













HCV ADVOCATE WEEKLY NEWS REVIEW

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

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April 12th, 2004

NIH Panel Examines Conflict-of-Interest Deals, Drafts Recommendations

*Candace Hoffmann
Source: First Word*

A National Institutes of Health panel looking into alleged conflicts of interest involving its directors and scientists has drafted a report of recommendations on handling consulting deals with biotechnology and pharmaceutical companies, the Los Angeles Times reports.

The NIH Blue Ribbon Committee on Conflict of Interest Policies has stopped short of recommending a ban on such consulting agreements but states in its report that there should be full public disclosure on such deals and that employees should not accept stock or stock options from the industry. The panel "recommends that paid consulting not exceed 500 hours a year and that 'special scrutiny be applied' if outside compensation exceeds half of an employee's yearly salary at NIH," the newspaper reports.

The 10-member committee was appointed by NIH director Elias A. Zerhouni after a Los Angeles Times article reported that two directors of NIH institutes received hundreds of thousands of dollars in company fees or stock options and that more than 94 percent of "top-paid NIH employees were not filing public income-disclosure reports." Three NIH directors contacted by the Times agreed that directors should not accept compensation from biotechs and drugmakers in the future, and Zerhouni said that as of January, institute directors were no longer accepting consulting fees.

Compensation to NIH scientists would be assessed on a case-by-case basis, he said, and an outright ban would not be implemented. "[The agreements] are designed to encourage government scientists to work with private sector scientists in order to speed the translation of research findings to the marketplace," Barbara M. McGarey, an NIH lawyer, is quoted as telling the panel last month. "The result is that government research doesn't sit around and never get developed into products."

The panel will submit its final report to Zerhouni in early May.

April 14th, 2004

HCV Superinfection Hazardous in Hepatitis B Patients

David Douglas

Source: Reuters Health

NEW YORK--- Acute hepatitis C virus (HCV) superinfection may have serious consequences in patients with chronic hepatitis B virus (HBV) infection, Taiwanese researchers report in the April issue of *Gastroenterology*. The outcome is ultimately worse than that following hepatitis delta virus (HDV) superinfection.

In fact, as lead investigator Dr. Yun-Fan Liaw told Reuters Health, "in view of the grave prognosis, especially of HCV superinfection, it is very important to prevent the transmission of these viruses to patients with underlying liver disease."

Dr. Liaw, and colleagues at Chang Gung University in Taipei, came to this conclusion following a study of various groups of HBV patients. These included 93 HBV patients with HCV superinfection and 190 HBV patients with HDV superinfection.

The acute HCV superinfection typically occurred as acute icteric hepatitis. Hepatic decompensation developed in 34% of these patients, hepatic failure was seen in 11% and 10% died. The corresponding proportions in HDV superinfection were 31%, 9% and 7%.

However, follow-up showed that in the HCV group, the 48% cumulative incidence of cirrhosis at 10 years was significantly higher than that in the HDV superinfection group or in those with chronic HBV infection alone. This was also true of hepatocellular carcinoma in the HCV group--the incidence at 10 years was 14% and reached 32% at 20 years.

The researchers conclude that the long-term prognosis of HCV superinfection in such patients is "much worse than that following acute HDV superinfection or active chronic hepatitis B." *Gastroenterology* 2004;126:1024-1029.

Organ Donations Stagnant in Canada Despite Growing Need for Transplants

Source: Canadian Press

TORONTO (CP) --- Despite continued appeals for Canadians to sign donor cards and for families who lose loved ones to give "the gift of life," the rate of organ donation for transplants has stagnated over the last decade, new research shows.

The Canadian Institute for Health Information, releasing its latest figures on organ procurement Wednesday, said the rate of donations across the country is continuing to fall far short of the need for transplants.

In 2003, 124 of every million Canadians - or almost 4,000 people - were waiting for new organs. But the rate of donations was a fraction of that, at just 13.5 organs per million in population, said the institute, an independent, not-for-profit organization working to improve the health of Canadians and the health-care system.

"The flat donor rate in Canada over the past 10 years is in part due to socio-demographic factors such as the aging population and fewer traumatic-injury deaths," Dr. John Gill, a kidney transplant specialist in Vancouver, said in a statement Wednesday.

"Canada's aging population not only contributes to increased demand for organ transplantation, but also affects donations, Gill said. "Many older donors have health conditions that preclude their organs from being retrieved and used for transplantation."

For the third year running, the number of living donors - those who donate one of their kidneys or part of their liver - was greater than the number of deceased donors: 438 compared with 428, the CIHI said.

Provincially, organ donation from cadavers was highest in Quebec and Saskatchewan (19 per million population) and lowest in British Columbia (nine per million) and Manitoba (10.3 per million). However, living organ donation rates were highest in Alberta (19.3), Manitoba (18.1) and British Columbia (17.8). The lowest rates were reported in Quebec (6.9) and Saskatchewan (9.0).

While the number of Canadians on waiting lists for organs at the end of 2003 was down slightly over the previous two years, to 3,914 from 3,956 patients in 2002 and 3,964 in 2001, Gill said he believes the decline doesn't "reflect a reduction in the need for organs."

"Rather, given the long waits for a transplant, there is a growing trend among physicians in Canada to list patients at later stages in their end-stage organ disease," he said.

At the close of 2003, patients needing kidney transplants made up 73 per cent of the waiting list. Overall, 250 Canadians - about five each week - died that year while waiting for new organs. Among them were 82 waiting for a kidney, 100 for a liver, 30 needing a heart, 26 a lung and 12 needing other organs or a combination transplant.

But when organs were available, each deceased donor helped an average of three patients. Living donors provided 403 kidneys and 35 liver lobes, representing 38 per cent of all kidney transplants and nine per cent of all liver transplants in 2003, CIHI said.

The only bright spot on the donation front was an increased number of lungs available: the number of lung/heart-lung transplants averaged 127, compared with an average of 86 during the previous four years. The CIHI attributes the change to increased retrieval of lungs from deceased donors in Canada and an increase in imports of lungs from the United States. (Cross-border organ sharing occurs when there are no matched recipients within the country of origin.)

Gill noted that next week is National Organ and Tissue Donor Awareness Week, a good time for Canadians to make plans for organ donation by signing donor cards and talking to family members about their wishes.

"One donor can save up to eight lives through organ donation and save or improve up to 50 lives through corneal, bone, skin and other tissue transplants," he said.

