











HCV ADVOCATE WEEKLY NEWS REVIEW

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

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Editor-in-Chief*

Week Ending: February 20th, 2004

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February 16th, 2004

Age at Infection, Degree of Inflammation Play Role in Rate of Progression of Hepatitis C

Source: Gut

By Harvey McConnell

A large scale British study finds that among patients with mild hepatitis C (HCV), the infection will rapidly worsen among 33%, particularly among those who are older when first infected and those who already have a degree of inflammation and fibrosis in the liver at diagnosis.

Dr Stephen Ryder, Queen's Medical Centre, University Hospital, Nottingham, and colleagues in The Trent HCV Study Group carried out a prospective repeat liver biopsy study among 214 patients HCV (126 men and 88 women) and their rate of progression of fibrosis without intervening treatment.

The cohort had a mean age of 36, and their disease was predominantly mild. Overall, 52% of the patients admitted to injection drug use and 23% received blood components prior to 1991 when screening for HCV was introduced in Britain.

There was a median interval of 2.5 years between biopsies. At first biopsy, the average Ishak (fibrosis) score was 3, with most patients having scores of 6 or less, considered to denote mild

disease. However, within 30 months, clinicians found the Ishak score increased by 1 or more points in 33% of patients, and by 2 or more points in 10%.

Independent predictors of progression were age at first biopsy and the presence of any fibrosis on first biopsy. Factors not associated with progression included necroinflammation, duration of infection, alcohol consumption, alanine aminotransferase levels, current or past hepatitis B virus infection, ferritin, HCV genotype, and steatosis or iron deposition in the initial biopsy.

These findings suggest that hepatitis C infection may somehow become more fibrogenic with advancing host age, the clinicians note. This may be one explanation for the apparent lack of fibrotic liver disease progression in young women who are infected with hepatitis C via immunoglobulin anti-D.¹⁴

"Our study avoided the pitfall of estimated duration of infection by prospectively following a relatively large group of patients selected to have mild or moderate liver disease," the clinicians say.

They conclude "that histologically mild hepatitis C is a progressive disease. The overall rate of fibrosis progression is low but increased in patients who are older or have fibrosis on their index biopsy. These data suggest that HCV infection will place an increasing burden on health care services in the next 20 years as the population infected with HCV ages."

Report Identifies Transplant Trends; Published in CD-ROM Format for First Time

*Source: UNOS News Bureau
newsroom@unos.org*

Richmond, Va. -- A newly released report documents key data and trends regarding organ donation and transplantation in the United States. For the first time the PTN/SRTR Annual Report, published since 1990, will be published exclusively in CD format in addition to being accessible on the World-Wide Web.

Early Effects of Revised Liver Policy

This is the first report to include a chapter of data about a significant change to liver policy adopted in February 2002. The policy assesses the medical urgency of most liver transplant candidates based on two formulas, one for adults known as the Model for End-Stage Liver Disease (MELD) and one for children known as the Pediatric End-Stage Liver Disease model (PELD). While the report can only address early effects of the policy, it notes that higher MELD scores (and thus more priority for a transplant) are associated with a higher risk of death awaiting a transplant, suggesting that the system is accurately prioritizing transplant candidates. The report also notes a decrease in liver transplant wait list registrations in 2002, which may be due in part to the new policy's de-emphasis on waiting time as a factor in liver allocation.

Waiting List Continues to Grow

The increasing need for more donor organs appears as a common theme in many chapters in this report, more so for pancreas, liver and kidney transplants. The organ transplant waiting list saw an increase in the decade of 150 percent in patients added from 31,694 in 1993 to 79,387 at the end of 2002. Long wait times for transplant candidates and/or the continued growth in the

waiting list size underscores the continued problem of the supply of organs not meeting the demand.

Living Donation More Common

Over the decade from 1993 to 2002, living donation has become much more common, with living donor kidney transplants increasing from 28 percent of the total kidney transplants performed in 1993 to 43 percent in 2002. The success of kidney transplantation prior to starting dialysis on patients with end-stage renal disease is well recognized and is being touted favorably, especially by living donor kidney recipients. Kidney transplantation continues to be recognized as the treatment of choice for medically suitable patients with end-stage renal disease, increasing the waiting list for a kidney transplant. The number of patients waiting for a kidney transplant continues to rise, from 47,830 in 2001 to 50,855 in 2002, well exceeding the number of donated kidneys.

