>

*- Phase 3 ADVANCE study of telaprevir in HCV completes enrollment*

CAMBRIDGE, Mass. — Vertex Pharmaceuticals Incorporated (Nasdaq: VRTX) today reported recent clinical progress and consolidated financial results for the quarter ended September 30, 2008.

"2008 has been a year of significant progress across all aspects of our business," said Joshua Boger, Ph.D., President and Chief Executive Officer of Vertex Pharmaceuticals. "We have made substantial clinical progress in two very important areas--hepatitis C and cystic fibrosis. Telaprevir, our protease inhibitor targeting the treatment of hepatitis C, is well into a broad registration program for HCV genotype-1 treatment naive and treatment failure patients, and recently we completed enrollment in the Phase 3 pivotal study known as ADVANCE for treatment naive patients. A further registration study, REALIZE, is ongoing for HCV treatment failure patients. Additionally, we have made great advancements in the area of cystic fibrosis. On the basis of positive results for our lead CFTR potentiator VX-770, we are engaged in discussions with global authorities to design a registration program for VX-770 in cystic fibrosis."

"Vertex could therefore be positioned to make a major impact on the treatment of two serious diseases, with the potential for registration programs underway in parallel in 2009," continued Dr. Boger. "We're well-positioned financially to undertake these investments, and our organization is excited about the possibility of improving outcomes for both HCV and CF patients."

**HCV - Telaprevir Development Program**

*Phase 3 Development in Treatment-Naive Population*

- Vertex and Tibotec have completed enrollment in the global 3-arm pivotal Phase 3 ADVANCE trial that is focused on 24-week telaprevir-based response-guided regimens. In the ADVANCE study, telaprevir is being dosed for 8 or 12 weeks. Vertex expects to have sustained viral response (SVR) data from the study in the first half of 2010.
- Vertex has begun enrollment in a study of 500 treatment-naive HCV patients that will include evaluation of 24-week and 48-week telaprevir-based regimens. These regimens include 12-week telaprevir dosing durations. The Company expects to complete enrollment in this study by the end of 2008 and expects to have SVR data from the study in the first half of 2010.

### *Phase 3 Development in Patients Who Failed to Achieve SVR with Prior Treatment*

- Patient dosing is underway in the Phase 3 REALIZE clinical study of telaprevir in patients who failed to achieve SVR with prior treatment of pegylated interferon (peg-IFN) and ribavirin (RBV). This study is focused on 48-week telaprevir-based regimens, which include dosing of telaprevir for 12 weeks. REALIZE is expected to complete enrollment of approximately 650 patients in the United States and Europe in the first quarter of 2009.

### **Interim Analysis of Telaprevir Twice-Daily Dosing Regimen**

- In July, Vertex reported results of an interim analysis of study C208, a four-arm Phase 2a clinical study of approximately 160 genotype 1 treatment-naive HCV patients. The interim results showed that greater than 80% of patients (intent-to-treat analysis) had undetectable HCV RNA (<10 IU/mL) at weeks 4 and 12 in both the twice-daily and three times daily dosing arms of telaprevir, with pegylated interferon alfa-2a (PEGASYS) and RBV. The type and frequency of adverse events across the study arms were generally consistent with previous studies of telaprevir. No substantial differences in safety profile between twice daily and three times daily dosing regimens were observed. These data support continued clinical evaluation of twice-daily dosing of telaprevir.

### **Telaprevir Clinical Data**

#### AASLD

- Six abstracts on telaprevir have been accepted for presentation at the 59th Annual Meeting of the American Association for the Study of Liver Diseases (AASLD), October 31st - November 4th in San Francisco, including presentations that include final results from the PROVE 2 study in treatment-naive patients, interim data from the PROVE 3 study and Study 107 in treatment failure patients, and interim results from study C208 evaluating twice-daily dosing of telaprevir.

Updates on the status of telaprevir clinical trials are available at [www.clinicaltrials.gov](http://www.clinicaltrials.gov).

### **Two Additional Novel HCV Protease Inhibitors in Clinical Development**

- Vertex is advancing a portfolio of HCV protease inhibitors with potentially differentiated profiles. Vertex has initiated a Phase 1b clinical trial of VX-500 in patients with HCV and expects data from this study in the first quarter of 2009. Vertex also has initiated Phase 1 clinical development of VX-813.

### ***Up to 2,700 Alberta patients to be tested after used syringes used on patients***

<http://ca.news.yahoo.com>

By Jim Macdonald And Dean Bennett  
The Canadian Press

HIGH PRAIRIE, Alta. - Up to 2,700 patients, including children, need to be tested for HIV and hepatitis because a handful of nurses in a northern Alberta hospital injected drugs with used syringes for nearly two decades.

Health officials said the risk of infection was low, but it was enough to put people in the community on edge.

"People are very frightened and rightfully so," said Pearl Calahasen, the government member for the area who said has been getting dozens of calls from people who may need to be tested.

"I think when people's lives are threatened in any way, shape or form that fear sets in."

Health officials revealed Monday that a handful of nurses at the High Prairie Health Complex were routinely injecting drugs into patient's intravenous lines with the same syringe.

Blood tests were being arranged for 1,300 patients who had endoscopy procedures over four years dating back to March 2004.

As many as 1,400 patients who had dental surgeries at the same hospital dating back to 1990 also needed to be tested, said Dr. Albert de Villiers, the region's medical health officer.

"We are assuming at this point that a large number of them will be children because it's more children that get dental surgery," he told a news conference Monday.

He said no infections have been found and the risk is very low, but "it is not an acceptable practice that we have identified and that's why we stopped the practice."

Infections disease experts in the U.S. have found cases of serious infections linked to using syringes on more than one patient.

Since 2001, the Center for Disease Control in the U.S. has identified several hepatitis C outbreaks associated with syringe reuse and other lapses in recommended infection control practices.

The problem in High Prairie was discovered earlier this month by a manager who observed a nurse using a used syringe. De Villiers said it took three weeks to sort out which patients may have been infected and whether blood testing was required.

Patients will be contacted by phone and registered mail for testing, which will be co-ordinated by Alberta Health.

"It might be tricky to track down all the patients," said de Villiers. "We will try our best."

The injections were performed by both registered nurses and licensed practical nurses, who both receive training on safe injection practices, said a spokesman for the health region.

Phil Hassen, chief executive officer of the Canadian Patient Safety Institute in Edmonton, said it's too early to say whether it was incompetence on the part of nurses.

"Why did the nurses do what they did?" Hassen asked in an interview. "So often there are a series of things that contribute to this."

"We need to be sure we know what the problem is. We need to fix this thing and we need to learn from it, so it never happens again."

But Margaret Hadley, president of the College and Association of Registered Nurses of Alberta, said there's an onus on registered nurses to be aware of infection control standards and to ensure that they're being followed.

"Part of that behaviour is expecting them to question any policy or procedures that are inconsistent with (patient safety)."

Robin Laughlin, a physician who does most of the endoscopies in the town and has worked in the region for 35 years, said he was surprised and disappointed by the news.

Laughlin said he doesn't know why the syringes were reused or what happened to quality control. "That's obviously one of the questions that has to be answered."

In endoscopy, a fibreglass scope is inserted into a patient's bowel or stomach and beams back video images to scan for cancers, colitis and digestive problems. Prior to the procedure, the patient is sedated by a syringe inserted into the intravenous line.

Intravenous lines sometimes have blood seeping into them from a vein and a syringe could come in contact with the blood and possibly spread an infection.

Alberta's Quality Health Council is investigating, but hospital staff were reportedly reluctant to answer questions.

"We're talking about a group of staff isolated in one department in the facility," said Tim Guest, a vice-president for the local health region. "It's not widespread in the entire facility. (It's) a very small number of employees - less than five."

High Prairie Mayor Rick Dumont was unavailable for an interview, but said in a news release, "I know people that have worked at the hospital for years, and I know they take great pride in their work and honestly care about residents in our community."

"I have trust that Peace Country Health will continue to ensure everyone's safety and welfare."

Health Minister Ron Liepert said he suspects human error is the root cause, but said the investigation will not focus on laying blame.

"We have a health system that is made up of hundreds of thousands of people. They're all human beings. There will be mistakes that will be made," said Liepert.

"As soon as we start pointing fingers or wanting to lay blame, people are not going to want to cooperate."

Liepert took heat in the legislature Monday from Calahasen, a former cabinet minister, who questioned whether her family and friends will lose faith in patient safety.

"Can they still trust the health-care system even when these kinds of things continuously happen?" she demanded of Liepert. "How long will it take to track all these patients down to test them so they can be sure they're not infected?"

Heather Smith, president of the Alberta Union of Nurses, said she's anxious to learn specific details about what was being done, why it was being done and for how long.

"Who was involved in establishing that protocol or that practice?" asked Smith, whose union represents 24,000 registered nurses. "Was this being driven in any part by a need to minimize costs by reusing the syringes?"

The Alberta Union of Provincial Employees cautioned that unsound practices should not be blamed on front-line workers.

"We do not think it would be in any way appropriate for blame in this case to be assigned to working people who are doing their best in very difficult circumstances," union president Doug Knight said in a release.

Knight said health-care employees have been "raising warning flags" for years about understaffing, overwork and cost-cutting policies that pose a risk to patients and hospital staff.

High Prairie, located on the west end of Lesser Slave Lake, has a population of 3,000, but administers to 17,000 in its service area. It is a regional centre serving a mixed farming, forestry and oil and gas community.

This is the second case involving poor sterilization procedures at an Alberta hospital in recent years.

In early 2007, poor sterilization techniques and the outbreak of a superbug forced 3,000 patients from St. Joseph's Hospital in Vegreville east of Edmonton to be tested for infection.

The 25-bed hospital was closed for several weeks after instruments were recirculated with flecks of blood and dead tissue on them.

A class-action lawsuit has since been filed, claiming the hospital failed to ensure the instruments were properly cleaned.

The opposition parties said Premier Ed Stelmach's government has failed to enforce heightened standards for infection prevention promised after the Vegreville outbreak.

"Imagine one of these blood-borne infections infecting someone," said Liberal legislature member David Swann.

"These are life-threatening illnesses. It's totally unacceptable. "

"This government spends more money to educate drug addicts about not reusing syringes than they do for health professionals," said NDP Leader Brian Mason.

"This is simply appalling and could happen again".

Oct 28, 2008

## **Phenomix Initiates Phase 1a Clinical Trial of Hepatitis C Protease Inhibitor PHX1766**

<http://www.marketwatch.com>

SAN DIEGO, Oct 28, 2008 (BUSINESS WIRE) -- Phenomix Corporation today announced it has begun administering subjects in a Phase 1a clinical trial of **PHX1766**, the company's internally discovered, orally available NS3/4A protease inhibitor for the treatment of chronic hepatitis C virus (HCV) infection. The study is being conducted at clinical sites in the Netherlands and will enroll approximately 24 healthy subjects and six HCV infected patients.

In this double-blind, randomized, placebo-controlled Phase 1a study, subjects will be treated with single ascending doses of PHX1766 in order to assess safety, tolerability and pharmacokinetics. Additionally, reductions in viral load will be measured in the patients with HCV infection.