Explores New Combination Therapy In Hepatitis B Clinical Trial

Trial Uses High Dose of ZADAXIN in Combination with Lamivudine

Source: Business Wire

SAN MATEO, Calif.--April 14, 2004--SciClone Pharmaceuticals (Nasdaq:SCLN - News) today announced an ongoing randomized placebo-controlled clinical trial in Taiwan using a high dose of ZADAXIN® in combination with lamivudine, the most widely used treatment for chronic hepatitis B, to explore the possibility of increasing the efficacy of current treatment for chronic hepatitis B patients. This SciClone sponsored study is designed to build on both the immunomodulator effects of ZADAXIN and the potent anti-viral capabilities of nucleoside analog drugs such as lamivudine. SciClone holds a granted U.S. patent for the treatment of hepatitis B using ZADAXIN in combination with lamivudine that does not expire until 2018. The primary objective of this study is to demonstrate that patients receiving the ZADAXIN lamivudine combination therapy could achieve a significantly higher sustained response rate than patients receiving lamivudine monotherapy, while limiting the use of lamivudine to one year. Lamivudine has been shown to be very effective in suppressing the hepatitis B virus. However, long-term use of lamivudine has been shown to lead to serious HBV mutations. Viral mutations are seen after one year of lamivudine therapy and the incidence of mutation continues to increase with time reaching approximately 55% after three years. Associated with these mutations is the development of viral resistance to lamivudine making therapy more difficult. In addition, lamivudine's overall efficacy is limited. Data show that lamivudine therapy produces a sustained seroconversion (the disappearance of HBV e-antigen and the detection of the antibody to the HBV e-antigen) in only 16% of Asian patients. A separate study using the latest approved HBV therapy, adefovir dipivoxil, a nucleotide analog with a similar mechanism of action as lamivudine, produced a sustained seroconversion in only 12% of patients. In comparison to these studies, ZADAXIN as a monotherapy in a completed phase 3 clinical trial in Japan has demonstrated a sustained seroconversion in 19% of patients receiving low dose (0.8 mg, twice weekly) ZADAXIN and in 22% of patients receiving standard dose (1.6 mg, twice weekly) ZADAXIN. Patients who achieve a sustained seroconversion are widely considered to be cured of chronic hepatitis B.

In this new combination study one group of patients is receiving a high dose of ZADAXIN (3.2 mg, twice weekly) for six months plus a standard dose of lamivudine (100 mg, once a day) for 12 months. The other group of patients is receiving the same dose of lamivudine (100 mg, once a day) for 12 months plus a placebo. Upon completing the 12 months of therapy, each patient will be followed for a six month observation period. Endpoints of the study are the disappearance of HBV DNA and the achievement of sustained seroconversion. The study is being led by Dr. Yun-Fan Liaw at Chang Gung Memorial Hospital in Taiwan, who plans to enroll by the end of 2004 a total of approximately 120 patients suffering from chronic hepatitis B.

Dr. Yun-Fan Liaw, Professor of Medicine at the Liver Research Unit, Chang Gung University and Memorial Hospital commented, "In this study, we intend to explore the theory that the immunomodulatory effects of ZADAXIN could enhance the immune response of HBV patients thereby achieving higher seroconversion rates for those patients using lamivudine to suppress the hepatitis B virus. We expect to observe a higher response rate from the two drugs combined than from the separate response rates of each drug alone, therefore demonstrating a more effective treatment option for patients suffering from chronic hepatitis B." The hepatitis B virus is one of the world's most prevalent blood borne chronic infectious diseases. The World Health Organization estimates that more than 350 million people worldwide, predominantly in Asia, are chronically infected with the hepatitis B virus.

Combination therapy using ZADAXIN is also being studied in clinical trials with pegylated interferon for the treatment of hepatitis C as well as with the chemotherapy drug decarbazine (DTIC) for the treatment of malignant melanoma. Similar to Dr. Liaw's study, these clinical trials are using ZADAXIN in combination with approved drugs with the objective of achieving higher response rates compared to current therapy. ZADAXIN is a pure synthetic preparation of thymosin alpha 1, a natural substance that circulates in the body and is instrumental in the immune response to fight viral infections and certain cancers. In over six years of commercial use and over a decade of clinical development, ZADAXIN, either used alone or in combination with anti-viral and anticancer drugs, has not produced any reported significant side effects or toxicities. ZADAXIN has been approved for sale by the ministries of health in over 30 countries and is marketed in China and selected other countries outside the U.S. SciClone is targeting to file a New Drug Application in Japan for ZADAXIN as a monotherapy for the treatment of chronic hepatitis B by the end of 2004.

About SciClone

SciClone Pharmaceuticals is a biopharmaceutical company engaged in the development of therapeutics to treat life-threatening diseases. SciClone is currently evaluating its lead product ZADAXIN in several late stage clinical trials, including two phase 3 hepatitis C clinical trials in the U.S., a completed phase 3 hepatitis B clinical trial in Japan, a phase 2 malignant melanoma clinical trial in Europe, two phase 2 liver cancer pilot studies in the U.S., and a hepatitis C triple therapy pilot clinical trial in Mexico. The Company's other principal drug development candidate is SCV-07, a potentially orally available therapeutic to treat viral and infectious diseases. For more information about SciClone, visit www.sciclone.com.

The information in this press release contains forward-looking statements including expectations and beliefs regarding the outcome of the hepatitis B study in Taiwan; the timing, number of patients enrolled and completion of enrollment for the study; the timing of filing of SciClone's Japanese New Drug Application and the fact that the experimental or clinical data described or compared may imply certain actual results in larger patient populations. Words such as

"expects," "plans," "believe," "may," "will," "anticipated," "intended" and variations of these words or similar expressions are intended to identify forward-looking statements. In addition, any statements that refer to expectations, goals, projections or other characterizations of future events or circumstances, including any underlying assumptions, are forward-looking statements. These statements are not guarantees of future performance and are subject to risks, uncertainties and assumptions that are difficult to predict. Therefore, actual results could differ materially and adversely from those expressed in any forward-looking statements as a result of various factors, including the progress or failure of the hepatitis B study in Taiwan, the statistical significance of data obtained from the study, unexpected results from the interaction of ZADAXIN in combination with lamivudine, the potential for receipt of data that is inconclusive or contradictory, the speed with which patients are enrolled in the study, competition for enrollment of patients meeting a particular patient profile, ability to enroll a sufficient number of eligible patients to yield statistically significant results, maintenance of the sufficiency and eligibility of the enrolled patient population, unexpected delays in preparation of the Japanese New Drug Application, delays in analyzing and synthesizing data obtained from SciClone's phase 3 hepatitis B clinical trial in Japan, the fact that experimental data and clinical results derived from studies with a limited group of patients may not be predictive of the results of larger studies and the fact that comparisons between clinical trials or studies conducted under varying conditions cannot be relied upon as conclusive evidence as to relative therapeutic benefit, as well as other risks and uncertainties described in SciClone's filings with the Securities and Exchange Commission.

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Source: *SciClone Pharmaceuticals*

No 'Safe' Alcohol Intake Found with Hepatitis C

Source: *Reuters Health*

NEW YORK--- Fibrous changes in the liver caused by hepatitis C infection are worsened with any level of alcohol consumption, a study shows. However, there may be trade-off between benefits and risk with low alcohol intake, according to the report in the journal *Hepatology*.

Heavy alcohol consumption may contribute to the progression of hepatitis C-related liver disease, the authors explain, but light alcohol intake has not been shown to do so and may, in fact, bestow other health benefits.

To look at this issue, Dr. Alexander Monto and colleagues from University of California at San Francisco compared liver biopsies and detailed records of daily alcohol intake from 800 patients with chronic hepatitis C virus infection.

The researchers found that there was a range of liver damage severity in each category of alcohol intake, though overall liver fibrosis was greater in patients who drank heavily than in those who did not.