Electronic Version Now Available

Over the past few years, the report was published in both print and electronic forms. With an increasing number of report users relying primarily on the electronic version, accessed via the Internet, the 2003 annual report eliminates paper copy and is being distributed in a new CD-ROM version. Advantages of the electronic version are clear: greater ease of navigation, portability, saving resources and rapid table or figure extraction for individual use.

The 13th Annual Report was produced by the Scientific Registry of Transplant Recipients (SRTR) contractor, University Renal Research and Education Association (URREA), in collaboration with the Organ Procurement and Transplantation Network (OPTN) contractor, United Network for Organ Sharing (UNOS), under contract with the Health Resources and Services Administration (HRSA) of the Department of Health and Human Services (HHS).

CDs may be ordered by calling 804-782-4841.

Hepatocellular Carcinoma in Anti-HCV Positive Cirrhotic Patients

Source: www.gastrohep.com

Doctors, in the latest issue of the *Journal of Internal Medicine*, compare prognostic systems in anti-HCV positive cirrhotic patients with hepatocellular carcinoma.

In this study, doctors from Italy investigated the usefulness of newly proposed hepatocellular carcinoma (HCC) prognostic systems in anti-HCV positive cirrhotic patients with HCC:

- The Cancer of the Liver Italian Program (CLIP) score
- The Groupe d'Etude et de Traitement du Carcinome Hépatocellulaire (GRETCH) model
- The Barcelona Clinic Liver Cancer (BCLC) staging classification

The team compared these with the known Okuda staging system. All staging systems were able to identify the various patient subgroups. *Journal of Internal Medicine*

The doctors retrospectively applied the Okuda stage, CLIP score, GRETCH model and BCLC stages in 81 anti-HCV positive cirrhotic patients with HCC.

They compared the ability of these methods to assess survival prognosis.

Overall, 51 patients died and median survival was 18 months.

The team found that all staging systems were able to identify the various patient subgroups with differing survival.

They determined that the CLIP score, the GRETCH model and the BCLC staging classification were better at characterizing 1-year prognosis, compared to the Okuda staging system.

Dr Giannini's team concluded, "The prognostic value and usefulness of the CLIP score, the GRETCH model and the BCLC staging classification was reproduced in a single-centre analysis of anti-HCV positive HCC cirrhotic patients".

"These scores provided a prognostic assessment of our patients which is superior to what was obtained by the Okuda staging system".

Hepatitis Drug Researched Here as Anthrax Treatment

BY JIM RITTER Health Reporter
Chicago Sun Times

University of Chicago biochemist Wei-Jen Tang was researching antidotes to anthrax poisoning when out of the blue he received a call from a researcher working for a drug company.

The researcher had read about Tang's work and suggested Tang try his company's hepatitis drug, Hepsera.

Tang was skeptical, but the researcher's hunch turned out to be a good one. In test tubes, Hepsera blocks the action of a deadly poison produced by anthrax bacteria.

"This is a classic example of serendipity in science," said Paula Flicker of the National Institute of General Medical Sciences, which is helping fund Tang's work. The study by Tang and colleagues is published in the online edition of the *Proceedings of the National Academy of Sciences*.

Anthrax is one of the most feared weapons of biological terrorism. In 2001, someone sent anthrax letters to politicians and journalists, and several people died. In 1993, Congress' Office of Technology Assessment said that spraying 221 pounds of anthrax above Washington could kill between 130,000 and 3 million people. However, such an attack would require access to advanced biotechnology.

Anthrax infection resembles a cold at first, then progresses to severe breathing problems and shock, and often is fatal. There are three weapons against anthrax: vaccines, including new ones under development; antibiotics, which work only if taken early in the disease, and antidotes against the poisons produced by anthrax bacteria.

Hepsera is one of several antidotes under study. The drug, approved for chronic hepatitis B, blocks the effects of edema factor, an anthrax poison that causes massive tissue damage.