"Phenomix initiated its HCV protease inhibitor program in August 2005 and just two years later we selected PHX1766 as our clinical candidate," said Julie Cherrington, Ph.D., president of Phenomix. "We expedited our HCV discovery program and have designed a unique Phase 1a program in order to obtain single day safety, tolerability and viral load information for PHX1766. We believe our HCV protease inhibitor PHX1766 will be distinguished by its favorable dosing, potency and selectivity attributes."

The World Health Organization estimates that nearly 180million people worldwide are infected with HCV. Of these individuals, 130million are chronic HCV carriers with an increased risk of developing liver cirrhosis or liver cancer. It is estimated that three to four million people worldwide are newly infected each year, 70 percent of whom will develop chronic hepatitis C. In response to the limitations of existing treatments for HCV infection, NS3/4A protease inhibitors have emerged as a potential alternative to the standard treatment.

### **About Phenomix Corporation**

Phenomix is a biopharmaceutical company focused on the discovery, development and commercialization of novel small molecule product candidates directed toward clinically validated targets in significant therapeutic markets. The company's lead product candidate, dutogliptin (PHX1149), is a dipeptidyl-peptidase-4, or DPP-4, inhibitor in Phase 3 development as an oral, once-daily treatment for Type 2 diabetes. Phenomix has a collaboration with Forest Laboratories to develop and commercialize dutogliptin in North America. The company's second product candidate, PHX1766, is a protease inhibitor in Phase 1 clinical development for the treatment of hepatitis C virus, or HCV, infection. Phenomix is based in San Diego, California. For more information, visit [www.phenomix.com](http://www.phenomix.com).

SOURCE: Phenomix Corporation  
Phenomix Corporation  
Laura K. Shawver, Ph.D., Chief Executive Officer  
858-731-5200

or  
Porter Novelli Life Sciences for Phenomix  
Parag Dave, Media & Investor Relations  
619-849-5378  
[pdave@pnlifesciences.com](mailto:pdave@pnlifesciences.com)

## ***Approach to the Treatment of HCV Nonresponders***

[www.medscape.com](http://www.medscape.com)

William F. Balistreri, MD

### **Question**

What is the recommended approach to managing the HCV-infected patient who is a nonresponder to the current standard of care (combination therapy with pegylated interferon + ribavirin)?

### **Response**

Failure to clear the hepatitis C virus (HCV) despite antiviral therapy is not an uncommon scenario. Treatment of patients with chronic hepatitis C with the current standard of care, pegylated interferon (PEG-IFN) and ribavirin, achieves overall sustained virologic response (SVR) rates of ~55%. [1-3] There are host factors and virologic characteristics that govern the response rate -- SVR rates are decreased due to obesity, insulin resistance (and/or nonalcoholic fatty liver disease), nonadherence, cirrhosis, black race, viral genotype 1, and baseline levels of HCV RNA > 800,000 IU/mL. These factors often occur in combination, making treatment difficult. [4] Therefore, in addressing the question, the first issue that arises is whether any (or several) of these predictors of poor response are present in the patient.

The approach to patients who fail to respond to treatment varies, depending on the nature of the initial response, the potency of the treatment, and host-viral factors. Although persons who relapse after an initial response will usually respond to retreatment, there is rarely an SVR with retreatment of true nonresponders. Thus, the current American Association for the Study of Liver Diseases (AASLD) recommendations are as follows: Retreatment with PEG-IFN plus ribavirin should be considered for nonresponders who have significant fibrosis or cirrhosis and who have undergone previous regimens of treatment using nonpegylated interferon. However, retreatment is not indicated in patients who have failed to respond to a previous course of PEG-IFN plus ribavirin, even if a different type of PEG-IFN is administered. [5] But, there is hope for the future. Emerging data suggest that improved sustained response rates can be achieved with new classes of drugs currently under investigation (eg, protease and polymerase inhibitors), with PEG-IFN and ribavirin serving as the backbone of triple-drug regimens. [6,7]

In the interim, there are several strategies that have been suggested to improve SVR rates in patients who are poorly responsive to therapy -- these include increasing the dose of PEG-IFN and/or ribavirin, and prolonging the duration of therapy. [8,9] Fried and colleagues [10] recently compared the efficacy of high-dose regimens of PEG-IFN alfa-2a and ribavirin with conventional-dose regimens in patients with features predictive of poor response to treatment, specifically, HCV genotype 1, high baseline HCV RNA levels, and body weight > 85 kg. Among patients receiving high-dose PEG-IFN alfa-2a (270 mcg/week), the magnitude of serum HCV RNA reduction was significantly greater than that for patients randomized to the conventional

dose of PEG-IFN alfa-2a (180 mcg/week). Patients randomized to the highest doses of PEG-IFN alfa-2a and ribavirin (1600 mg/day) experienced the highest rates of SVR and the lowest relapse rate. As expected, for the treatment arm that received the higher doses of both drugs, the regimen was less well-tolerated. Thus, higher fixed doses of PEG-IFN alfa-2a and ribavirin may increase SVR rates compared with lower doses of both drugs in patients with multiple difficult-to-treat characteristics. The results of this pilot study, although encouraging, should be confirmed by larger randomized clinical trials.

*William F. Balistreri, MD is the Dorothy M. M. Kersten Professor of Pediatrics, University of Cincinnati College of Medicine, Cincinnati, Ohio; Medical Director, Liver Transplantation Program, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio*

## **Why Are Some Veterans Who Are Coinfected With Hepatitis C and HIV More Likely to Be Treated for HCV Than Others?**

<http://www.ibtimes.com>

SAN FRANCISCO, Oct. 28 /PRNewswire/ -- Researchers from the Michael E.DeBakey VA Medical Center, led by Jennifer Kramer, Ph.D., looked at a population of U.S. veterans to determine the patient, provider, and facility characteristics that determined how likely after diagnosis for hepatitis C virus patients who have HIV are treated for HCV. This retrospective study used the Hepatitis C Clinical Case Registry to identify patients who had both infections and who had visited a VA facility at least twice in a six-year period. "This is a very large cohort (N=7,103) of patients with laboratory confirmed HCV-HIV coinfection (maybe one of the largest ever examined) that is very representative of VA users," said Dr. Kramer, but she cautions, "It is difficult to draw conclusions to all patients with HCV-HIV coinfection because the VA cohort tends to be predominately male and relatively low income."

Of those patients in the registry who had HCV and HIV, 10.3% were treated within two years of HCV diagnosis. The researchers went on to identify the factors that resulted in treatment for those patients. Race was a patient factor that determined who was more likely to be treated for HCV. Patients who were black or Hispanic were not as likely to be treated as compared to white patients after HCV diagnosis. Other determining factors were sex (males weren't as likely to be treated as females), drug use, psychosis, high HIV viral load, and genotype 1 or 4. Patients were more likely to be treated if they were diagnosed with HCV more recently; were also diagnosed with cirrhosis; and had high CD4 counts, hemoglobin, and persistently high liver enzyme scores.

The study's authors also identified provider and facility characteristics that determined if a patient who also had HIV was treated for HCV. Patients were more likely to be treated if the facility in which they were seen had only one inpatient hospital compared to those with multiple sites and if the provider was a specialist for HCV.

"The study highlights the important role of facilities and providers, in addition to the known patient-related factors, in explaining variation and possibly outcomes of care in HCV-infected patients," said Hashem El-Serag, MD. "These factors have been largely ignored in current research. We plan to investigate the role of facility factors in HCV treatment receipt in coinfecting patients further by including data from a recently completed facility survey addressing facility factors specifically involved in HCV care."

**Abstract title:**

Patient, provider, and facility characteristics of HCV antiviral treatment among US veterans with HCV-HIV coinfection.

AASLD is the leading medical organization for advancing the science and practice of hepatology. Founded by physicians in 1950, AASLD's vision is to prevent and cure liver diseases. This year's Liver Meeting, held in San Francisco, California, October 31 - November 4, will bring together more than 7,000 researchers from 55 countries.

A pressroom will be available from November 1 at the annual meeting. For copies of abstracts and press releases, or to arrange for pre-conference research interviews contact Gregory Bologna at 703-299-9766. To pre-register, call Ann Tracy at 703-299-9766.

Press releases and all abstracts are available online at [www.aasld.org](http://www.aasld.org).

*SOURCE American Association for the Study of Liver Diseases*

## **Romark Laboratories Announces Presentation of New Nitazoxanide Data at 59th Annual AASLD Meeting and 50th Anniversary IASL Meeting in San Francisco**

<http://au.sys-con.com>

*Company Also Announces Completion of Enrollment in U.S. Phase II Study of Nitazoxanide in Treatment-Naive Patients with Chronic Hepatitis C Genotype 1*

TAMPA, Fla., Oct. 28 /PRNewswire/ -- Romark Laboratories, a privately held biopharmaceutical company, today announced the presentation of studies of nitazoxanide at the upcoming 59th Annual Meeting of the American Association for the Study of Liver Diseases (AASLD), also known as The Liver Meeting(R), and the 50th Anniversary Meeting of the International Association for the Study of the Liver (IASL) in San Francisco, October 31 - November 4, 2008.

### **Nitazoxanide Abstracts**

- "Evaluation of a 4 Week Lead-In Phase with Nitazoxanide (NTZ) Prior to Peginterferon (PEGIFN) Plus NTZ for Treatment of Chronic Hepatitis C: Final Report," J. Rossignol et al., Sunday, November 2, 4:15 PM PST (Oral Session IASL #87), and Tuesday, November 4, 8:00 AM - 12:30 PM PST (AASLD Presidential Poster #1848)
- "Potential Role for Nitazoxanide in Combination with STAT-C Agents for the Inhibition of HCV Replication Without the Development of Resistance," Korba, et al. Sunday Nov. 2, 5:30 PM PST (Oral Session #115)
- "Nitazoxanide (NTZ) is an Inducer of eIF2a and PKR phosphorylation," Elazar et al., Tuesday, November 4, 8:00 AM - 12:30 PM PST (Poster #1881)

### **STEALTH C-3 Fully Enrolled**

In addition, Romark announced it has completed enrollment of patients into its U.S. clinical trial to evaluate nitazoxanide for the treatment of chronic hepatitis C genotype 1 (STEALTH C-3).

The STEALTH C-3 (Studies to Evaluate Alinia for Treatment of Hepatitis C) study began enrollment in April 2008, and 112 patients were ultimately enrolled at 13 centers in the U.S. Data from a planned interim analysis is expected in early 2009.

A Phase II randomized, double-blind, placebo-controlled clinical trial, STEALTH C-3 is designed to evaluate the safety and efficacy of nitazoxanide in combination with peginterferon alfa-2a (Pegasys(R), Roche) and ribavirin (Copegus(R), Roche) in treatment naive patients with chronic hepatitis C infected with genotype 1. The primary objective of this trial is to evaluate sustained virologic response (SVR) with a treatment regimen of 4 weeks of nitazoxanide lead-in therapy followed by 48 weeks of standard of care plus nitazoxanide versus 4 weeks of placebo lead-in followed by 48 weeks of standard of care and placebo.