The findings were somewhat different in women, the investigators report. Their fibrosis scores were lower, and the association between alcohol intake and fibrosis was less clear.

"One important question has been: is there a 'safe' level of alcohol intake in patients with chronic HCV infection?" Monto's team writes. "This study does not find this to be the case."

They point out, "Light and moderate intake exert less of an effect on fibrosis than heavy intake, however, and may indeed have minimal or no effect."

Balancing this "small risk of liver disease progression against potential cardiovascular benefit may be particularly pertinent to middle-aged men, who worldwide constitute the majority of patients with HCV, and who are also at high risk for cardiovascular disease," the researchers point out.

They conclude that risks and benefits should be individually assessed for each patient.

SOURCE: Hepatology, March 2004.

April 15th, 2004

Results of Largest Controlled Clinical Trial in Hepatitis B "e" Antigen-negative Patients; Resistance Analysis and Post-Seroconversion Data Presented

Source: Business Wire

BERLIN -- Gilead Sciences today announced 144-week data from a clinical trial (Study 438) of its oral antiviral drug Hepsera® (adefovir dipivoxil 10 mg) in patients with hepatitis B "e" antigen-negative/anti-hepatitis B "e" positive (HBeAg-negative/anti-HBe positive, or precore mutant) chronic hepatitis B virus. HBeAg-negative hepatitis B is a mutant strain of the hepatitis B virus (HBV) that lacks the ability to produce the envelope ("e") antigen. In this study, patients treated with Hepsera showed progressive reductions in serum HBV DNA replication and sustained ALT normalization through 144 weeks of treatment. The development of Hepsera-related resistance mutations was delayed and infrequent among patients treated for 144 weeks. Study results were presented today at the 39th Annual Meeting of the European Association for the Study of the Liver (EASL) in Berlin, Germany.

It is estimated that more than 400 million people worldwide have chronic hepatitis B, which is caused by infection with the hepatitis B virus. One quarter to one third of these individuals develop progressive liver disease, which can lead to cirrhosis and/or liver cancer. Approximately one million people die annually from complications of chronic hepatitis B, making it one of the leading causes of death worldwide. HBeAg-negative chronic hepatitis B infects approximately 14 to 24 percent of chronic hepatitis B carriers in North America and Europe, and is most prevalent in countries of the Mediterranean and Southeast Asia, where between 30 and 80 percent of chronic hepatitis B patients are estimated to be infected with this strain.

"Long-term antiviral therapy is typically needed to control HBeAg-negative chronic hepatitis B, and high rates of viral resistance can limit other treatment options," said Professor Stephanos Hadziyannis, MD, Department of Medicine, Henry Dunant Hospital, Athens, Greece, and a lead investigator for Study 438. "The durable antiviral efficacy, good tolerability profile and low rate of resistance we continue to see in this study suggest that Hepsera is a valuable treatment option for patients with HBeAg-negative hepatitis B."

Study 438 Design

The efficacy, tolerability and safety data through 144 weeks from Study 438 were presented today by Dr. Hadziyannis (Oral Presentation #46). This 96-week randomized, double-blind, placebo-controlled clinical trial was designed to evaluate the long-term safety and efficacy of Hepsera in patients with HBeAg-negative chronic hepatitis B and compensated liver function. Following 96 weeks, patients treated with Hepsera during the second year of the study were offered the drug for up to three additional years. This study was conducted in Australia, Canada, France, Greece, Israel, Italy and Southeast Asia. To date, it is the largest placebo-controlled clinical trial in HBeAg-negative patients.

Three-year Study Results

Among patients who received continuous Hepsera treatment over 144 weeks (n=70), 79 percent of patients achieved undetectable levels of serum HBV DNA (less than 1,000 copies/mL, Roche Amplicor Monitor(TM) PCR assay, compared with 69 percent after 96 weeks. The median reduction in serum HBV DNA levels among Hepsera-treated patients was 3.63 log₁₀ copies/mL at week 144.

Hepsera also provided sustained improvement in liver function through 144 weeks, as measured by blood levels of the liver enzyme alanine aminotransferase (ALT). The proportion of patients with ALT levels above the upper limit of normal at baseline whose ALT levels returned to normal at 144 weeks was 88 percent (n=62).

The safety profile of Hepsera over 144 weeks was consistent with that seen over 48 weeks, which was similar to placebo. The most common adverse reactions considered at least possibly related to Hepsera treatment through the third year of the study were headache, abdominal pain and asthenia (weakness). Three patients had an increase in serum creatinine of greater than or equal to 0.5 mg/dL from baseline by week 144. All cases resolved, one while continuing Hepsera therapy and two with discontinuation of Hepsera therapy. No patients had a serum phosphorus level less than 1.5 mg/dL through 144 weeks.

Probability of Resistance at 144 Weeks

Data further characterizing the long-term resistance profile of Hepsera were also presented today at EASL by Dr. Shelly Xiong of Gilead Sciences (Oral Presentation #57). To determine the incidence of Hepsera resistance after 144 weeks of treatment, data were analyzed from five clinical studies, including two pivotal studies of the drug. This analysis included 629, 293 and 167 patients who received 48, 96 and 144 weeks of Hepsera. Two mutations (rtN236T and rtA181V) in the viral polymerase have been associated with resistance to the drug. The cumulative probability of developing resistance after 144 weeks of treatment with Hepsera across these five studies remains low (3.9 percent), based on this analysis using the life table method. Through 48 weeks of treatment no Hepsera-related resistance mutations were identified and among patients treated for 96 weeks, less than 2 percent (1.6 percent) developed resistance. Resistance surveillance will continue for up to five years in long-term clinical efficacy and safety studies.

Durability of Seroconversion after Hepsera Discontinuation

To evaluate the durability of hepatitis B "e" antigen seroconversion following treatment with Hepsera, patients with compensated liver function who had undergone seroconversion in a prior clinical study (patients were from Studies 437 and 412) were enrolled in a long-term off-treatment follow-up study (Study 481). Seroconversion was defined as both the disappearance of

hepatitis B "e" antigen (HBe-antigen negative), a marker of HBV replication, and the appearance of antibodies specific for "e" antigen (HBe-antibody positive). Data from an interim analysis of 66 patients were described today in a poster presentation (Presentation #424). In this study, seroconversion was shown to be durable in 91 percent of patients following discontinuation of Hepsera. Patients were followed for a median of 55 weeks after stopping treatment with Hepsera.

About Hepsera

Hepsera, the first nucleotide analogue for the treatment of chronic hepatitis B, is administered as a once-daily 10 mg tablet and works by inhibiting HBV DNA polymerase, an enzyme involved in the replication of the virus in the body. To date, Hepsera has been studied in 35 clinical trials and has been prescribed to approximately 24,000 patients. Hepsera is now available in the United States and 13 countries in Europe. In April 2002, Gilead signed a licensing agreement with GlaxoSmithKline (GSK), granting to GSK rights to commercialize Hepsera in Asia, Latin America and other territories. Hepsera has been launched in five Asian markets to date, including Hong Kong and Singapore.

In the United States, Hepsera is indicated for the treatment of chronic hepatitis B in adults with evidence of active viral replication and either evidence of persistent elevations in serum aminotransferases (ALT or AST) or histologically active disease.