In 2002, Tang and colleagues published a paper on the toxin. After reading the paper, Craig Gibbs, a researcher for Hepsera maker Gilead Sciences, contacted Tang. Gibbs told Tang about Hepsera and later sent him samples.

Hepsera might block similar toxins produced by bacteria that cause whooping cough, plague and hospital infections, Tang said. Hepsera's side effects include weakness, headache, stomach pain and nausea.

Tang is testing Hepsera on mice infected with anthrax, and if he gets funding, would like to do tests on rabbits and monkeys.

February 17th, 2004

Schering-Plough Announces Availability of Peg-Intron Redipen, Providing The Proven Efficacy of Peg-Intron in an Easy-to-Use Pen

FIRST AND ONLY PRECISION DOSING PEN FOR ADMINISTERING PEGINTERFERON THERAPY FOR CHRONIC HEPATITIS C

Source: Company Press Release

Schering-Plough Corporation (NYSE: SGP) today announced the U.S. launch of PEG-INTRON REDIPEN™, which provides the proven efficacy of PEG-INTRON® (peginterferon alfa-2b) Powder for Injection in an easy-to-use pen. The PEG-INTRON REDIPEN is the first and only pen delivery system approved for administering pegylated interferon therapy for chronic hepatitis C, a potentially lethal virus that has overtaken HIV as the most common blood-borne infectious disease in the United States. An estimated 2.7 million Americans are chronically infected with hepatitis C.

PEG-INTRON REDIPEN is designed to be patient-friendly with features such as an easy-to-read dial-up dosing button for precise, individualized weight-based dosing of PEG-INTRON, a self-priming action that automatically removes air bubbles from the pen prior to patient self-administration and a small needle size (30-gauge) to minimize patient discomfort.

“For successful treatment of patients with hepatitis C, it is important that they take their medicine consistently and get the appropriate dose for their individualized therapy,” said Bruce R. Bacon, M.D., professor of internal medicine, director, division of gastroenterology and hepatology, Saint Louis University School of Medicine. “With the small needle, self-priming feature and large, easy-to-read dosing knob, PEG-INTRON REDIPEN is designed to help patients feel confident that they are getting an accurate dose and offers an easy-to-use alternative for people who may be intimidated by a traditional needle and syringe system.”

PEG-INTRON used in combination with REBETOL® (ribavirin, USP) has proven effective in treating patients with chronic HCV infection, including American patients infected with genotype 1 virus, the most common and difficult to treat form of the disease.

The PEG-INTRON REDIPEN is a disposable, one-time use precision dosing system that allows patients to administer PEG-INTRON in three easy steps: Mix, Dial and Deliver. Mixing occurs by simply pushing down on the pen to combine the PEG-INTRON powder with sterile water, both of which are stored in the body of the pen; Dialing allows patients to accurately select their

predetermined individualized dose; and Delivery allows patients to inject their individualized dose of the medication. The PEG-INTRON REDIPEN is available in four different strengths (50, 80, 120 and 150 mcg), each indicated by a color-coded label and dosing button. An instructional videotape and brochure are available for use by patients and healthcare professionals.

“Schering-Plough is committed to providing innovative products and patient services to people with chronic hepatitis C,” said Robert J. Spiegel, M.D., senior vice president of medical affairs and chief medical officer, Schering-Plough Research Institute. “We are pleased to introduce PEG-INTRON REDIPEN to further help meet the needs of the hepatitis C patient community,” he said.

Since the introduction of PEG-INTRON and REBETOL combination therapy in 2001, more than 300,000 hepatitis C patients worldwide have received this treatment, including more than 200,000 U.S. patients.

Commitment to Hepatitis C Patients

As the leading innovator of interferon-based treatments for hepatitis C, Schering-Plough on Sept. 23, 2003, announced plans to initiate the IDEAL trial (Individualized Dosing Efficacy vs. flat dosing to Assess optimaL pegylated interferon therapy), a major clinical study involving 2,880 patients that for the first time will directly compare the two approved forms of pegylated interferon therapy for chronic hepatitis C: PEG-INTRON versus PEGASYS (peginterferon alfa-2a/Hoffmann-La Roche, Inc.), both used in combination with ribavirin. Schering-Plough Research Institute, in collaboration with leading medical centers, will conduct the comparative study in response to requests by the hepatitis C medical and patient communities, and to clear up misperceptions in the marketplace about these two treatments.