SOURCE Romark Laboratories

## ***OraSure Technologies Files For FDA Approval of OraQuick Rapid Hepatitis C Test***

<http://www.marketwatch.com>

*When Approved, OraQuick(R) HCV is Expected to be the First Rapid HCV Test in U.S.*

OraSure today announced that it has submitted a pre-market approval ("PMA") application to the U.S. Food and Drug Administration ("FDA") for a rapid test for antibodies to the Hepatitis C virus ("HCV") utilizing OraSure Technologies' OraQuick(R) technology platform. When approved, the OraQuick(R) HCV test is expected to be the first rapid HCV test approved by the FDA for use in the United States.

The Company is seeking FDA approval for use of its OraQuick(R) HCV test on five specimen types - oral fluid, fingerstick whole blood, venous whole blood, plasma and serum. The submission reflects the successful completion of clinical studies which include data from over 3,000 subjects.

The Company also intends to submit a request for CE mark approval of the OraQuick(R) HCV test within the next several months. CE mark approval is needed to sell the test in the European Union.

"The completion of our FDA submission for the OraQuick(R) HCV test is the result of a tremendous effort by our regulatory, research and development and operations groups, and we are very grateful for all of their efforts," said Douglas A. Michels, President and CEO of OraSure Technologies. "We believe the market opportunity for a rapid HCV test, both here in the U.S. and around the world, is very significant and this submission represents the achievement of an important milestone towards commercialization. We look forward to launching this product in the U.S. in collaboration with Schering-Plough Corporation once FDA approval is obtained."

On a world-wide basis, there are an estimated 180 million people who are chronically infected with HCV, with an estimated three to four million individuals newly infected each year. The prevalence of Hepatitis C infection is estimated to be four times that of HIV around the world.

According to the World Health Organization, as many as fifty percent of persons infected with HCV are undiagnosed and up to eighty percent who have HCV show no signs or symptoms. In the U.S., there are an estimated four million Americans, or 1.3 percent of the population, that are or have been infected with HCV. According to the Centers for Disease Control and Prevention ("CDC"), new infections in the U.S. are estimated at approximately 20,000 per year.

As previously announced, OraSure has entered into agreements with Schering-Plough Corporation to collaborate on the development and promotion of the OraQuick(R) HCV test. Under the terms of these agreements, the Company has been and will be reimbursed by Schering-Plough for a portion of its costs to develop the test and obtain regulatory approvals, and Schering-Plough will provide detailing and other promotional support for the test in the physicians' office markets in the United States and internationally.

*SOURCE: OraSure Technologies, Inc.*

[www.orasure.com](http://www.orasure.com)

## ***Drug prices highest in poorest neighborhoods***

[www.reuters.com](http://www.reuters.com)

By Anne Harding

NEW YORK (Reuters Health) - In a study conducted in Florida, researchers found that drugstores in the poorest areas charge more, on average, for four widely used prescription medications than do pharmacies in wealthier neighborhoods.

Fortunately for patients who are uninsured but able to shop around, every ZIP code does include pharmacies that charge less for these drugs, the study team found.

"If it's a medication you're going to be on for a while it's probably worth making a few phone calls," Dr. Walid F. Gellad of the University of Pittsburgh School of Medicine and RAND Corporation told Reuters Health. Gellad conducted the research while at Brigham and Women's Hospital in Boston.

Florida pharmacies that fill prescriptions for Medicaid patients are required by law to post their prices for the 100 most commonly used medications on a web site, MyFloridarx.com.

Using this web site, Gellad and colleagues looked at data for November 2006 on the ulcer drug Nexium, the asthma drug Advair, the heart drug Plavix, and the antibiotic azithromycin, specifically the "Z-Pak" formulation. They then categorized all of Florida's 627 ZIP codes into four groups based on median income.

Across the board, the researchers found, the four drugs were priced highest in the poorest ZIP codes, averaging 9 percent more than the average for the state.

Independent pharmacies charged an average of 15 percent more for each of the drugs than the statewide average, but there was little geographic variation in the prices chain drugstores charged.

Drug stores in ZIP codes with median incomes below \$20,000, for example, charged \$176 for a month's supply of Nexium, \$213 for Advair, \$163 for Plavix, and \$55 for a Z-Pak, compared to \$160, \$198, \$149, and \$50, respectively, at pharmacies in ZIP codes where median income was greater than \$60,000.

"Even small increases in drug prices can dramatically affect medication adherence among the poor," the researchers note in their report.

While the higher costs in poorer neighborhoods were largely driven by higher prices at independent drugstores, they point out, every ZIP code also had independent pharmacies that charged about the same as did chain drug stores.

But people living in poorer areas may have a tougher time shopping around, the researchers add, given limitations in health literacy, difficulty finding transportation, and other factors.

There are options available for people without health insurance to cut down on their out-of-pocket medication costs, Gellad noted, such as programs run by the pharmaceutical industry and by individual states.

Given that other states, including New York, Michigan and Minnesota, also have online drug price databases, "it would be interesting to see if these kinds of issues of geographic variation in price are present in those areas as well," Gellad said.

*SOURCE: Health Services Research 2008.*

### ***U.S. study says doctors subconsciously favor whites***

[www.reuters.com](http://www.reuters.com)

CHICAGO (Reuters) - Doctors subconsciously favor whites over blacks, U.S. researchers said on Tuesday in a finding that may explain widespread racial disparities in health care in the United States.

A long line of studies have found that U.S. blacks get inferior care for cancer and a variety of other ailments compared to whites but experts concerned about the disparities have struggled to understand why.

"This supports speculation that subtle race bias may affect health care, but does not imply that it will," said Janice Sabin of the University of Washington in Seattle, who presented the study at the American Public Health Association's annual meeting in San Diego.

Sabin said it was too early to know if there was a direct link between the findings and the quality of care delivered to blacks in the United States.

She said the findings reinforce other studies showing racial bias is common in the general population.

"But we have to remember people are not racist if they hold an implicit bias," she said in a statement.

Sabin used data from a study of more than 400,000 people who took an online test between 2004 and 2006 about their attitudes on race.

More than 2,500 of the test-takers said they were doctors.

Rather than overt racism, the test looks for subconscious signs of bias by asking a series of questions.

For example, people were asked to quickly say whether photos of blacks and whites were positive or negative.

"We don't call what these tests show prejudice. We talk about it as hidden bias or unconscious bias, something that most people are unaware they even possess," said Anthony Greenwald of the University of Washington, who created the test and helped with the study.

Overall, 86 percent of people who took the test said they lived in the United States. Out of 2,535 physicians, 76 percent said they were U.S. residents.

Of the entire sample, 69 percent said they were white, while 66 percent of those who said they were doctors identified themselves as white.

Doctors in all racial and ethnic groups showed an implicit preference for whites versus blacks except for black doctors, who did not favor either group.

"The implicit bias effect among all the test-takers is very strong," Sabin said. "People who report they have a medical education are not different from other people, and this kind of unconscious bias is a common phenomenon."

Sabin said the study shows diversity training should be a part of medical education in the United States.

Studies have shown blacks in the United States are more likely than whites to die from diabetes, strokes, heart attacks and cancer. Some studies have shown this disparity persists when incomes, education and insurance coverage are equal.

(Editing by John O'Callaghan)

**Oct 29, 2008**

## ***Gene Signature Predicts Late Recurrences in Liver Cancer***

[www.medscape.com](http://www.medscape.com)

Zosia Chustecka

October 17, 2008 — Patients with liver cancer in the developed world are often diagnosed when the tumor is small, so treatment is likely to be successful. Despite this, most patients go on to

have recurrences, and in many cases where the primary tumor is found at an early stage and is resected, the recurrence appears late, 2 years or more after resection.

A new study shows that a certain gene-expression signature found in the liver tissue adjacent to the primary tumor can predict such a late recurrence. The results also suggest that these late recurrences are in fact new primary tumors arising in a damaged organ (from the so-called "field effect"), rather than arising from residual tumors cells from the original primary tumor, the researchers comment.

The findings were published online October 15 in the *New England Journal of Medicine*. First author Yujin Hoshida, MD, PhD, from the Massachusetts Institute of Technology and Harvard University, in Cambridge, collaborated with other centers in the United States, and centers in Japan, Italy, Norway, and Spain.

"Our results suggest that a gene-expression signature can serve as a sensitive 'read-out' of the biological state of the liver in at-risk patients," the researchers write. "It is likely that the survival signature reflects the extent of liver damage and the presence and absence of a proinflammatory milieu, which is mediated in part by gene products involved in an inflammatory response." They add, however, that a heritable basis for the signature, although improbable, cannot be ruled out.

This finding has "direct implications for the prediction of survival and late recurrence after resection for hepatocellular carcinoma," comments Morris Sherman, MB, BCh, PhD, from the department of medicine at Toronto University, in Ontario, in an accompanying editorial.

Dr. Sherman agrees that this finding might make it possible to apply more intense prevention interventions for patients who carry the recurrence signature. "This approach makes sense, although it is hard to see what more can be done for those patients than is done already."

It is hard to see what more can be done for those patients than is done already.

Patients with hepatocellular carcinoma are already carefully monitored and continue to undergo surveillance indefinitely after resection, he points out. Chemoprevention has been explored in such patients but "is not yet practical."

"Perhaps the only realistic method for improving outcome in these patients might be to offer liver transplantation, thereby removing the field defect," he comments. But although liver transplantation is a recognized therapy for hepatocellular carcinoma, it is not currently offered to those who undergo hepatic resection as the first-line therapy, he notes.

The researchers have disclosed no relevant financial relationships. Dr. Sherman reports receiving consulting fees, lecture fees and grant support from Bayer, and consulting fees from Bristol-Myers Squibb.

*N Engl J Med. Published online October 15, 2008.*

## **Vertex Gears up for Big Liver Disease Conference**

<http://www.xconomy.com>

Luke Timmerman

Vertex Pharmaceuticals is preparing to unveil some long-awaited data that will show just how well its drug is performing for some of toughest-to-treat hepatitis C patients.

I spoke with Vertex's chief commercial officer, Kurt Graves, to do some pre-game reporting for the American Association for the Study of Liver Disease's annual meeting October 31 through November 4 in San Francisco. The Cambridge, MA-based biotech company (NASDAQ: VRTX) and competitors from Schering-Plough and Roche will be facing some intense scrutiny by Wall Street analysts at this meeting. So I figured it's a good time to look at what's already known about Vertex's experimental drug, telaprevir, and what to expect.

As a reminder, telaprevir is aiming to be a first-in-class protease inhibitor against hepatitis C, a chronic liver disease. The drug is being watched closely because it has the potential to change the standard of treatment for the disease. Patients currently are prescribed almost a yearlong regimen of pegylated interferon alpha and ribavirin, which cures about one-third of them. Telaprevir, when added to those drugs, can almost double that cure rate, and shorten the regimen to just under six months, previous studies have shown. Telaprevir can also kill the virus for large numbers of patients who have failed on a prior course of therapy. If these findings are confirmed in ongoing Phase III trials and the drug is approved by the FDA, it could generate \$2.6 billion in U.S. sales in 2013, according to Rachel McMinn, an analyst with Cowen & Co. in San Francisco.