In the European Union, Hepsera is indicated for the treatment of chronic hepatitis B in adults with compensated liver disease with evidence of active viral replication, persistently elevated serum alanine aminotransferase levels and histological evidence of active liver inflammation and fibrosis; or decompensated liver disease.

The adverse reactions considered at least possibly related to treatment reported in 3 percent or greater of patients in the first 48 weeks in Hepsera pivotal clinical studies were asthenia, headache, abdominal pain, nausea, flatulence, diarrhea and dyspepsia. With extended treatment, mild to moderate increases in serum creatinine were observed uncommonly in patients with chronic hepatitis B and compensated liver disease treated with Hepsera for a median of 49 weeks and a maximum of 109 weeks. Changes in serum creatinine were observed very commonly in patients with pre- and post-transplantation lamivudine-resistant liver disease and multiple risk factors for changes in renal function who were treated with Hepsera for up to 129 weeks, with a median time on treatment of 19 and 56 weeks, respectively. Clinical and laboratory evidence of exacerbations of hepatitis have occurred after discontinuation of treatment with antiviral therapies for hepatitis B, including Hepsera. Special warnings and precautions for use are included in the package insert regarding monitoring of renal function, post-treatment exacerbations of hepatitis, use in patients with underlying renal impairment, patients co-infected with HIV, the occurrence of nucleoside analogue-associated lactic acidosis and severe hepatomegaly with steatosis.

About Gilead

Gilead Sciences is a biopharmaceutical company that discovers, develops and commercializes therapeutics to advance the care of patients suffering from life-threatening diseases worldwide. The company has six marketed products and focuses its research and clinical programs on anti-infectives. Headquartered in Foster City, CA, Gilead has operations in the United States, Europe and Australia.

This press release includes forward-looking statements, within the meaning of the Private Securities Litigation Reform Act of 1995 that are subject to risks, uncertainties and other factors that could cause actual results to differ materially from those referred to in the forward-looking statements. Such risks and uncertainties include the risk that these 144-week data will not be observed through longer treatment periods and uncertainty regarding inclusion of these data in the Hepsera product label. These and other risks are described in detail in the Gilead Annual Report on Form 10-K for the year ended December 31, 2003 and in Gilead's Quarterly Reports on Form 10-Q, all of which are on file with the U.S. Securities and Exchange Commission. All forward-looking statements are based on information currently available to Gilead and Gilead assumes no obligation to update any such forward-looking statements.

Hepsera is a registered trademark of Gilead Sciences, Inc.

For more information on Gilead, please call the Gilead Public Affairs Department at 1-800-GILEAD-5 (1-800-445-3235) or visit www.gilead.com.

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Source: Gilead Sciences, Inc.

PEGASYS and COPEGUS Now Offers Benefits in a Wider Range of Hepatitis C Patients

Source: Roche Press Release

New Data Presented At European Liver Meeting On Two Multinational Trials

Basel, Switzerland — New data from two pioneering hepatitis C (HCV) studies with PEGASYS® plus COPEGUS® will be presented this week at the 39th Annual Meeting of the European Association for the Study of the Liver (EASL) in Berlin. The multinational trials – one in patients with HIV-HCV co-infection and the other in HCV patients with persistently normal levels of alanine aminotransferase (ALT) – demonstrate that PEGASYS plus COPEGUS is an effective, safe and predictable treatment option.

Final results of APRICOT report highest ever treatment response in co-infected patients
The final results of APRICOT (AIDS PEGASYS—Ribavirin International CO-infection Trial) – the largest and only multinational study evaluating the efficacy and safety of pegylated interferon combination therapy in people co-infected with HIV and HCV – found that the combination of PEGASYS and COPEGUS achieved a 40% sustained virological response (SVR) – the highest ever reported in a trial of co-infected patients.

“APRICOT provides the guidance that we have wanted on how best to treat co-infected patients and there is no doubt that the combination of PEGASYS and COPEGUS represents the best we can currently offer this patient population,” said Dr. Francesca Torriani, Associate Professor of Medicine, Antiviral Research Centre, University of California at San Diego and one of the APRICOT lead investigators. “What’s more, we now have data from this trial on our ability to confidently predict as early as week 12 of therapy which patients are likely to achieve a sustained virological response.”

The key APRICOT findings that Dr. Torriani will present on Sunday, April 18th are:

- 40% of patients treated with PEGASYS plus COPEGUS achieved an SVR compared to 20% of patients treated with PEGASYS monotherapy and 12% of patients treated with conventional interferon/ribavirin.
- Genotype 1 patients treated with PEGASYS plus COPEGUS achieved a four-fold increase in SVR compared to conventional interferon/ribavirin (29% vs 7%).
- 62% of genotype 2/3 patients treated with PEGASYS plus COPEGUS combination therapy achieved an SVR compared to 20% with conventional interferon/ribavirin.

New APRICOT data identifies patients most likely to respond

New data will be presented on APRICOT that will help physicians identify those patients with the best chance of achieving an SVR. 71% of co-infected patients achieved an EVR following 12 weeks of a fixed 180µg/week dose of PEGASYS and 800mg daily of COPEGUS (ribavirin), and of those, more than half (56%) achieved an SVR. Among patients with the more difficult-to-treat HCV genotype 1, 45% who had an EVR went on to achieve a sustained virological response. The ability to tell patients at week 12 if their treatment is likely to generate an SVR, is now recognized as having an important role in the motivation of patients to start with, and stay on, therapy.

Real world patient population in APRICOT

The patients in this landmark study were predominantly male, middle-aged with stable HIV disease. However, patients had a wide range of HIV status; the majority were on anti-retroviral therapy and they had very high HCV viral loads (10-15 million copies/ml). The very low (12%) response achieved by patients to the arm receiving conventional interferon combination therapy is illustrative of the challenging nature of the co-infection present in these patients.

European Union contributes nearly half the patients

422 of the 868 patients randomized in APRICOT came from 11 European Union countries – a total of 19 countries participated. These patients were randomized to receive either PEGASYS 180µg once weekly plus COPEGUS 800mg daily; PEGASYS 180µg monotherapy once weekly (plus placebo COPEGUS tablets), or conventional interferon alfa-2a 3MIU three times a week in combination with ribavirin 800mg daily, all for 48 weeks.

New data on quality of life from second landmark trial in patients with normal ALT

A substantial proportion of hepatitis C patients have ‘normal’ levels of ALT (an enzyme present in the blood used historically as a marker for liver injury and disease). Because these levels are ‘normal’, these patients were traditionally considered to have ‘mild’ hepatitis and therefore did not need to be treated. More recently, however, there has been a growing awareness that ALT is actually a poor marker of liver disease. Indeed, all patients in this trial had evidence of liver inflammation and nearly one third had some degree of fibrosis.

In the only global trial in this group of patients, 514 patients were randomized to receive either PEGASYS 180µg once weekly plus COPEGUS 800mg daily for either 24 or 48 weeks, followed by a 24-week treatment-free follow-up period. A third arm was an untreated control group, since no treatment was considered the standard of care at the time the study was designed.