In addition to its ongoing commitment to research and development, Schering-Plough is committed to supporting hepatitis C patients with education and service programs as well as to help locate financial assistance for patients in need. The company’s programs for patients in the United States are among the most comprehensive in the industry, providing support and guidance to patients, and ensuring that all eligible patients have access to the company’s hepatitis C products.

Schering-Plough’s Be In Charge hepatitis C patient-support program has enrolled approximately 95,000 U.S. patients since its inception in 1997. This U.S. program is designed to support patients treated with Schering-Plough hepatitis C products through the use of educational materials and telephone contact with personal nurse counselors skilled in the management of hepatitis C.

The company’s Commitment to Care program is designed to ensure that eligible U.S. patients have access to Schering-Plough’s hepatitis products, either by assisting patients in obtaining the reimbursement or assistance for which they qualify, or by providing products free of charge to eligible patients. The market value of treatment provided to hepatitis C patients through this program exceeded \$150 million in 2003.

PEG-INTRON and REBETOL combination therapy is indicated for the treatment of chronic hepatitis C in patients with compensated liver disease who have not been previously treated with interferon alpha and are at least 18 years of age.

PEG-INTRON is a longer-acting form of INTRON® A (interferon alfa-2b, recombinant) Injection that uses proprietary PEG technology developed by Enzon, Inc. (NASDAQ: ENZN) of Bridgewater, N.J.

PEG-INTRON, recombinant interferon alfa-2b linked to a 12,000 dalton polyethylene glycol (PEG) molecule, is a once-weekly therapy that is designed to achieve an effective balance between antiviral activity and elimination half-life. Schering-Plough holds an exclusive worldwide license to PEG-INTRON.

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

REBETOL is an oral formulation of ribavirin, a synthetic nucleoside analog. Schering-Plough has worldwide rights to market oral ribavirin for hepatitis C through a licensing agreement with Valeant Pharmaceuticals International (NYSE: VRX), formally ICN Pharmaceuticals, of Costa Mesa, Calif.

WARNING

REBETOL monotherapy is not effective for the treatment of chronic hepatitis C virus infection and should not be used alone for this indication. (See WARNINGS.)

- The primary toxicity of ribavirin is hemolytic anemia. The anemia associated with REBETOL therapy may result in worsening of cardiac disease that has led to fatal and nonfatal myocardial infarctions. Patients with a history of significant or unstable cardiac disease should not be treated with REBETOL. (See WARNINGS, ADVERSE REACTIONS, and DOSAGE AND ADMINISTRATION.)
- Significant teratogenic and/or embryocidal effects have been demonstrated in all animal species exposed to ribavirin. In addition, ribavirin has a multiple-dose half-life of 12 days, and so it may persist in nonplasma compartments for as long as 6 months. Therefore, REBETOL therapy is contraindicated in women who are pregnant and in the male partners of women who are pregnant. Extreme care must be taken to avoid pregnancy during therapy and for 6 months after completion of treatment in both female patients and in female partners of male patients who are taking REBETOL therapy. At least two reliable forms of effective contraception must be utilized during treatment and during the 6-month post-treatment follow-up period. (See CONTRAINDICATIONS, WARNINGS, PRECAUTIONS-Information for Patients and Pregnancy Category X.)
- Alpha interferons, including PEG-INTRON and INTRON A, may cause or aggravate fatal or life-threatening neuropsychiatric, autoimmune, ischemic and infectious disorders. Patients should be monitored closely with periodic clinical and laboratory evaluations. Patients with persistently severe or worsening signs or symptoms of these conditions should be withdrawn from therapy. In many but not all cases these disorders resolve after stopping therapy with PEG-INTRON or INTRON A. (See WARNINGS, ADVERSE REACTIONS.)