Analysts at this upcoming meeting are also going to carefully scope out the competition, namely Schering Plough's boceprevir and Intermune and Roche's ITMN-191. Based on the abstracts submitted in advance of the meeting, which provide a partial picture of what's to come, Vertex says it remains confident. "We're not seeing any antiviral that's as good or better than telaprevir," Graves says. "Telaprevir is still setting the standard."

### **Here's what to watch from Vertex:**

- **Prove 3.** This study of telaprevir for patients who failed on previous therapy, released in June, found that 60 of 115 patients (52 percent) who got the Vertex drug along with the standard drugs had no signs of the virus after about three months of follow-up after finishing treatment, the company said. Only 9 out of 114 patients (8 percent) on the standard drugs did that well at an interim three-month analysis. That measurement isn't directly comparable because those patients were undergoing a longer course of treatment, the company said. The key here is that liver experts and the FDA only consider a patient cured after the virus is wiped out for a full 24 weeks, or about six months. Vertex will present more follow-up data at the conference, Graves said, but he wouldn't say whether it will actually include that critical 24-week cure rate. "Historically we haven't seen a big difference between the 12-week and 24-week," Graves says.
- **The '107 study.** This trial, also in patients who didn't respond to previous treatment, found that telaprevir killed the virus in 49 of 60 patients, or 82 percent, after four weeks. When an early peek at that study's results were released in March, it drove Vertex shares up 28 percent in one day, the single-biggest gain in the company's history. Nothing has been presented publicly on this study since April, when Vertex showed it at the European Association for the

Study of the Liver meeting in Milan, Italy. This trial has had more time for follow-up data to emerge, from more patients, and it will be released at the meeting, Graves says.

- C208. This trial is all about convenience. This study looks at whether a twice-daily dose of telaprevir is as good as the original three-times-a-day dosing regimen. This could provide a convenience advantage over Schering-Plough's boceprevir, which is taken three times a day, Graves says. "It's important for patients and clinicians, and also for competitive reasons," he says.

Vertex, and many of the leading physicians, will also keep their eyes open at this meeting for innovative new treatments that are at earlier stages of development than telaprevir. Two different types of antiviral drugs, polymerase inhibitors and NS5A inhibitors, are being tested along with telaprevir to see if they can help boost the cure rates even higher, Graves says. "Can we get rid of interferon and ribavirin while we improve cure rates?" Graves said. "That's the ultimate goal, and the next major step forward."

**Oct 30, 2008**

### ***Liver risk, death seen with Glaxo's Avandia: group***

[www.reuters.com](http://www.reuters.com)

By Susan Heavey

WASHINGTON (Reuters) - More than one dozen cases of liver failure and death were reported in patients taking GlaxoSmithKline Plc's Avandia, advocacy group Public Citizen said on Thursday in a petition calling for a ban of the diabetes drug.

But GlaxoSmithKline defended its drug, saying its own review by an independent panel earlier this year said the liver risks were acceptable.

"We do not believe there is a connection between liver toxicity and this medicine," the company said in a statement, adding it had not yet read the group's petition.

Public Citizen said its review of U.S. Food and Drug Administration data found 14 previously unpublished cases of severe drug-induced liver failure, including 12 deaths.

That risk, coupled with other known complications that include heart failure, fractures and vision loss, was too great to allow the drug to continue to be sold in the United States, especially with other treatments available, it said in a petition to the FDA.

"The evidence for this unique combination of toxicities is compounded by the accompanying lack of evidence of any clinical benefit, compared to other approved drugs for diabetes," the petition said.

Sales of Avandia -- also known as rosiglitazone and part of a new class of drugs to treat type 2 diabetes called glitazones -- have plunged in the past year after the heart risk surfaced in an analysis of available clinical studies.

Since then, experts at two major diabetes associations have withdrawn their support of the drug, instead backing lifestyle changes such as diet and exercise as well as other treatments.

Still, Public Citizen estimated about 10,000 prescriptions continue to be filled each day. "Thus, it is urgent for the FDA to immediately ban rosiglitazone," it said.

Representatives for the FDA did not immediately return requests for comment.

The British drugmaker's shares trimmed earlier gains and were off 94 cents, or 2.5 percent, at \$36.37 in morning trading on the New York Stock Exchange. In London, its shares were down more than 2 percent.

(Editing by Maureen Bavdek)

## **Scientists closer to Hepatitis C cure**

<http://www.mysanantonio.com>

Wendy Rigby - KENS 5 Eyewitness News

For years scientists have said that a cure for Hepatitis C was on the horizon. Now, the horizon is coming into sharp focus, and San Antonio scientists have their sights set on it.

Virologist Dr. Robert Lanford at the Southwest Foundation for Biomedical Research is a man on a mission. His molecular biology lab is helping test some promising new anti-viral drugs. The blood being studied behind the closed doors is from animals — chimpanzees that have been infected with the Hepatitis C virus to test new compounds.

"Chimpanzees are the only animal other than human beings that can be infected with HCV, so even today that's the only animal model that we can tell whether a drug can really work," Dr. Lanford said.

Of the 160 chimpanzees that live in the enclosures on San Antonio's Northwest Side, more than 30 are Hepatitis C models. By giving them the experimental drug and monitoring them, scientists can find out answers to important questions, like how potent a drug is and how quickly it reduces the level of virus in the blood.

Hepatitis C is the No. 1 cause of liver transplants in the United States. The virus causes swelling and cysts to develop. Eventually, scar tissue forms, then gradually cirrhosis of hardening of the liver, tumors form and eventually the liver fails.

That's the reason why finding a combination of drugs to stop the virus in its tracks is so crucial.

"The viruses are like little factories. And we have to find certain parts of the machinery that's essential to the factory and attack that machinery. And that's what these drugs do," Dr. Lanford said.

The Southwest Foundation for Biomedical Research is testing half a dozen hepatitis C anti-virals now.

Dr. Lanford said he's confident an effective cocktail of drugs will be on the market in five to 10 years.

## ***By imaging live cells, researchers show how hepatitis C replicates***

<http://newswire.rockefeller.edu>

The hepatitis C virus is a prolific replicator, able to produce up to a trillion particles per day in an infected person by hijacking liver cells in which to build up its viral replication machinery. Now new research — in which scientists have for the first time used fluorescent proteins to image hepatitis C virus replication in live cells — shows that the microscopic viral factories are a diverse mix of big, immobile structures and tiny replication complexes that zip zany around inside the cell. The scientists say their results, published in the *Journal of Virology*, offer new insights into how this difficult-to-treat virus, and perhaps others in its class, ensures efficient reproduction of itself — knowledge that could help design next-generation treatments.

“There is so much that we don’t know about this virus, so a better understanding of how the pathogen cleverly forms lots of large and small factories to reproduce itself so that it can infect new hosts may be of great benefit,” says study coauthor Benno Wölk, a former postdoctoral researcher in the Rockefeller University Laboratory of Virology and Infectious Disease. He is now a researcher and physician at Hannover Medical School in Germany.

An estimated 170 million people worldwide are chronically infected with hepatitis C, which is a major cause of liver cirrhosis and liver cancer. So progress in understanding and treating the infection is crucial, says the study’s senior investigator, Charles M. Rice, Maurice R. and Corinne P. Greenberg Professor in Virology and director of the Center for the Study of Hepatitis C. “There is no vaccine available for hepatitis C, and current therapies are not always effective because the virus fights back against drugs developed to block replication,” Rice says.

Scientists had until now believed that the virus’s replication process occurred in one or several large complexes inside a cell. It was hard to learn more because in order to see the virus it had to be killed. “Up to this study, researchers have only been able to look at infected cells when they were fixed and immobile,” Wölk says. “They found areas where the cell membrane was altered and found viral proteins in these structures that suggested that was where replication took place.”

To visualize the replication process, the researchers selected one of the proteins that the hepatitis C virus uses to make its replication factories and fused it to a green fluorescent protein, which emits a green glow when exposed to a specific wavelength of light. They were surprised to see that the small hepatitis C virus replication complexes were transported around the cell. “It’s remarkable that the virus hijacks the cell’s transport machinery to move the viral replication complex around,” Wölk says. “We also learned that for the first several hours after infection only small structures, like dots, formed, which were quickly spread all over the cell. Then the big structures took shape, and they didn’t move.”

The researchers theorize that the small structures are the actual sites of viral replication and that the big structures are clusters of the smaller factories — perhaps formed after the virus has already successfully settled in with the cell. “It is questionable whether the virus even needs the big structures to replicate. They could be performing other functions or they could just represent garbage cans of the cell,” Wölk says. “This is very different from the traditional view.”

Although they can’t say for sure, the group, which also includes Benjamin Büchele of the University of Freiburg in Germany, and Darius Moradpour of the University of Lausanne in

Switzerland, suspects that these small, mobile, replication complexes are more efficient and elegant than large structures because they do two things: distribute the factories so that the integrity of the cell is maintained, and keep the complexity of the replication factories to independent, small, manageable units that are easier to control for the virus.

What the researchers discovered in the hepatitis C virus may also prove to be true for related single-strand RNA viruses in the Flaviviridae family, Wölk says. "If that is the case, then we may be able to find a new treatment target for not just one, but many viral infections."

*Journal of Virology* 82(21): 10519–10531 (November 2008)

## **Anadys Pharmaceuticals Commences Dosing ANA773 in Hepatitis C Patients**

<http://biz.yahoo.com>

SAN DIEGO, Oct. 30 /PRNewswire-FirstCall/ -- Anadys Pharmaceuticals, Inc. (Nasdaq: ANDS - News) announced today that it has initiated dosing ANA773 in patients chronically infected with hepatitis C virus (HCV) in Part B of a two-part protocol designed to test ANA773 in both healthy volunteers and HCV patients. ANA773 is the Company's investigational oral TLR7 agonist prodrug. In Part B of the study, patients in the first cohort will receive 800 mg of ANA773 every other day for 28 days. Doses for subsequent cohorts will be selected based on viral load and tolerability data from the 800 mg cohort.

"The initiation of patient dosing in this study of ANA773 marks the second study that Anadys has initiated in HCV patients this quarter, having commenced patient dosing earlier this week with ANA598, our non-nucleoside polymerase inhibitor," said Steve Worland, Ph.D., President and CEO of Anadys. "With two independent and potentially complementary HCV programs advancing toward viral load data, we look forward to demonstrating the breadth of our portfolio in this important therapeutic area."

### **ANA773 Phase I Study in HCV - Part B**

In Part B of the study, patients in the first cohort will receive 800 mg of ANA773 every other day for 28 days. Doses for subsequent cohorts will be selected based on viral load and tolerability data from the 800 mg cohort. Anadys expects to have viral load data from the 800 mg cohort in the first quarter of 2009 and a complete data set in the second quarter of 2009.