The key trial findings were: ^{i,ii}

- Overall 52% of hepatitis C patients with ‘normal’ ALT levels achieved an SVR while none in the control arm did. These results are consistent with the excellent results seen in other patient populations treated with PEGASYS plus COPEGUS.
- 72% of PEGASYS patients infected with genotypes 2 or 3 who were treated for 24 weeks and 40% of PEGASYS patients infected with the ‘difficult-to-treat’ genotype 1 who were treated for 48 weeks achieved an SVR.

New data presented at EASL noted that:

- Those who achieved an SVR reported a better QoL including reduced fatigue than both the untreated control group and those who failed to achieve an SVR.
- Those patients who failed to achieve an EVR following 12 weeks of therapy were highly unlikely to achieve an SVR. As in other HCV patient groups, this provides an early and meaningful time point for physicians and patients to discuss the benefits of continuing with treatment if viral eradication may not be achieved.

“The results of this trial are very important because until now it was not clear if there were benefits to treating these patients – which account for about 30% of patients with chronic hepatitis C,” said Professor Stefan Zeuzem, from Saarland University, Homburg, Germany. “Now, we know these patients can be effectively treated like other patients with hepatitis C and experience improvements in their quality of life.”

New trial underway by Roche in another difficult-to-treat group of patients

Recently Roche announced the launch of the first global trial to study the efficacy of PEGASYS plus COPEGUS in another difficult-to-treat patient population: hepatitis C patients who failed to respond to peginterferon alfa-2b plus ribavirin combination therapy. This trial is known as REPEAT, which stands for "Retreatment with PEGASYS in patients not responding to prior peginterferon alfa-2b/ribavirin combination therapy". The REPEAT study will evaluate the efficacy and safety of the combination of PEGASYS and COPEGUS given for a longer, 72-week period, as well as examining the role of an induction regimen in this treatment-resistant population.

Close to 1,000 patients will participate in this study from Europe, North America and Latin America.

About PEGASYS

PEGASYS, a new generation hepatitis C therapy that is different by design, provides significant benefit over conventional interferon therapy in patients infected with HBV and HCV. The benefits of PEGASYS are derived from its new generation large 40 kilodalton (KD) branched-chain polyethylene glycol (PEG) construction, which allows for sustained drug levels over the course of a full week. PEGASYS also distributes more readily to the liver (the primary site of infection) than conventional interferon. In HCV PEGASYS provides superior efficacy compared to conventional interferon combination therapy in HCV patients of all genotypes. PEGASYS is the only pegylated interferon available as a ready-to-administer solution. Each weekly subcutaneous injection contains 180mcg of pegylated interferon alfa-2a (40KD) which is the approved dose for all patients, regardless of body weight.

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Film footage is available for broadcast journalists from The NewsMarket at www.thenewsmarket.com. Video is compressed in MPEG2 and is available for download to your FTP server.

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The Tainted-Blood Scandal Lives On

Andre Picard

Public Health Reporter

Source: www.theglobeandmail.com

Ten years ago, public hearings began into the tainted-blood tragedy, one of Canada's most devastating public-health fiascos. About 2,000 hemophiliacs and transfusion recipients contracted HIV-AIDS and another 10,000 or so were infected with the hepatitis C virus (HCV) from contaminated blood and blood products.

In that decade, much has changed, thanks, in large part, to Mr. Justice Horace Krever's searing dissection of what went wrong and his pointed recommendations on how to make amends.

Canada has a new, better blood system. Health Canada takes its regulatory function more seriously. The Canadian Patient Safety Institute has been created. The Canadian Public Health Agency is under construction.

But, for the victims of tainted blood, has justice been done?

One of Judge Krever's central recommendations was that everyone who suffers "serious adverse consequences from the administration of blood components or blood products" -- past, present and future -- should receive financial compensation. This no-fault approach, he said, was the surest, most cost-efficient way to provide help to those who were harmed.

The veteran judge cautioned that the alternative -- using litigation to determine who was wronged and to what degree, or creating compensation programs for specific groups in a piecemeal fashion -- was a recipe for disaster.

Yet this is precisely what happened. Compensation programs were created for those infected with HIV-AIDS, and they were modified when there was too much media attention or a worrisome lawsuit.

Then the forgotten victims -- those with HCV -- came along. This was the group Judge Krever had in mind when he said no-fault was the way to go. But governments were terrified by the number of potential claimants with HCV -- by some estimates at the time as many as 60,000.

Governments ignored Judge Krever's sage counsel and decided to compensate people infected between 1986, when many U.S. blood banks started testing for HCV, and 1990, when Canada actually began testing. This, despite the fact that it became increasingly obvious that the cutoff dates were arbitrary: A surrogate test for HCV was available as early as 1981 and there were still some infections after testing was implemented in 1990.

It was a short-sighted, money-driven decision, eerily similar to the kind of decisions that caused so many people to be infected by tainted blood in the first place.

With much fanfare, and no small measure of hypocrisy, \$1.1-billion was set aside to settle lawsuits from 1986-90 victims. It was believed by then that there were about 22,000 potential claimants, but that number is now thought to be still lower.

Today, most of that money is sitting in a trust fund. So far, \$265- million in payments have been approved to claimants. The fund has probably generated more than that from its investments, but we can only guess because even basic information about how \$1-billion in tax dollars is being disbursed is a tightly guarded secret. Without a doubt, the biggest beneficiaries have been lawyers, actuaries and accountants. In the first year of the program, lawyers were paid \$53-million, and administration fees topped \$9-million.

There have been 8,851 applications for compensation approved, but probably only a fraction of those are from victims infected by tainted blood, the rest being family members and others. Again, the fund administrators refuse to say for sure. Regardless, only a fraction of the expected 22,000 claimants in the 1986-90 period have come forward.

That tells us two things: There are likely only a few thousand other potential claimants in the pre-1986/post-90 group, and there is plenty of money available to compensate them.

What possible justification can there be to not do so? To date, Ontario, Quebec, Manitoba and B.C. have come around and provided some compensation to the HCV sufferers excluded from the settlement. But the inequities are glaring. Why are Ontarians eligible for help, but not Nova Scotians?

Judge Krever made clear that the tainted-blood scandal had its roots in prevarication, misplaced penny-pinching and a patronizing, secretive attitude toward the public -- the victims in particular.

Sadly, those characteristics remain in the handling of the more than \$1-billion in blood money and, as a result, the tainted-blood scandal lives on.

PEGASYS® More Effective than Lamivudine, the Drug Most Commonly Used in Difficult-to-Treat Chronic Hepatitis B

Source: Roche Press Release

HBeAg-negative HBV accounts for over 80 per cent of patients in Southern Europe

Basel, Switzerland — A landmark international trial in patients with HBeAg-negative chronic hepatitis B, the most difficult-to-treat form of hepatitis B, has concluded that PEGASYS monotherapy is more effective than lamivudine, the current standard treatment for this condition. Moreover the data showed that the combination of lamivudine to PEGASYS did not improve response rates over PEGASYS alone. These results will be presented at the 39th Annual Meeting of the European Association for the Study of Liver Disease (EASL) in Berlin.