PEG-INTRON

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

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

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

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

INTRON A

All patients receiving INTRON A therapy experienced mild-to-moderate side effects. Some patients experienced more severe side effects, including neutropenia, fatigue, myalgia, headache, fever, chills and increased SGOT. Other frequently occurring side effects were nausea, vomiting, depression, alopecia, diarrhea and thrombocytopenia. DEPRESSION AND SUICIDAL BEHAVIOR, INCLUDING SUICIDAL IDEATION, SUICIDAL ATTEMPTS, AND COMPLETED SUICIDES, HAVE BEEN REPORTED IN ASSOCIATION WITH TREATMENT WITH ALFA INTERFERONS, INCLUDING INTRON A THERAPY.

DISCLOSURE NOTICE: The information in this press release includes certain “forward-looking” statements concerning PEG-INTRON REDIPEN in the United States, the market for drugs to treat hepatitis C and Schering-Plough’s products. Forward-looking statements are subject to risks and uncertainties, which may cause actual results to differ materially. These risks and uncertainties include product availability, current and future branded, generic and OTC competition, market acceptance of new products, timing of trade buying, and patent positions. For further details and a discussion of these and other risks and uncertainties, see the company’s Securities and Exchange Commission filings, including the third quarter 2003 Form 10-Q.

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

For more information about Schering-Plough, visit the company’s website at www.schering-plough.com.

For information about hepatitis and for full prescribing information regarding PEG-INTRON and REBETOL, visit www.hepatitisinnovations.com.

PEGASYS is a trademark of Hoffmann-La Roche Inc. See the PEGASYS product insert for information on this product.

Mild Hepatitis C Infection Will Rapidly Worsen in 1 in 3 People Affected

Newswise -- Mild hepatitis C infection will rapidly worsen in one in three of those affected, suggests new research published in the medical journal *Gut*. This is particularly likely in those who are older when first infected, and those who already have a degree of inflammation and fibrosis in their liver at diagnosis.

The viral liver infection hepatitis C (HCV) is mainly passed on through injecting drug use and blood transfusions before 1991, when the screening of blood products for the virus was introduced. HCV is an important cause of chronic liver disease, eventually leading to liver cancer. But treatment with interferon is complicated and expensive, and only works in around one in two of those treated.

The authors base their conclusions on 214 patients with HCV whose average age was 36; 126 of them were men and their liver disease was mostly mild. None of the patients was given any treatment, and they were monitored by tissue sampling of their liver every 2.5 years.

One in two of the patients admitted to having used intravenous drugs in the past; almost one in four had been transfused with infected blood products.

At the first biopsy, the average fibrosis score (Ishak score) was 3. Most patients had scores of 6 or less; scores of up to 6 are considered to denote mild disease. Within 30 months, when the next tissue sample was taken, the Ishak score had increased by one or more points in a third (70) of the patients, and by two or more points in one in 10 of them.

The factors influencing progression of the disease were older age at infection, rather than the length of infection, and degree of inflammation and scarring at the first biopsy.

Unlike the results of previous research, gender, alcohol consumption, virus type and other indicators of poor liver function did not seem to have any effect on the rate of progression, although the authors point out that it is important to reduce alcohol consumption once infected.

The authors conclude that even mild HCV is a progressive disease, and those patients affected are likely to require a considerable degree of health care as they age over the next 20 years.

To read the entire paper, go to: http://press.psprings.co.uk/gut/march/451_gt21691.pdf
Source: British Medical Journal

February 18th, 2004

NP/PA Clinical Hepatology Fellowship - Application Deadline March 15, 2004

Source: AASLD E-News

AASLD has established a Clinical Hepatology Fellowship Program for NP's/PA's which provides one-year salary and benefit support for certified and licensed physician assistants or nurse practitioners and is designed to:

- Increase the number of trained nurses/mid-level practitioners in clinical hepatology.
- Facilitate the transition (or shift in emphasis) into clinical hepatology for nurses/mid-level practitioners.
- Increase access for liver disease patients to adequately trained clinicians.

In order to be eligible for this award, the applicant must meet the following criteria:

- The applicant's training will be sponsored by a Clinical Hepatologist, practicing in an environment conducive to training in hepatology.
- The mentor must be a member of AASLD and must dedicate at least 50% of his/her time to the care of patients with liver diseases.
- The applicant must be a citizen or permanent resident of the U.S.
- The majority of the applicant's time (greater than 80%) will be focused on clinical care in hepatology.
- The applicant will not hold other, similar research awards during the fellowship period (July 1, 2004 - June 30, 2005).