### **About ANA773 and TLR Pharmacology**

In July, Anadys announced that it was resuming clinical investigation of the TLR7 mechanism in HCV by taking ANA773 into a clinical trial under a two-part protocol designed to test ANA773 in both healthy volunteers and patients with HCV. In October, Anadys completed dosing in healthy volunteers. Subjects received a single dose followed by four doses taken every other day, at levels from 200 mg to 1600 mg (with six subjects receiving active and two receiving placebo in each dose cohort). No serious adverse events were reported. Biomarker induction indicative of immune activation was seen in a majority of subjects beginning at 800 mg. Some side effects commonly seen with interferon treatment, including fever and chills, were observed at higher doses, with the frequency and intensity of interferon-like side effects increasing with dose. One

subject at the 1200 mg dose and two subjects at the 1600 mg dose discontinued from the trial before completion of dosing.

ANA773 is an orally administered prodrug of a novel TLR7-specific agonist. Results from preclinical pharmacology studies have shown that ANA773 can elicit desired immune responses and that the profile of response can be modulated by both dose and schedule of administration. Results of completed 13-week GLP toxicology studies have shown that with every-other-day dosing of ANA773, immune stimulation of a magnitude believed to confer therapeutic potential can be achieved without adverse toxicology findings. The immune stimulation observed with every-other-day dosing of ANA773 in monkeys included induction of interferon-alpha and interferon dependent responses at levels that are sustained over 13 weeks of dosing.

### **Clinical Need and Market Opportunity in HCV Infection**

Chronic HCV infection is a serious public health concern affecting approximately 3.2 million people in the United States and approximately 170 million people worldwide. HCV causes inflammation of the liver, which can lead to fibrosis and cirrhosis, and may ultimately lead to liver failure and/or liver cancer if not successfully treated. Cirrhosis of the liver resulting from chronic HCV infection is the leading indication for liver transplantation in the United States. Due to the asymptomatic nature of HCV infection, it often goes undetected for up to 20 years following initial infection. Each year, 8,000 to 10,000 people in the United States die from complications of HCV.

The current standard of care is a combination of pegylated interferon and ribavirin. Inadequate response rates, in particular for patients infected with genotype 1 HCV, along with significant side effects of approved therapy support the medical need for improved treatment options. It is estimated that fewer than 5% of people with chronic HCV infection living in the United States are under treatment today. Most infected individuals are unaware of their infection status and the large majority of individuals who know their condition do not currently receive drug therapy. There is also a growing number of individuals who have failed interferon-based regimens who may be successfully treated with combinations of two or more direct antivirals. It is expected that the next generation of therapies for treatment of HCV will include small molecules, such as ANA598, that directly act upon specific viral enzymes to inhibit viral replication and orally administered agents such as ANA773, which are being developed to potentially replace injectable interferon. These new therapies are expected to improve overall therapy by increasing cure rates and potentially improving tolerability and convenience of treatment if doses of currently used agents can be reduced or eliminated.

### ***Glaxo Will Buy Genelabs for \$57 Million Seeking Hepatitis Drug***

<http://www.bloomberg.com>

By Andrew Pollack

Oct. 30 (Bloomberg) -- GlaxoSmithKline Plc, the world's second-largest drugmaker, said it will buy Genelabs Technologies Inc. for \$57 million in an effort to strengthen its research into treatments against hepatitis C.

Glaxo will offer \$1.30 a share in cash for Genelabs, based in Redwood City, California, the companies said today in a statement on Business Wire. The offer is almost six times the biotechnology company's closing share price today of 23 cents.

Andrew Witty, chief executive officer, said Oct. 22 that London-based Glaxo is keeping its cash available for acquisitions because smaller companies facing difficulty finding funding were turning to the drugmaker as a possible buyer. Glaxo said today that Genelabs, which has no products on the market, will become part of its drug discovery organization. Genelabs is concentrating its research on experimental drugs for hepatitis C, the leading cause of liver failure in the U.S.

“Genelabs has demonstrated a strong track record in hepatitis C virus drug discovery and identified numerous novel classes of inhibitors that target unprecedented mechanisms in the virus's life cycle,” said Zhi Hong, senior vice president of the infectious disease centers for excellence in drug discovery at Glaxo, in the statement.

About 3 million people in the U.S. and 170 million worldwide have hepatitis C, a blood-borne infection. The virus causes no symptoms in about 80 percent of people and is responsible for about two-thirds of all liver transplants. About 80,000 people in the U.S. start treatment each year, creating a market worth \$2 billion or more, analysts have said.

#### December Close Expected

Glaxo said the tender offer, subject to customary conditions, is expected to close in December. The board of Genelabs has unanimously recommended shareholders accept the deal, according to the companies' statement.

Genelabs shares were sold at \$9.13 during the first public offering in June 1991, according to data compiled by Bloomberg. The company, with a market value of \$10 million, has lost 82 percent of its value this year. Genelabs has never made an annual profit, according to Bloomberg data.

Genelabs has a partnership with Glaxo to develop a vaccine for hepatitis E, a virus that is uncommon in the U.S. The biotechnology company also has partnerships with Novartis AG, Watson Pharmaceuticals Inc. and Genovate Biotechnologies on other compounds under development, according to Genelabs' Web site.

To contact the reporter on this story: Andrew Pollack in San Francisco at [apollack1@bloomberg.net](mailto:apollack1@bloomberg.net)

### ***Growing Number of Consumers Trust Online Resources Over Other Media for Researching Drug Treatment Information – Prospective Survey Reveals***

<http://www.pharmalive.com>

WAKEFIELD, MA – October 28, 2008 – A recent online survey conducted by

Prospectiv gathering responses from 3,500 consumers revealed growing consumer reliance on online resources for researching health and drug treatment information. Eighty-three percent of consumers responding to Prospectiv's 2008 Pharmaceutical Online Resources Poll who said that they have previously used the Internet to research ailments and drug treatments also reported that online media is their most trusted and reliable resource for health-related information – up from 75 percent when a similar Prospectiv survey was conducted in 2007.

Prospectiv, a provider of online customer acquisition solutions to leading consumer brands, is the owner of the online properties Eversave.com and Healthier.com, and operates a lead generation platform used by publishers across the Web.

For additional information about Prospectiv's 2008 Pharmaceutical Online Resources Poll, previous Prospectiv pharmaceutical studies, data samples and polling methodology, please visit [http://www.prospectiv.com/request\\_infoc.jsp](http://www.prospectiv.com/request_infoc.jsp).

### **Online Health Resources Draw Consumers**

According to the survey, 74 percent of respondents have used the Internet to research ailment or drug treatment information. As reported, 83 percent said they rely on the Internet as their most trusted resource, followed by print media (11 percent) and broadcast media (5 percent).

### **Where do consumers go online and what are they looking for?**

When respondents were asked where they conduct the majority of their online research:

- 50 percent said they used general health-focused Web sites
- 43 percent conduct research on specific ailment-focused sites
- 5 percent rely on online communities
- Only 3 percent go to branded drug sites operated by pharmaceutical companies

Consumers conducting health and drug treatment research online said that they were looking for the following types of information:

- 49 percent are seeking symptom information about a specific ailment or condition
- 29 percent want drug treatment information for specific ailments or conditions
- 22 percent look for tips for managing ailments and health conditions

### **Consumers consistently favor health newsletters**

Prospectiv's 2008 poll confirms the findings of previous Prospectiv studies – consumers overwhelmingly prefer newsletters for receiving health, drug treatment and ailment information. Asked which online health resource they would be most likely to sign up for:

- 60 percent would sign up for newsletters
- 25 percent would join email groups
- 15 percent would prefer to join an online forum or community

Even among the cohort of consumers who said they do not typically rely on online resources for health and drug treatment information, the majority of this group said they would prefer newsletters (43 percent) for receiving health information in the future, followed by email groups (21 percent) and online forums/communities (36 percent).

Prospectiv's poll results also show that newsletters play an important role for budget conscious consumers at a time when inflation is causing price increases across the board.

- 87 percent of consumers polled said that they are concerned about the continually escalating costs of medicines and prescription drug treatments for their ailments
- 82 percent would welcome receiving prescription drug vouchers and free sample offers directly from pharmaceutical companies
- 65 percent polled would prefer enewsletters for receiving prescription vouchers and free samples, followed by joining email groups (18 percent) or an online forum/community (17 percent)

### **Consumer trust and online health resources**

When asked additional questions regarding their online resources preferences, the cohort who said they did not prefer branded pharmaceutical company sites replied as follows:

- 49 percent said that they didn't know about such sites
- 38 percent reported a lack of trust in the company-run sites
- 13 percent said that they don't find the pharmaceutical sites helpful

The 2007 poll findings revealed that 31 percent of consumers expressed a lack of trust in pharmaceutical branded sites, revealing a 7 percent up-tick in consumer trust concerns this year.

Prospectiv's 2008 study also polled consumers about interactive online health resources such as email groups, forums, blogs and online communities. When asked which type of moderated interactive resource they would trust the most, consumers revealed the following:

- Online resources moderated by doctors (67 percent)
- Online resources moderated by pharmaceutical companies (6 percent)
- Online resources moderated by consumers (27 percent)

“More people are relying on the Internet for their ailment and drug treatment research, and we've found this increasing year over year since Prospectiv began conducting these polls,” said Jere Doyle, Prospectiv's President and CEO. “Based on the 2008 results and previous polls, pharmaceutical marketers seeking to reach consumers online should focus on enewsletters that provide information about ailment symptoms and drug treatments, in addition to offers for drug treatment savings and vouchers. Prospectiv's poll results also consistently show that pharmaceutical marketers should build and host ailment-focused Web sites that provide information about symptoms, drug treatment options and useful tips for managing ailments.”

For additional information about Prospectiv's 2008 Pharmaceutical Online Resources Poll, previous Prospectiv pharmaceutical studies, data samples and polling methodology, please visit [http://www.prospectiv.com/request\\_infoc.jsp](http://www.prospectiv.com/request_infoc.jsp)

**Oct 31, 2008**

### **Roche Receives FDA Approval for Hepatitis C Viral Load Test on Its Fully Automated Real-Time PCR Platform**

<http://www.marketwatch.com>

*Improved laboratory efficiencies and standardization to personalize patient care*

PLEASANTON, Calif., Oct 30, 2008 /PRNewswire via COMTEX/ -- Roche Molecular Diagnostics today announced that the U.S. Food & Drug Administration (FDA) has approved the COBAS(R) AmpliPrep / COBAS(R) TaqMan(R) HCV Test for use in the United States. The test uses Roche's proprietary real-time PCR technology to quantify the amount of Hepatitis C RNA in a patient's blood. Physicians use Hepatitis C viral load testing results to establish a baseline level of hepatitis C infection and to serially monitor viral load levels and treatment effectiveness in patients on therapy.

"This new Roche test enables laboratories to deliver reliable healthcare information with ease and allows physicians to more efficiently monitor their patients and improve treatment outcomes," said Daniel O'Day, President and CEO of Roche Molecular Diagnostics. "We are pleased to offer this new solution for laboratories and physicians to optimize their turnaround time, workflow and patient care with simultaneous processing of HIV and HCV patient samples."