The efficacy of PEGASYS is further reinforced by new data showing that PEGASYS monotherapy produced a beneficial histological response (improvement in the health of the liver) in nearly half (47%) of the patients. Also in a small group of patients, PEGASYS monotherapy achieved the rare occurrence of HBV surface antigen loss and/or seroconversion to anti-HBs – the most complete response possible to treatment and indicative of complete remission.

“These results are extremely encouraging for patients with this form of chronic hepatitis B,” said Professor Patrick Marcellin, Hepatologist at the Hôpital Beaujon, Clichy, France and the lead investigator for the study. “Until now, conventional interferon or lamivudine have been the first-line treatments for chronic hepatitis B. However this trial indicates that 24 weeks after cessation of treatment, PEGASYS had superior efficacy to lamivudine, which has been the most commonly used therapy for chronic hepatitis B. This points to there being a strong role for this particular pegylated interferon in the treatment in chronic hepatitis B,” added Professor Marcellin.

This Phase III study, the largest and only multinational study of pegylated interferon in patients with HBeAg-negative chronic hepatitis B, is also the first large-scale head-to-head study to compare Roche’s PEGASYS against lamivudine.

About the study

A total of 537 patients from 13 countries were enrolled in the study. Almost 40% were Caucasian and all had HBeAg-negative chronic hepatitis B and raised blood levels of ALT, a specific liver enzyme serving as a marker for liver inflammation. Patients were treated for 48 weeks with either PEGASYS 180µg once weekly plus placebo, lamivudine 100mg once daily, or a combination of PEGASYS and lamivudine. Treatment response was assessed following a 24-week treatment-free follow-up period.

The study examined the effect of treatment on ALT and HBV DNA levels (primary endpoints), the condition of the liver (liver histology) and HBsAg response. HBsAg response (loss of the HBV HBsAg and the development of antibodies to HBsAg) is a very rare event indicative of a complete remission.

Key findings

At the end of the treatment-free follow-up period, it was found that:

- 43% of patients treated with PEGASYS monotherapy reduced their hepatitis B viral DNA to less than 20,000 copies per/ml compared to only 29% of those treated with lamivudine. This result is highly statistically significant. The combination of PEGASYS and lamivudine yielded a reduction in hepatitis B viral DNA in 44% of patients, demonstrating that the addition of lamivudine to PEGASYS does not improve the treatment outcome.
- PEGASYS had a better impact on normalisation of liver transaminases than lamivudine: 59% of patients treated with PEGASYS had their elevated ALT levels return to normal; compared to only 44% of lamivudine-treated patients. The combination of PEGASYS and lamivudine (60%) was not statistically different to PEGASYS alone.
- HBsAg response – an extremely rare finding – was reported in 12 patients treated with PEGASYS (with or without lamivudine) and none of the patients treated with lamivudine alone. Although the numbers are low, clinically this is a very significant result as it is indicative of complete remission.
- Patients who showed a reduction in hepatitis B viral DNA levels to less than 20,000 copies/ml, or whose ALT levels returned to normal, showed an improvement in their liver histology.

About Hepatitis B

Hepatitis B is a blood-born virus that attacks the liver and is the most common serious liver infection in the world.

Despite a highly effective vaccine, more than two billion people have been infected with hepatitis B and 350 million people have chronic infection, which can be easily transmitted by blood-to-blood contact, during birth, sex, and by sharing needles. Hepatitis B and C rank among the top four causes of cancer deaths in most countries in Asia and the Western Pacific rim. For those chronically infected with hepatitis B, treatment is the only option.

About HBeAg-negative HBV

HBeAg-negative chronic hepatitis B, also known as ‘variant’ or ‘pre-core mutant’ hepatitis B, is caused by a genetic mutation to the virus. Patients infected with HBeAg-negative chronic hepatitis B are more likely to have severe destructive inflammatory changes to their liver and fibrosis when they first see their physician than those infected with the HBeAg-positive disease. Patients typically relapse after treatment is stopped. HBeAg-negative chronic hepatitis B accounts for approximately 40% of cases in the US and over 80% of cases in Southern Europe.

About PEGASYS

PEGASYS, a new generation hepatitis therapy that is different by design, provides significant benefit over conventional interferon therapy in patients infected with chronic hepatitis B and C. The benefits of PEGASYS are derived from its new generation large 40 kilodalton branched-chain polyethylene glycol (PEG) construction, which provides sustained drug levels over the course of a full week. PEGASYS also distributes more readily to the liver (the primary site of infection) than conventional interferon. In chronic hepatitis C, PEGASYS provides superior efficacy compared to conventional interferon combination therapy in HCV patients of all genotypes. PEGASYS is the only pegylated interferon available as a ready-to-administer solution. Each weekly subcutaneous injection contains 180µg of pegylated interferon alfa-2a

which is the approved dose for all patients, regardless of body weight. In a Phase II trial in HBeAg-positive chronic hepatitis B, PEGASYS has proven more effective than conventional interferon. A larger scale Phase III trial in patients with HBeAg-positive chronic hepatitis B is currently underway.

Roche in hepatitis

Roche is committed to the viral hepatitis disease area, having introduced Roferon-A for hepatitis B and C, followed by PEGASYS in hepatitis C and now PEGASYS also demonstrates superior efficacy over current treatments: conventional interferon and lamivudine in hepatitis B. Roche has also launched its own brand of ribavirin, COPEGUS®, to be used in conjunction with Roferon A or PEGASYS for HCV. Roche also manufactures HBV and HCV diagnostic and monitoring systems: The COBAS AMPLICOR™ Test, and the AMPLICOR™ MONITOR Test, two testing systems used to detect the presence of, and quantity of, HBV DNA or HCV RNA in a person's blood.

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NOTES TO THE EDITOR:

- This trial was conducted in the following countries:
 - Europe: France, Germany, Greece, Italy, Poland, Spain, Switzerland, Turkey, North America: Canada
 - Asia: China, Hong Kong, Taiwan, Thailand
 - Australasia: New Zealand

New guidelines on HBV were recently developed by the European Association for the Study of Liver (EASL). Conventional interferon monotherapy was recommended as the first therapeutic approach when treating these patients. The EASL Jury noted, however, that the optimal treatment of hepatitis B will require regular revision in light of new data.

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Vertex Pharmaceuticals (VRTX) Reports Data on Investigational Hepatitis C Therapies Suggesting Potential For Novel Treatment Approaches

Source: PRNewswire

BERLIN, -- New data for proprietary investigational antiviral therapies for hepatitis C virus (HCV) infection being developed by Vertex Pharmaceuticals Incorporated were presented today at the Annual Meeting for the European Association for the Study of the Liver (EASL) in Berlin,

Germany. The clinical and preclinical data presented highlight the potential of these therapies to address significant unmet medical needs in the treatment of HCV.

Vertex's extensive drug development portfolio includes two different approaches for advancing the future standard-of-care in HCV. Merimepodib, Vertex's lead oral therapy targeting HCV, is being developed in combination with the current therapeutic standard, pegylated interferon alpha (peg-IFN) and ribavirin, with the goal of enhancing antiviral efficacy and increasing the proportion of patients who achieve a sustained response to treatment. Vertex is also developing VX-950, an investigational HCV protease inhibitor and one of the most advanced of a new class of direct antiviral agents for the treatment of chronic HCV infection. Vertex owns worldwide development and commercialization rights for both merimepodib and VX-950.