Contact Lee Claassen (lclaassen@aasld.org) or Denise Davis (ddavis@aasld.org) at 703-299-9766.

Support of this award by Roche Laboratories Inc. and Schering Hepatitis Innovations is gratefully acknowledged.

SciClone Pharmaceuticals (SCLN) Reports Data: 41% Of Hepatitis C Non-Responder Patients Test HCV RNA Negative After 24 Weeks Of ZADAXIN Triple Therapy

Pilot Trial Treating Patients Not Responding to Prior Therapy Continues to Show Positive Results SciClone Pharmaceuticals, Inc.

SAN MATEO, Calif.--SciClone Pharmaceuticals, Inc. today reported positive data from a pilot clinical trial in hepatitis C patients who have not responded to previous therapy. 41% of the non-responder patients tested HCV RNA negative and 50% showed a virologic response after 24 weeks of a new triple therapy of ZADAXIN® in combination with pegylated interferon alpha and ribavirin. By comparison, separate recent studies show that after 24 weeks of double therapy with pegylated interferon alpha plus ribavirin, approximately 30% of hepatitis C non-responder patients tested HCV RNA negative.

Dr. Eduardo Martins, Vice President of Medical Affairs of SciClone Pharmaceuticals, commented, "As we continue to explore ways to further improve therapy options for the nearly half of hepatitis C patients that do not respond to the current standard of care, we are pleased to see ZADAXIN used in combination with standard dose pegylated interferon and low dose ribavirin has improved response rates in this patient group without adding toxicity. Building on these positive interim data, we are closely monitoring the progress of this trial and are

considering future triple therapy studies. Our primary focus remains our two ongoing U.S. phase 3 clinical trials targeting ZADAXIN in combination with pegylated interferon alpha to be the first FDA approved therapy to specifically address the needs of non-responders."

About the Triple Therapy Trial

This ongoing open label clinical trial plans to enroll a total of 50 hepatitis C non-responder patients, none of which have responded to prior therapy of at least six months of interferon alpha in combination with ribavirin. During the course of this study, patients will receive 12 months of triple therapy and will be observed for six months after completing therapy to measure sustained response, defined as negative HCV RNA by PCR test measured at week 72.

Of the 22 patients who had completed 24 weeks of triple therapy of ZADAXIN in combination with pegylated interferon alpha and ribavirin, 41% (9/22) tested negative for HCV RNA by PCR test and 50% (11/22) showed a virologic response to therapy, defined as a 2 log or greater reduction in the level of HCV RNA. Of the 19 patients infected with the difficult to treat HCV genotype 1, 42% (8/19) tested negative for HCV RNA and 58% (11/19) showed a virologic response to therapy. As in all previous ZADAXIN studies, the safety profile was excellent without significant ZADAXIN related side effects or toxicities.

In October 2003, SciClone reported 12 week interim data from this trial. After 12 weeks of triple therapy, 61% (14/23) of hepatitis C non-responder patients reported an early virologic response, or EVR, defined as a 2 log or greater reduction in the level of HCV RNA, and 48% (11/23) tested negative for HCV RNA. Of the 20 patients infected with the difficult to treat HCV genotype 1, 60% (12/20) reported an EVR and 50% (10/20) tested negative for HCV RNA.

During the course of this pilot clinical trial, patients will receive 12 months of triple therapy of a standard dose of ZADAXIN (1.6 mg/bi-weekly) plus a standard dose of pegylated interferon alfa-2a (180 mcg/week) and a low dose of ribavirin (800-1,000 mg/day) and will be observed for six months after completing therapy to measure sustained response. The primary endpoint of the study is negative HCV RNA by PCR test measured at weeks 48 and 72. The secondary endpoints are normalization of ALT (a liver enzyme) measured at weeks 48 and 72 and reduction in HCV load measured at weeks 12, 24, 48, and 72.

This multicenter study is being conducted by a team lead by Dr. Jorge L. Poo, Chief Scientific Officer of CIF-Biotech at the Medica Sur hospital in Mexico City (www.cifbiotec.org.mx). The triple therapy study is being funded and conducted by Laboratorios Colombia in Mexico with ZADAXIN provided free of charge by SciClone and PEGASYS® brand pegylated interferon alpha provided free of charge by F. Hoffman La-Roche. ZADAXIN, PEGASYS and ribavirin are approved in Mexico for the treatment of hepatitis C.