The new test offers a broad dynamic range from high levels of virus in a patients blood to the "undetectable" low levels of viremia -- the goal of therapy. To ensure accurate quantification, the test has been calibrated to World Health Organization (WHO) traceable standards and can detect down to 18 IU/mL with 100% certainty. In a 1,281 patient clinical trial, the COBAS(R) AmpliPrep / COBAS(R) TaqMan(R) HCV Test confirmed the importance of viral load testing to personalize Hepatitis C patient care by accurately predicting treatment response, from onset of therapy through end of treatment.

#### **About the COBAS(R) AmpliPrep/COBAS(R) TaqMan(R) System**

The COBAS(R) AmpliPrep / COBAS(R) TaqMan(R) HCV Viral Load Test is designed for use on the first fully automated, FDA approved, real-time PCR platform, providing sample-in/results-out capability. The platform is flexible and customizable to meet the space and workflow needs of any laboratory. In the United States, more than 130 laboratories already utilize this fully automated platform for HIV testing.

The COBAS(R) AmpliPrep / COBAS(R) TaqMan(R) HCV Test is the third Roche COBAS(R) TaqMan(R) real-time PCR test approved by the FDA in the last eighteen months. The COBAS(R) AmpliPrep / COBAS(R) TaqMan(R) System menu includes an FDA approved HIV viral load test, with continuous loading of samples in addition to parallel processing of HIV and HCV tests. In September 2008, Roche received FDA approval of the COBAS(R) TaqMan(R) HBV Test to monitor Hepatitis B viral load in patients on therapy.

*SOURCE Roche Molecular Diagnostics*

<http://www.roche.com>

#### **Protein Signature May Predict Who Responds to Hepatitis C Treatment**

<http://www.physorg.com>

*-- A tell-tale set of newly-identified proteins may be able to predict who will most likely respond to standard therapy for hepatitis C infection, say researchers in the Duke Clinical Research*

*Institute (DCRI). It is a development that could help patients facing one of the most taxing therapeutic regimens in medicine.*

The research was presented today at the annual meeting of the American Association for the Study of Liver Disease.

The findings are also the first to emerge from a \$35 million grant to Duke from real estate developer David Murdock, who created the North Carolina Research Campus in Kannapolis, N.C., to support genomic studies that help match treatments to patients' unique genetic profiles.

"Those of us who treat patients with hepatitis C (HCV) know that treatment can be very difficult, in terms of side effects, and most patients need to be in therapy for almost a year," says Dr. John McHutchison, the senior author of the study and associate director of the Duke Clinical Research Institute. "When treatment demands this much commitment, it would be nice if we had something to help us - and our patients - decide in advance who is most likely to benefit, and who should try other options."

Hepatitis C is the most common blood-borne viral infection in the United States and it is one of the main causes of chronic liver disease. Some people with HCV can lead long lives with few symptoms, but for others, HCV leads to end-stage liver disease, cancer and death. It is estimated that at least four million people in the U.S. and 170 million people world-wide are infected with HCV.

Standard treatment for the disease includes weekly injections of interferon and the oral antiviral agent, ribavirin. While the regimen can be curative - roughly 40 percent of patients with the most common subtype of HCV in the U.S., called genotype 1, will respond to it - it's not clear who is likely to respond and who is not. The result is that thousands of people spend long months on treatment without any significant long-term benefit.

Sifting through an extensive DCRI biorepository of blood and tissue samples from three thousand patients with HCV, investigators selected serum samples from 30 patients. Ten were from patients with genotype I who responded to therapy and were cured; ten samples were from patients with genotype I who did not respond to therapy and the rest were from patients with genotypes 2 or 3 who had also responded to therapy and were cured.

Researchers broke down the proteins in the serum into peptides and then used liquid chromatography/mass spectrometry to sort the peptides according to molecular weight and charge. Using factor modeling in conjunction with software designed to analyze proteomic data (Rosetta Elucidator) Duke scientists Will Thompson, Joe Lucas and Art Moseley discovered three factors representing clusters of proteins or peptides that can predict in nine cases of out ten who will respond to therapy and who will not.

"This is just a first step," says Moseley, who is director of the proteomics laboratory in the Duke Institute for Genome Science & Policy. "We still have to figure out which protein pathways these clusters are associated with. That, in turn, may yield information that could lead to new treatment options or more informed treatment decisions using current therapies."

"We have needed something like this for a long, long, time," says Keyur Patel, M.D., the lead author of the study and a member of the DCRI. "We are now validating our initial findings in a second set of 30 serum samples from the same biorepository. We are hoping to use these protein signatures in a clinical trial within a year or so."

Additional authors on the study include Laura Dubois, Diane Uzarski, Hans Tillman, Robert Califf and Jeanette McCarthy, all from Duke.

The North Carolina Research Campus, located in Kannapolis, North Carolina, is a private-public venture designed to foster collaborative research in biotechnology, agriculture and nutrition that will improve the health of people world-wide.

Nov 1, 2008

## ***New Clinical Data Support Broad Profile for Telaprevir in Patients with Genotype 1 Hepatitis C Virus (HCV) Infection***

<http://www.businesswire.com>

*-- PROVE 3 data show 52% SVR12 in HCV treatment-failure patients with 24-week treatment duration --*

*-- PROVE 2 final results confirm 69% SVR in HCV treatment-naïve patients with 24-week treatment duration --*

*-- C208 study interim analysis supports potential for future twice-daily telaprevir dosing --*

SAN FRANCISCO--(BUSINESS WIRE)-- New clinical data from four Phase 2 clinical trials of the investigational hepatitis C protease inhibitor **telaprevir (VX-950)** to be presented at the 59th Annual Meeting of the American Association for the Study of Liver Diseases (AASLD) in San Francisco support a broad profile for telaprevir in the treatment of chronic genotype 1 hepatitis C virus infection. Telaprevir is being developed by Vertex Pharmaceuticals Incorporated (Nasdaq: VRTX) in collaboration with Tibotec.

"Data from Phase 2 telaprevir clinical studies in genotype 1 HCV patients are encouraging as responses were seen in treatment-naïve patients, as well as in those who had previously failed treatment with the current standard of care regimen," said John McHutchison, M.D., Principal Investigator for the PROVE 3 study and Associate Director of the Duke Clinical Research Institute. "PROVE 3 data showed that a telaprevir regimen produced a 52% SVR12 in treatment-failure subjects, which is noteworthy as patients who have failed therapy are very difficult to manage due to limited available treatment options and are at greater risk for developing progressive liver disease."

"The data being presented at AASLD support the potential for telaprevir to have a broad role in genotype 1 HCV patients, including those naïve to treatment and those who have previously failed one or more courses of pegylated interferon and ribavirin," said Freda Lewis-Hall, M.D., Executive Vice President, Medicines Development at Vertex. "In addition to the positive data seen in treatment-failure patients, in the final results from PROVE 2 we see the potential for a

significant proportion of treatment-naïve genotype 1 HCV patients to achieve SVR with a 24-week telaprevir-based regimen.”

### **PROVE 3 Interim Analysis for Patients Who Failed to Achieve SVR with Prior Therapy**

The PROVE 3 data show a 52% SVR12 in HCV treatment-failure patients, with a 24-week treatment duration. Results are an interim analysis of a Phase 2b randomized, double-blind, placebo-controlled study in 453 patients who failed prior treatment with pegylated-interferon (peg-IFN) and ribavirin (RBV), including non-responders, prior relapsers and prior breakthroughs. PROVE 3 patient dosing was completed earlier this year and all patients are currently being followed post-treatment.

A summary of PROVE 3 antiviral response rates in one of two 24-week telaprevir-based treatment arms (12 weeks telaprevir in combination with peg-IFN/RBV, followed by 12 weeks peg-IFN/RBV only) categorized by patients’ prior response to peg-IFN/RBV treatment is presented below.

<b>PROVE 3 Treatment Arms</b>	<b>Interim Undetectable HCV RNA (&lt;10 IU/mL) in PROVE 3 24-week regimen (intent-to-treat analysis)</b>
	SVR12(4)
Non-responders (n=66)(1)	41% (27 of 66)
Relapsers (n=40)(2)	73% (29 of 40)
Breakthroughs (n=9)(3)	44% (4 of 9)
Total (n=115)	52% (60 of 115)

[1] Non-responders are defined as patients who never achieved undetectable HCV RNA during prior therapy.

[2] Relapsers are defined as patients who achieved undetectable HCV RNA at the completion of prior treatment, but relapsed during post-treatment follow-up.

[3] Breakthroughs are defined as patients who had undetectable HCV RNA during prior treatment, but had detectable HCV RNA before the end of prior treatment.

[4] SVR12 = undetectable HCV RNA (<10 IU/mL) measured at 12 weeks post-treatment.

In the PROVE 3 control arm (48 weeks of peg-IFN/RBV), 30% (34 of 114) of patients had undetectable HCV RNA at week 36 on treatment (intent-to-treat analysis). At week 12 on treatment, 8% of these patients (9 of 114) had undetectable HCV RNA.

### **Study 107 Interim Analysis in Treatment-Failure Genotype 1 HCV Patients**

In Study 107, a separate study of telaprevir-based regimens in well-characterized treatment-failure patients, researchers found that a high proportion of these patients had a rapid viral response and maintained undetectable HCV RNA (<10 IU/mL) through 24 weeks of treatment, further supporting the role for telaprevir in the treatment-failure population. A large number of patients enrolled in Study 107 had prior null-response. Interim efficacy results include data for patients who have reached respective visits or who had discontinued therapy for any reason or who became detectable at each timepoint. These interim results from Study 107 are summarized in the table below.

<b>Prior Virologic Response in Phase 2 PROVE control arm Studies(1)</b>	<b>Interim Undetectable HCV RNA (&lt;10 IU/mL) by Response to Prior Peg-IFN/RBV</b>
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	Treatment at Week 4, 12 and 24(1)		
	Week 4 <10 IU/mL	Week 12 <10 IU/mL	Week 24 <10 IU/mL
Null-responder (n=48)(2)	40% (19 of 48)	61% (28 of 46)	43% (18 of 42)
Partial responder (n=33)(3)	85% (28 of 33)	90% (26 of 29)	82% (18 of 22)
Relapsers (n= 22)(4)	91% (20 of 22)	94% (16 of 17)	83% (5 of 6)
Breakthrough (n=1)(5)	100% (1 of 1)	100% (1 of 1)	0% (0 of 1)

[1] Patients are unique in each of the non-response categories.

[2] Null-responders defined as patients who had less than a 1 log(10) decrease in HCV RNA at week 4 or less than a 2 log(10) decrease in HCV RNA by week 12.

[3] Partial-responders defined as patients who had a greater than or equal to 2 log(10) decrease in HCV RNA at week 12, but had detectable HCV RNA at week 24.

[4] Relapsers defined as patients who had undetectable HCV RNA at the end of treatment, but reverted to detectable levels of HCV RNA during follow-up.

[5] Breakthrough defined as patients who had detectable HCV RNA after achieving undetectable HCV RNA during treatment with standard therapy.