In a poster session at EASL today, clinical investigators presented results for patients enrolled in the extension phase of a pilot Phase IIa study designed to evaluate the safety and tolerability of merimepodib in combination with peg-IFN and ribavirin in a treatment-refractory population. Additionally, in oral presentations at EASL, Vertex scientists reported preclinical data highlighting the promising antiviral profile of VX-950, including in vitro data assessing the antiviral activity of VX-950 in combination with interferon alpha.

"The results presented at EASL provide strong support for initiating late-stage clinical development of merimepodib, as well as the first clinical studies of VX-950," stated John Alam, M.D., Senior Vice President for Drug Evaluation and Approval at Vertex. "These are key milestones for Vertex and its interest in providing new therapies in HCV, and are anticipated in 2004. Vertex's goal is to commercialize innovative therapies that will provide additional options for patients and enhance HCV clinical care."

Merimepodib Results and Clinical Plans

In 2003, Vertex completed the treatment arms of a placebo-controlled triple combination Phase II study of merimepodib (MMPD) in combination with peg-IFN and ribavirin. This trial was designed to evaluate the safety of the triple combination in 31 patients with genotype 1 infection who did not respond to a previous course of interferon alpha in combination with ribavirin. The study provided for six months of treatment, with an optional six-month extension phase for patients who responded to therapy. Data presented by clinical investigators in 2003 demonstrated that the triple combination of MMPD + peg-IFN + ribavirin was well-tolerated and did not appear to exacerbate the incidence of hematological toxicities associated with peg-IFN and ribavirin treatment. Study results also indicated that the addition of merimepodib enhanced the antiviral activity of the peg-IFN + ribavirin combination at 24 weeks.

In a poster presented at EASL today, clinical investigators presented data on 11 patients (three subjects receiving placebo + peg-IFN + ribavirin and eight subjects receiving MMPD + peg-IFN + ribavirin) who were eligible to continue into the extension phase of the study. Ten patients completed 48 weeks of treatment. At the end of 48 weeks of treatment, the safety profile of MMPD was similar to the core 24-week study, and the majority of adverse events reported were consistent with the known side effect profile of peg-IFN and ribavirin. One of three patients in the placebo group and three of seven patients receiving MMPD who completed the extension phase achieved a sustained viral response at week 72 (24 weeks post-treatment). Based on the Phase IIa results, Vertex is planning to initiate larger studies to evaluate the ability of merimepodib to increase sustained viral response rates (SVR) in HCV-infected patients. These larger studies may involve, as before, an initial treatment period with MMPD in combination

with peg-IFN and ribavirin, but followed by continued treatment with peg-IFN and ribavirin alone, a clinical approach suggested by the clinical and preclinical data to optimize the SVR.

"Merimepodib demonstrated a good tolerability profile and showed important signs of antiviral activity in this study," stated Dr. Patrick Marcellin, Professor of Medicine at University of Paris VII, and the lead investigator for the study. "Genotype 1 HCV is associated with the lowest response to therapy, and patients who are non-responsive to prior combination therapy have very limited treatment options available. These results support larger well- controlled studies in treatment-refractory patients to evaluate the ability of merimepodib to effect an increase in sustained viral response in combination with peg-IFN and ribavirin."

Vertex anticipates initiating in 2004 a Phase IIb clinical study of merimepodib in patients who are non-responsive to prior treatment with peg-IFN + ribavirin. The primary goal of this placebo-controlled study will be to evaluate the antiviral activity of a triple combination regimen and to perform an assessment of sustained virologic response (SVR) rates. SVR is defined as an HCV- undetectable value at the end of a 24-week post-treatment follow-up period (week 72).

VX-950 Results and Clinical Plans

In oral presentations at EASL on Thursday and Friday, Vertex researchers presented a variety of preclinical results highlighting the emerging profile of VX-950. Vertex researchers demonstrated that treatment of HCV replicon cells with VX-950 decreased viral replication by 10,000-fold to undetectable levels; when the drug was subsequently removed, no rebound of viral replication was observed, suggesting that the HCV replicon had been eradicated from the treated cells. A second line of experiments showed that combination of interferon alpha with VX-950 in the HCV replicon system allowed scientists to reduce the level of VX-950 and still obtain the same degree of antiviral potency obtained with a 5-fold higher concentration of VX-950 alone.

Data presented last year at the AASLD and International HCV meetings showed that the dominant mutation(s) selected in the laboratory against VX-950 remained sensitive to BILN 2061, a protease inhibitor developed by another company which has shown antiviral activity in HCV patients, and BILN 2061 resistant mutants remained sensitive to VX-950. In the studies presented at EASL, researchers analyzed minor mutations that were cross-resistant to VX-950 and BILN 2061 in the laboratory and found that enzymatic activity of the cross-resistant HCV protease was reduced approximately 4 to 7-fold, a condition which could impair the ability of the virus to grow.

"Vertex's leadership position in the discovery of novel approaches to HCV treatment has been enhanced by the development of new technologies and approaches for evaluating the clinical potential of experimental compounds," commented Dr. Alam. "The results we have seen with VX-950 confirm our selection of HCV protease as an excellent target for the development of powerful antiviral therapies and that VX-950 has the potential of becoming a highly valuable therapeutic agent for the treatment of HCV patients."

Vertex anticipates that it will initiate a Phase I clinical trial of VX- 950 in healthy volunteers in 2004. Positive results from this first Phase I study will pave the way for the first evaluation of VX-950's antiviral activity in HCV-infected patients.

Clinical Need and Market Opportunity in HCV Infection

HCV infection is a serious disease that causes inflammation of the liver, which may lead to fibrosis and cirrhosis, liver cancer, and ultimately, liver failure. Chronic hepatitis C infection afflicts approximately 2.7 million people in the U.S., many of whom are unaware of their infected status. Current treatments provide a sustained viral response for only 40 to 50 percent of patients chronically infected with genotype 1 HCV, the most difficult viral strain to treat and the most common form in the U.S. Patients who are non-responsive to current HCV therapy have limited treatment options, and clinical experience suggests that only a very low proportion of such patients achieve a sustained viral response with subsequent treatment regimens. HCV may go undetected for up to 20 years following initial infection. Worldwide, the disease strikes as many as 185 million people. Each year, 8,000 to 10,000 people in the U.S. die from complications of HCV.

About Vertex

Vertex Pharmaceuticals Incorporated is a global biotechnology company committed to the discovery and development of breakthrough small molecule drugs for serious diseases. The Company's strategy is to commercialize its products both independently and in collaboration with major pharmaceutical partners. Vertex's product pipeline is principally focused on viral diseases, inflammation, autoimmune diseases and cancer. Vertex co-promotes the new HIV protease inhibitor, Lexiva(TM), with GlaxoSmithKline.