About ZADAXIN

ZADAXIN is a pure synthetic preparation of thymosin alpha 1, a substance which circulates in the blood naturally and is instrumental in the body's immune response to fight viral infections and certain cancers. ZADAXIN is easily and safely administered just under the skin twice a week. After administration, thymosin alpha 1 circulates at 50 to 100 times its normal level in the body. 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 estimates that over 10,000 patients have used ZADAXIN in both clinical and commercial use, alone and in

combination with anti-viral and anticancer drugs, without any reported significant ZADAXIN-specific side effects or toxicities.

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 recently 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 pilot clinical trial in Mexico. Other drug development candidates include SCV-07, a potentially orally available therapeutic to treat viral and infectious diseases, and other products to treat cystic fibrosis. For more information about SciClone, visit www.sciclone.com.

The information in this press release contains forward-looking statements including the prospective development, commercialization and regulatory approval of ZADAXIN in the U.S. 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, 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, our actual results could differ materially and adversely from those expressed in any forward-looking statements as a result of various factors, including the fact that results from studies with a limited group of patients may not be predictive of the results of larger studies, 24-week results are not always predictive of the achievement of a sustained viral response which is the endpoint of the hepatitis C clinical trial, the speed with which patients are enrolled in the hepatitis C clinical trial, maintenance of the sufficiency and eligibility of the enrolled patient population, unexpected adverse results to patients and other events that could prolong the clinical trial or result in unanticipated expense, we may not receive hepatitis C approval for ZADAXIN in the U.S., future actions that may be taken by regulatory agencies, as well as other risks and uncertainties described in SciClone's filings with the Securities and Exchange Commission.

Contact:

SciClone Pharmaceuticals, Inc. Richard A. Waldron, 650-358-3437

Source: SciClone Pharmaceuticals, Inc.

BioSpace

February 19th, 2004

Anadys Pharmaceuticals Announces Initiation Of Clinical Trial Of ANA971, An Orally Administered Prodrug Of Isatoribine

Anadys Pharmaceuticals initiates Phase I clinical trial of isatoribine prodrug for study as a hepatitis C therapy

SAN DIEGO--(BUSINESS WIRE)--Anadys Pharmaceuticals, Inc. ("Anadys") announced today that it has initiated a clinical trial of ANA971, an orally administered prodrug of isatoribine. Isatoribine is a nucleoside analog in development for the treatment of chronic hepatitis C virus (HCV) infection. To date, isatoribine has been administered to 48 subjects, including 28 patients chronically infected with HCV. A recent clinical study showed that intravenous administration of isatoribine was well tolerated and safe at all doses tested. Interim results from that study have

also shown preliminary biological activity and viral load reduction in the patient populations whose clinical data has been completed and analyzed. ANA971, which was discovered by Anadys, is a prodrug designed to improve the oral bioavailability of isatoribine. Anadys has exclusive rights to market and commercialize isatoribine and ANA971 worldwide.

In preclinical animal studies, oral administration of ANA971 resulted in higher levels of isatoribine in the blood than were present after oral administration of isatoribine itself. The objectives of this clinical trial are to assess safety and pharmacokinetics in healthy volunteers following oral administration of ANA971.

"Initiation of this clinical trial represents another important step toward our goal of improvement of HCV patient care, and builds on the results of clinical work we have conducted with isatoribine," said Devron Averett, Ph.D., Senior Vice President of Drug Development for Anadys.

About isatoribine (ANA245)

Isatoribine is a nucleoside analog Anadys is evaluating in ongoing clinical trials for the treatment of HCV infections. Isatoribine represents one of a new class of drugs being developed by Anadys to regulate innate immunity, combat HCV infection, and overcome limitations of current anti-HCV therapies. Anadys believes isatoribine interacts with a specific receptor, Toll-like receptor 7, or TLR7, that is present on certain immune system cells. Although results of initial clinical trials may not be predictive of future results, interim results of the Phase 1B clinical trial show that isatoribine is biologically active in adults with chronic HCV infection and results from dosing a cohort of six HCV infected patients with 800mg of isatoribine showed a statistically significant reduction of viral load ($p=0.03$) at the end of one week, with a median change in viral load from baseline of $-0.94 \log_{10}$ units(a). Anadys is currently enrolling patients for an isatoribine Phase I/II study.