The Study 107 results presented at AASLD represent an interim analysis of the ongoing, open-label Phase 2 study designed to evaluate telaprevir in patients who failed to achieve SVR in the 48-week control arms of the Phase 2 PROVE studies. In Study 107, at entry patients had been well-characterized as null responders, partial responders, relapsers or breakthroughs to prior peg-IFN and RBV treatment as a result of their participation in a prior Vertex PROVE clinical trial. The analysis includes data from all 104 patients enrolled in Study 107 who received at least one dose of study drug and who completed at least the Week 4 assessment. Patients continued treatment at week 4 and 12 if they did not meet the stopping rule criteria, defined as HCV RNA >100 IU/mL and HCV RNA >25 IU/mL (Roche Taqman assay, version 2.0) at week 4 or 12, respectively.

### **PROVE 2 Final Results in Genotype 1 HCV Treatment-Naïve Patients**

PROVE 2 final results confirm 69% SVR in HCV treatment-naïve patients with 24-week telaprevir-based treatment durations. A more detailed summary of final intent-to-treat SVR rates from PROVE 2, a study of 323 genotype 1 treatment-naïve patients, is presented below.

PROVE 2 Treatment Arms	SVR %
24-week telaprevir treatment arm	69% (56/81)
12 weeks telaprevir/peg-IFN/RBV, followed by 12 weeks peg-IFN/RBV	
12-week telaprevir treatment arm with ribavirin	60% (49/81)
12 weeks telaprevir/peg-IFN/RBV	
12-week telaprevir treatment arm without ribavirin	30% (28/78)
12 weeks telaprevir/peg-IFN	
48-week control arm	46% (38/82)
48 weeks peg-IFN/RBV	

### **Safety and Tolerability Across PROVE 3, Study 107 and PROVE 2**

In Phase 2 clinical studies to date, more than 1,000 patients with genotype 1 HCV have received a telaprevir-containing combination regimen, and the adverse event profile is generally consistent across studies and prior analyses. In the PROVE 3, Study 107 and PROVE 2 telaprevir studies, the most common adverse events reported more frequently in patients receiving telaprevir were gastrointestinal events, skin events (rash, pruritus) and anemia. There have been reports of severe rashes in clinical studies of telaprevir-based therapy. Other adverse events reported were similar in type and frequency to those reported with peg-IFN and RBV treatment.

In the PROVE 3 interim analysis, 16% of patients in the telaprevir-based treatment arms discontinued due to adverse events prior to week 36, while 4% of patients in the 48-week control arm discontinued treatment in the same time period. Rash was the most common reason for discontinuation in 6% of patients. In the Study 107 interim analysis, 8% of patients discontinued due to adverse events. The most common reason for discontinuation was rash in 4% of patients. In the PROVE 2 final analysis, 14% of patients receiving a 24-week telaprevir-based treatment regimen discontinued all study drugs due to adverse events, compared to 7% in the 48-week control arm. The discontinuation of all treatment in the telaprevir-based treatment arms due to rash was 7%.

### **Interim Analysis of C208 Study – Evaluation of Twice-Daily Dosing in HCV Genotype 1 Patients**

Interim results from an ongoing, Phase 2, open-label, randomized study examining a twice-daily (q12h) telaprevir dosing regimen versus a three-times-daily (q8h) regimen in combination with RBV and peg-IFN-alfa-2a (PEGASYS®) or peg-IFN-alfa-2b (PEGINTRON™) in treatment-naïve genotype 1 HCV patients suggest the potential for twice-daily dosing of telaprevir. A summary of this interim analysis is shown below:

C208 Treatment Assignment	Interim Undetectable HCV RNA (<10 IU/mL) at Week 4 and 12	
	Week 4	Week 12
q8h alfa-2a (n=40) <sub>(1)</sub>	80% (32 of 40)	93% (37 of 40)
q8h alfa-2b (n=42) <sub>(1)</sub>	69% (29 of 42)	93% (39 of 42)
q12h alfa-2a (n=40) <sub>(2)</sub>	83% (33 of 40)	83% (33 of 40)
q12h alfa-2b (n=39) <sub>(2)</sub>	67% (26 of 39)	85% (33 of 39)

[1] Patients receiving telaprevir (750mg)/peg-IFN/RBV (800-1200mg/d).

[2] Patients receiving telaprevir (1125mg)/peg-IFN/RBV (1000-1200mg/d).

In this analysis, 4 patients (10%) in the q8h alfa-2a and 2 patients (5%) in the q8h alfa-2b arms discontinued due to adverse events and 1 patient (3%) and 3 patients (7%), respectively, experienced virologic breakthrough. In the q12h alfa-2a and q12h alfa-2b arms, 4 patients (10%) and 3 patients (8%), respectively, discontinued due to adverse events, and 2 patients (5%) and 3 patients (8%), respectively, experienced virologic breakthrough.

### Phase 3 Registration Programs – ADVANCE and REALIZE

Vertex and Tibotec have completed enrollment in the global 3-arm pivotal Phase 3 ADVANCE trial that is focused on 24-week telaprevir-based response guided regimens in genotype 1 treatment-naïve HCV patients. In the ADVANCE study, telaprevir is being dosed for 8 or 12 weeks. Vertex expects to have SVR data from the ADVANCE study in the first half of 2010. Patient dosing is underway in the Phase 3 REALIZE clinical study of telaprevir in genotype 1 HCV patients who failed to achieve SVR with prior treatment of peg-IFN and RBV. This study is focused on 48-week telaprevir-based regimens, which include dosing of telaprevir for 12 weeks. REALIZE is expected to complete enrollment of approximately 650 patients in the United States and Europe in the first quarter of 2009.

### **Boceprevir Phase II Study Showed High Rate Of Sustained Response With 28- And 48-Week Regimens In Genotype 1 Treatment-Naive Hepatitis C Patients**

[www.schering-plough.com](http://www.schering-plough.com).

*Interim results of HCV SPRINT-1 study presented at AASLD annual meeting*

*Pivotal Phase III studies ongoing in treatment naïve patients and those who failed prior treatment*

San Francisco, Nov. 1, 2008 – Schering-Plough Corporation (NYSE: SGP) today reported that a planned interim analysis of a Phase II study showed that boceprevir, its investigational oral hepatitis C protease inhibitor, in combination with peginterferon and ribavirin markedly increased sustained virologic response (SVR) rates with 28 weeks of therapy and nearly doubled SVR with 48 weeks of therapy compared to current standard of care, peginterferon and ribavirin (control group) for 48 weeks. These results from the HCV SPRINT-1 study in 595 treatment-

naïve patients with chronic hepatitis C virus (HCV) genotype 1 were presented at the 59th American Association for the Study of Liver Diseases (AASLD) Annual Meeting.<sup>1</sup>

In a 48-week boceprevir regimen, the SVR rate was 74 percent at 12 weeks after the end of treatment (SVR 12) in patients who received 4 weeks of PEGINTRON™ (peginterferon alfa-2b) and REBETOL® (ribavirin, USP) prior to the addition of boceprevir (800 mg TID) (P/R lead-in). In a 28-week boceprevir regimen, the SVR rate was 56 percent at 24 weeks after the end of treatment (SVR 24) in patients who received the P/R lead-in. These results compared to a 38 percent SVR rate (SVR 12) for patients in the control group receiving 48-weeks of PEGINTRON and REBETOL alone (ITT).<sup>2-4</sup>

Importantly, predictability of attaining SVR 12 or 24 based on rapid virologic response (RVR) was greater for boceprevir patients in the lead-in arms compared to the no lead-in arms. In addition, fewer patients in the lead-in arms discontinued treatment due to viral breakthrough. RVR is defined as undetectable virus (HCV-RNA) in plasma on or before week 4 of boceprevir treatment.

“The high response rates seen with boceprevir in this study are very exciting, especially given that genotype 1 is the most common and hardest to treat form of hepatitis C,” said Paul Kwo, M.D., associate professor of medicine and medical director, liver transplantation, Department of Medicine, Division of Gastroenterology/Hepatology, Indiana University School of Medicine, Indianapolis, and lead investigator of the study. “Boceprevir was well tolerated by patients in this study, and the use of the 4-week lead-in prior to the addition of boceprevir appears to reduce the incidence of viral breakthrough regardless of treatment duration and may improve SVR over a 48-week treatment period.”

The rationale for this novel lead-in treatment regimen is based on the fact that both PEGINTRON and REBETOL reach steady-state concentrations by week 4, so patients have the protease inhibitor added at a time when the backbone drug levels have been optimized. In addition, the patient’s immune system will have been activated and primed by PEGINTRON at the time that boceprevir is added to the regimen. This approach may minimize the period of time when there is a “functional monotherapy” with a direct antiviral, potentially reducing the likelihood for the development of resistance.

Safety data from the study showed that the most common adverse events reported in the boceprevir arms were fatigue, anemia, nausea and headache. No increase in skin adverse events (rash or pruritus) was observed in the boceprevir arms beyond what was seen in the PEGINTRON and REBETOL control arm.

Treatment discontinuations due to adverse events were between 9 and 19 percent for patients in the boceprevir arms, compared to 8 percent for the control arm. Treatment discontinuations for boceprevir patients due to viral breakthrough were fewer in the 28- and 48-week lead-in arms (4 and 5 percent, respectively) compared to the no lead-in arms (7 and 11 percent, respectively).

### **About the HCV SPRINT-1 Study**

In this Phase II study, known as HCV SPRINT-1 (HCV Serine Protease Inhibitor Therapy-1), boceprevir (800 mg TID) was evaluated in three treatment regimens: 4 weeks of PEGINTRON (1.5 mcg/kg once weekly) and REBETOL (800-1400 mg daily based on patient weight) therapy

followed by the addition of boceprevir to the combination for 24 or 44 weeks (totaling 28 or 48 weeks of treatment), boceprevir in combination with PEGINTRON and REBETOL at the doses described above for 28 or 48 weeks, and, in Part II of the study, boceprevir in combination with PEGINTRON and low-dose REBETOL (400-1000 mg daily based on patient weight) for 48 weeks, compared to a control of PEGINTRON (1.5 mcg/kg once weekly) and REBETOL (800-1400 mg daily based on patient weight) alone for 48 weeks (an approved treatment regimen). The primary endpoint of the study is SVR after 24 weeks of follow up (SVR 24). This is an ongoing study and SVR 24 rates are not yet available for patients in the 48-week boceprevir arms or the 48-week control arm of the study. In addition, SVR rates are not yet available and consequently results are not being reported for the boceprevir arm with low-dose REBETOL (n=59) compared to contemporaneous control (n=16) as described above.

Sustained Virologic Response (ITT)\*

<u>Treatment Arm</u>	<u>All patients</u>
No P/R Lead-in 28 Weeks	55% (59/107)
P/R Lead-in 28 Weeks	56% (58/103)
No P/R Lead-in 48 Weeks	66% (68/103)
P/R Lead-in 48 Weeks	74% (76/103)
P/R Control 48 Weeks	38% (39/104)

P/R Lead-in = PEGINTRON and REBETOL for 4 weeks prior to the addition of boceprevir

P/R Control = PEGINTRON and REBETOL alone for 48 weeks

\* SVR 12 for 48 week arms; SVR 24 for 28 week arms 2-4

In the study, predictability of attaining SVR (12 or 24) based on rapid virologic response (RVR) following 28 or 48 weeks of the boceprevir regimen was greater for patients in the lead-in arms (82 and 92 percent respectively) compared to the no lead-in arms (74 and 82 percent, respectively).