This press release may contain forward-looking statements, including statements that (i) Vertex anticipates commercializing new therapies, including merimepodib and VX-950, for the treatment of hepatitis C and that merimepodib and VX-950 each have the potential to address significant unmet needs in HCV treatment; (ii) merimepodib and VX-950 each hold promise as part of combination therapy for HCV patients who have limited treatment options and represents an attractive commercial opportunity for Vertex; (iii) further clinical study of merimepodib will be initiated in 2004; and (iv) clinical study of VX-950 will be initiated in 2004. While management makes its best efforts to be accurate in making forward-looking statements, such statements are subject to risks and uncertainties that could cause Vertex's actual results to vary materially. These risks and uncertainties include, among other things, the risks that clinical trials for merimepodib or VX-950 may not be initiated or, if initiated, may not proceed as planned due to technical, scientific, or patient enrollment issues, that results from planned clinical trials with merimepodib will not reflect the positive results from earlier trials, that positive nonclinical study results for either merimepodib or VX-950 will not be duplicated in future nonclinical or clinical studies and other risks listed under Risk Factors in Vertex's form 10-K filed with the Securities and Exchange Commission on March 15, 2004. Lexiva(TM) is a registered trademark of the GlaxoSmithKline group of companies.

Vertex's press releases are available at <http://www.vrtx.com/>.

Vertex Pharmaceuticals Incorporated will host a conference call on Monday, April 26, 2004 at 5:00 pm (EDT) to discuss its first quarter 2004 financial results, at which time it will review and update its HCV product development programs. The conference call also will be webcast, and the webcast will be available to all interested parties through Vertex's website, <http://www.vrtx.com/>. To access the webcast, go to the investor center and select "conference calls." To ensure a timely connection to the webcast, it is recommended that users register at least 15 minutes prior to the scheduled webcast.

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Company News On-Call: <http://www.prnewswire.com/comp/938395.html>

Metabasis Therapeutics Reports the Earning of A Milestone Payment Based on Continued Development of Remofovir for the Treatment of Hepatitis B

Source: PRNewswire

SAN DIEGO-- Metabasis Therapeutics, Inc. (Metabasis) announced today that Valeant Pharmaceuticals International has agreed to pay a \$1 million milestone payment to Metabasis in recognition of a decision to initiate a Phase II clinical evaluation of remofovir (formerly known as Hepavir B) in patients with chronic hepatitis B infection. Valeant licensed remofovir, an orally active prodrug of the proven antiviral agent adefovir, from Metabasis in October 2001 and is primarily responsible for the clinical development of the drug. The decision to proceed with development was based on results recently obtained from the first clinical evaluation of remofovir in patients infected with the hepatitis B virus.

About Metabasis

Metabasis Therapeutics, Inc. (<http://www.mbasis.com/>) is a biopharmaceutical company focused on the discovery, development and commercialization of novel small molecule drugs principally to treat liver diseases and metabolic diseases linked to pathways in the liver. The company has established a broad product pipeline targeting large markets with significant unmet medical needs. Metabasis currently has three internally discovered product candidates in clinical trials indicated for the treatment of type 2 diabetes, hepatitis B and primary liver cancer.

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Gilead Sciences (GILD) Release: New Data Support Hepsera's Long-Term Efficacy Against Chronic Hepatitis B

April 17th, 2004

Valeant Pharmaceuticals Presents Details of 24-Week Data for Viramidine Phase 2 Clinical Trials

Source: PRNewswire

Data Shows a Sustained Reduction in Viral Titre for All Three Doses of Viramidine, Comparable to Ribavirin

COSTA MESA, California Valeant Pharmaceuticals (NYSE: VRX) today presented 24-week data from Phase 2 clinical trials of Viramidine, a nucleoside (guanosine) analog Valeant is developing in oral form for the treatment of chronic hepatitis C (HCV) in conjunction with a

pegylated interferon. Valeant presented its data at the European Association for the Study of the Liver (EASL) Conference in Berlin, Germany.

The Viramidine Phase 2 study consists of 180 treatment-naïve subjects with chronic HCV. The on-going study was an open-label, randomized, active control trial, being conducted at multiple centers in the United States and with patients stratified by genotype. The study consists of four demographically comparable treatment groups: Viramidine 400 mg BID, Viramidine 600 mg BID, Viramidine 800 mg BID and ribavirin 1000/1200 mg daily all in combination with peginterferon alfa-2a. Treatment duration was based on genotype, with genotypes two and three receiving 24 weeks of treatment and genotype one receiving 48 weeks of treatment, each with a post-treatment follow-up period of 24 weeks.

The interim 24-week data shows that Viramidine demonstrates antiviral activity comparable to that of ribavirin, when used in combination with peginterferon alfa-2a in treatment naïve patients, but with a lower incidence of anemia.

The data demonstrates a sustained reduction in HCV RNA of approximately two-and-a-half log(10) for all three doses of Viramidine, comparable to the ribavirin group in the same study. The proportion of patients with greater than or equal to 2 log(10) reduction or non-detectable HCV RNA was 83 percent for both Viramidine (800-1600 mg/day) and ribavirin at 24 weeks. The results also show the percent of patients with non-detectable HCV RNA at 12 weeks and 24 weeks were similar between all treatment groups.

There were also fewer patients in the Viramidine groups with anemia (defined as hemoglobin < 10g/dL) when compared with the ribavirin arm (2 percent versus 24 percent; $p < 0.001$). In the Viramidine 400 mg BID and 600 mg BID dosage groups, defined anemia (hemoglobin < 10g/dL) did not occur, while there were only two occurrences of anemia in the 800 mg BID group. Other adverse events were similar among treatment groups.

Data was presented by Robert Gish, M.D., the lead investigator on the Viramidine Phase 2 study and Medical Director of the Liver Transplant Program at California Pacific Medical Center in San Francisco.

A Phase 3 clinical trial of Viramidine compared to ribavirin in combination with pegylated interferon was initiated in the fourth quarter of 2003 and is ongoing. The Phase 3 trial compares the 600 mg BID dose of Viramidine to ribavirin, each in conjunction with pegylated interferon alpha 2b.

About Valeant

Valeant Pharmaceuticals International (NYSE: VRX) is a global, publicly traded, research-based specialty pharmaceutical company that discovers, develops, manufactures and markets a broad range of pharmaceutical products. More information about Valeant can be found at www.valeant.com.

FORWARD-LOOKING STATEMENTS

This press release contains forward-looking statements within the meaning of the federal securities laws relating to expectations, plans or prospects for Valeant Pharmaceuticals, including funding and conducting clinical trials and expected research and development

expenses. These statements are based upon the current expectations and beliefs of Valeant Pharmaceuticals' management and are subject to certain risks and uncertainties that could cause actual results to differ materially from those described in the forward- looking statements. These risks and uncertainties include market conditions and other factors beyond Valeant Pharmaceuticals' control, the company's success in identifying and enrolling patients in the clinical trials program, the absence of adverse events that would require the clinical trials to be prematurely terminated, clinical results that indicate continuing clinical and commercial pursuit of Viramidine is advisable, and the risk factors and other cautionary statements discussed in Valeant Pharmaceuticals' filings with the U.S. Securities and Exchange Commission. For further information, please contact: Jeff Misakian of Valeant Pharmaceuticals, +1-714-545-0100, ext. 3309.

Web site: <http://www.valeant.com>

Source: Valeant Pharmaceuticals International

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