About hepatitis C

HCV causes inflammation of the liver and degradation of liver function. HCV infection is currently the most common chronic blood-borne infection in the United States. Approximately 2.7 million people in the United States are chronically infected with HCV, and it causes 10,000 to 12,000 deaths a year in the United States. The Centers for Disease Control and Prevention, or CDC, estimates the annual mortality rate in the United States could increase to 38,000 by the year 2010, surpassing the number of deaths attributed annually to HIV/AIDS. HCV is transmitted primarily through significant or repeated exposures to infected blood. Approximately two thirds of new infections progress to chronic infection. Chronic HCV infection may also progress to more serious complications such as cirrhosis of the liver, liver cancer, and death.

About Anadys Pharmaceuticals, Inc.

Anadys Pharmaceuticals, Inc. (www.anadyspharma.com) is a biopharmaceutical company committed to advancing patient care by discovering, developing and commercializing novel and powerful small molecule, anti-infective medicines for the treatment of chronic viral hepatitis, including HCV and HBV, and bacterial infections. Anadys integrates biology and chemistry into a seamless, feedback-based, iterative process to facilitate rapid and successful drug discovery. The approach is designed to advance a strong and continual pipeline of drug candidates into the clinic and ultimately the market.

For more information, please visit www.anadyspharma.com

Statements in this press release that are not strictly historical in nature constitute "forward-looking statements." Such statements include, but are not limited to, references to the biological activity of isatoribine in HCV infected patients, the trend toward viral load reduction resulting from administration of isatoribine in those patients, the believed mechanism of action of isatoribine and its effect on a patient's immune system, and expectations regarding further clinical trials of isatoribine and ANA971. Such forward-looking statements involve known and unknown risks, uncertainties and other factors, which may cause the actual results of Anadys Pharmaceuticals to be materially different from historical results or from any results expressed or implied by such forward-looking statements. In particular, the results of initial clinical trials may not be predictive of future results, and Anadys can provide no assurances that ANA971 will have favorable results in clinical trials, that isatoribine will have favorable results in later clinical trials, or that either isatoribine or ANA971 will receive regulatory approval. This and other factors that may cause actual results to differ are more fully discussed in the "Risk Factors" section of Anadys' Registration Statement on Form S-1 on file with the SEC. Anadys is providing this information as of this date and does not undertake any obligation to update any forward-looking statements contained in this document as a result of new information, future events or otherwise.

(a) Note to editors: In the value $-0.94 \log_{10}$ units, the 10 in \log_{10} should be subscript.
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Source: *Anadys Pharmaceuticals, Inc.*

Source: *BioSpace*

February 20th, 2004

Complementary and Alternative Therapies for Chronic Hepatitis C

Source: www.gastrohep.com

Doctors, in the March issue of the *Journal of Hepatology*, identify several promising complimentary therapies for the treatment of chronic hepatitis C.

Complementary therapies are widely used by patients with hepatitis C.

In this study, doctors from England assessed the efficacy of complementary therapies in treating chronic hepatitis C.

The team conducted systematic searches of 6 databases. The reference lists of all identified papers were checked for further relevant publications and information was requested from experts. No language restrictions were imposed.

The team identified 27 eligible randomized clinical trials were located involving herbal products and supplements. No trials were identified for any other complementary therapy.

In 14 of the trials, patients received interferon-alpha in combination with the complementary therapy.

The team determined that less than half the trials were of good methodological quality.

They found that significant improvements in virological and/or biochemical response were seen in trials of vitamin E, thymic extract, zinc, traditional Chinese medicine, Glycyrrhiza glabra and oxymatrine.

Drs Joanna Thompson Coon and Edzard Ernst concluded, "We identified several promising complementary therapies, although extrapolation of the results is difficult due to methodological limitations".

"More research is warranted to establish the role of these and other therapies in the treatment of hepatitis C".

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