The HCV SPRINT-1 study was conducted at sites across the United States, Canada and Europe. Overall, 77 percent of the 595 patients in the study were enrolled in the United States. African-Americans represent 16 percent of the patients enrolled and 7 percent of patients in the study are cirrhotic.

**Update on Boceprevir Phase III Studies**

Schering-Plough is conducting two large ongoing pivotal Phase III studies of boceprevir in patients chronically infected with HCV genotype 1. One study is in treatment-naïve patients and the other in patients who failed prior treatment (relapsers and nonresponders). The two randomized, double-blind, placebo-controlled studies evaluate the efficacy of boceprevir in combination with PEGINTRON and REBETOL compared to standard of care with PEGINTRON and REBETOL alone.

The study in treatment-naïve patients is known as HCV SPRINT-2 and the study in patients who failed prior treatment is known as HCV RESPOND-2. The two studies are expected to enroll a total of more than 1,400 patients at U.S. and international sites.

For more information about these ongoing Phase III studies, please visit [www.clinicaltrials.gov](http://www.clinicaltrials.gov) , search term boceprevir.

## **Gilead Announces Two-Year Data from Pivotal Phase III Studies Evaluating Viread(R) for Chronic Hepatitis B**

<http://www.gilead.com>

*- No Resistance Observed Through Two Years of Treatment -*

*- Significant Viral Suppression Seen in Patients Switching to Viread –*

SAN FRANCISCO--(BUSINESS WIRE)--Nov. 1, 2008--Gilead Sciences, Inc. (Nasdaq:GILD) today announced the presentation of two-year (96-week) data from two Phase III pivotal clinical trials, Studies 102 and 103, evaluating the safety and efficacy of once-daily **Viread(R) (tenofovir disoproxil fumarate)** among adult patients with chronic hepatitis B virus (HBV) infection. These data will be presented during oral sessions at the annual meeting of the American Association for the Study of Liver Diseases (The Liver Meeting 2008) being held this week in San Francisco (October 31-November 4).

Studies 102 and 103 will evaluate treatment with Viread for up to eight years among patients with HBeAg-negative and HBeAg-positive chronic hepatitis B, respectively, with compensated liver disease. Patients in both studies were originally randomized to receive Viread or Hepsera(R) (adefovir dipivoxil). After the completion of 48 weeks of randomized blinded therapy, all eligible patients were rolled over to open-label Viread monotherapy.

These new data show that patients who received Viread for up to 96 weeks experienced sustained suppression of HBV levels in the blood (91 percent and 78 percent for Studies 102 and 103, respectively). The studies also show that all Hepsera-treated patients whose HBV levels were suppressed at week 48 maintained viral suppression after rolling over to Viread, while Hepsera-treated patients with HBV DNA levels above 400 copies/mL at week 48 experienced significant viral suppression after rolling over to Viread. Additionally, by week 96 of Study 103, 6 percent of all patients continuing treatment in both groups experienced "s" antigen (HBsAg) loss, which contributes to resolution of chronic hepatitis B infection (HBsAg seroconversion rates were 4 percent among patients originally randomized to receive Viread and 5 percent for patients who rolled over from Hepsera).

Notably, no mutations associated with resistance to Viread were reported among patients receiving Viread monotherapy for up to 96 weeks or in Hepsera-treated patients who rolled over to Viread.

"In this study, Viread produced a significant and sustained effect over two years of treatment with no evidence of resistance, which is a substantial clinical finding," said Patrick Marcellin, MD of Hopital Beaujon in Clichy, France, the principal investigator of Study 102. "Additionally, patients in this study taking Hepsera were rolled over to Viread without new safety signals and without compromising the efficacy of anti-HBV treatment."

The U.S. Food and Drug Administration (FDA) approved Viread for chronic HBV in adults in August 2008 based on earlier (48-week) results from these studies. Viread and Hepsera are both manufactured by Gilead.

"One of the most important considerations in treating chronic hepatitis B is resistance. It is reassuring to see that no patients from either arm of the study demonstrated resistance to Viread at 96 weeks of treatment," said Jenny Heathcote, MD of the University of Toronto, Canada, the principal investigator for Study 103. "It is also notable that 6 percent of HBeAg-positive patients experienced "s" antigen loss."

Chronic HBV affects an estimated 400 million people worldwide, including two million people in the United States. Many are unaware that they are infected because the disease may not produce obvious symptoms.

One in four people with chronic hepatitis B die from complications such as cirrhosis and liver cancer. In the United States, Asian Americans are disproportionately affected: Foreign-born Asians are 100 times more likely to have the disease compared to non-Asians in the U.S. population. In September 2008, partly in response to advances in HBV therapy, the U.S. Centers for Disease Control and Prevention (CDC) published new HBV screening guidelines recommending that all individuals from Asian countries be tested for the disease.

In addition to its indication for HBV, Viread is also indicated in combination with other antiretroviral agents for the treatment of HIV infection in adults, and is currently the most-prescribed molecule in antiretroviral therapy in the United States.

### **About Studies 102 and 103**

Studies 102 and 103 were multi-center, randomized, double-blind Phase III clinical trials comparing Viread to Hepsera among patients with compensated liver disease and HBeAg-negative presumed pre-core mutant (n=375) and HBeAg-positive (n=266) chronic hepatitis B, respectively. The majority of patients were treatment-naïve, although some patients (n=75) were lamivudine-experienced.

Patients originally randomized to Hepsera in both studies rolled over to Viread (n=196) at week 48, while patients originally randomized to Viread continued Viread treatment in the second 48 weeks (n=389). After 72 weeks, patients with confirmed viremia (HBV DNA levels at or above 400 copies/mL on two consecutive visits) had the option of adding emtricitabine treatment in the form of Truvada(R), an investigational product for the treatment of chronic hepatitis B.

#### *Study 102 Results (Oral Presentation #146)*

##### *HBeAg-negative patients*

Using a long-term evaluation, intent-to-treat analysis algorithm through 96 weeks, which excluded some patients who discontinued the study for administrative reasons and had HBV DNA below 400 copies/mL at last study visit (n=7), 91 percent of those originally randomized to Viread achieved HBV DNA levels below 400 copies/mL compared to 89 percent of those originally randomized to Hepsera who rolled over to Viread at week 48 (p=0.672).

Among patients who received Viread for the entire 96 weeks, 99 percent achieved HBV DNA levels below 400 copies/mL. In addition, all patients who rolled over from Hepsera to Viread at

week 48, regardless of whether they were well controlled on Hepsera or viremic, achieved viral load suppression below 400 copies/mL with Viread by week 96.

Two patients in Study 102 added emtricitabine treatment in the form of Truvada between week 72 and week 96 due to confirmed viremia. One of these patients achieved viral suppression by week 96 and is counted among the 91 percent of patients who experienced sustained suppression with Viread throughout the 96-week period.

Levels of alanine aminotransferase (ALT, an enzyme that serves as a measure of liver damage), which had been high at baseline, remained at near-normal levels between 48 and 96 weeks of treatment in both Viread and Hepsera-to-Viread groups (mean of 35 and 34 U/L, respectively, at week 96;  $p=0.827$ ).

Viread was generally well tolerated by study subjects. The incidence of drug-related serious adverse events was low, with one event reported in the Viread group and none reported in the Hepsera-to-Viread group. There was one death in the study, in the Viread group, due to metastatic liver carcinoma, a known complication of chronic hepatitis B infection. The incidence of grade 3-4 laboratory abnormalities was 10 percent for both Viread and Hepsera-to-Viread groups. No patients experienced a confirmed 0.5 mg/dL increase in serum creatinine or creatinine clearance of less than 50 ml/min. No resistance to Viread was detected among patients who received Viread monotherapy over two years.

#### *Study 103 Results (Oral Presentation #158)*

##### *HBeAg-positive patients*

Using a long-term evaluation, intent-to-treat analysis algorithm through 96 weeks, which excluded some patients who discontinued the study for administrative reasons and had HBV DNA below 400 copies/mL at last study visit ( $n=8$ ), 78 percent of those originally randomized to Viread achieved HBV DNA levels below 400 copies/mL compared to 78 percent of those originally randomized to Hepsera who rolled over to Viread at week 48 ( $p=0.801$ ).

Among patients who received Viread for the entire 96 weeks, 89 percent achieved HBV DNA levels below 400 copies/mL compared to 85 percent of patients who remained on Viread at week 96 after switching from Hepsera at week 48 ( $p=0.374$ ). As in Study 102, all patients who were well controlled at week 48 on Hepsera ( $n=12$ ) maintained viral suppression after switching to Viread. Viremic Hepsera patients responded rapidly after rolling over to Viread, with 82 percent achieving HBV suppression below 400 copies/mL by week 96.

Twenty-eight patients in Study 103 added emtricitabine treatment in the form of Truvada between 72 and 96 weeks due to confirmed viremia. Five of these patients achieved viral suppression by week 96, two of whom were counted among the 78 percent of patients who experienced sustained suppression with Viread over 96 weeks and three of whom were counted among the 78 percent who achieved suppression after rolling over from Hepsera.

As with Study 102, ALT levels, which had been elevated at baseline in both patient groups, remained stable at near-normal levels by week 96 in both Viread and Hepsera-to-Viread groups (mean of 35 and 39 U/L, respectively;  $p=0.765$ ).

Among patients who continued treatment to week 96, a similar proportion of patients in the Viread and Heps-era-to-Viread groups experienced HBeAg seroconversion (26 percent versus 24 percent, respectively;  $p=NS$ ). Seroconversion is defined as both the disappearance of the hepatitis B "e" antigen, a marker of HBV replication (rendering the patient "HBe-antigen negative"), and the appearance of antibodies specific for this antigen (making the patient "HBe-antibody positive"). In addition, 6 percent of patients in both treatment groups experienced "s" antigen (HBsAg) loss, which contributes to resolution of chronic hepatitis B infection (HBsAg seroconversion rates were 4 percent among patients originally randomized to receive Viread and 5 percent for patients who rolled over from Heps-era).

As in Study 102, the incidence of drug-related serious adverse events was similar between the Viread group (one patient) and the Heps-era-to-Viread group (two patients). The incidence of grade 3-4 laboratory abnormalities was also similar: 7 percent for the Viread-only patients and 10 percent for the Heps-era-to-Viread patients. No patients experienced creatinine clearance of less than 50 ml/min. Two patients in the Heps-era-to-Viread group had a confirmed 0.5 mg/dL increase in serum creatinine, compared to none in the Viread group. As with Study 102, no resistance was detected among patients who received Viread monotherapy over two years.

Continued treatment with Viread for 96 weeks did not reveal any new adverse reactions and no change in the tolerability profile observed during the first 48 weeks of treatment. Treatment-related adverse events observed in greater than 5 percent of patients during the first 48 weeks of studies 102 and 103 included: nausea, abdominal pain, diarrhea, headache, dizziness, fatigue, nasopharyngitis, back pain and skin rash.

*SOURCE: Gilead Sciences, Inc.*