



Investor Update

May 21, 2002

9 in 10 Hepatitis C Patients with Cirrhosis Virus Free On Treatment In A New Study with PEGASYS Interim data supports PEGASYS' unsurpassed efficacy in patients with difficult to treat disease

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Early results from an ongoing study by the Swiss Association for the Study of the Liver show that PEGASYS used in combination with a standard dose of ribavirin (1000-1200 mg) reduces hepatitis C virus (HCV) below detection levels in 93 per cent of patients with advanced fibrosis or compensated cirrhosis after the first 24 weeks of therapy.

"These positive interim results continue to reinforce that PEGASYS combined with ribavirin is highly effective and acceptably tolerated among patients with difficult to treat disease who are in high need of therapy," said the study's principal investigator, Dr. Eberhard Renner, Head of Hepatology at the University Hospital in Zurich, Switzerland.

"Due to their advanced liver disease, these patients are at risk for relevant morbidity and mortality so therapies that work are much needed and until now, advanced fibrosis usually was not associated with positive outcomes," said Dr. Beat Helbling, Department of Gastroenterology and Hepatology at the University Hospital of Zurich, Switzerland, who presented the results at the Digestive Disease Week (DDW) congress going on in San Francisco.

Until now, trials on antiviral treatment of chronic hepatitis C have traditionally included only small numbers of patients with advanced fibrosis or cirrhosis, despite their high medical need for therapy. This trial is designed to advance medical knowledge about the efficacy and tolerability of pegylated interferons and ribavirin in these difficult to treat patients.

This multicenter, randomized Swiss trial had enrolled 116 patients by April 2002. The interim analysis presented at DDW covers the first 61 patients who have completed 24 weeks of therapy. Adverse events are noted by the study authors to be frequent, typical for interferon and/or ribavirin, but usually mild. Dose modifications were necessary in many patients, but only 10% had to discontinue treatment.

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The preliminary findings from this 48-week trial, support the results of a recent landmark study with PEGASYS involving the largest cohort of patients (25% of the patients in the trial) with HCV-related cirrhosis. Presented last month at the annual meeting of the European Association for the Study of the Liver in Madrid, Spain, the Roche Study on the effect of treatment duration and ribavirin dose, found that the combination of PEGASYS and ribavirin resulted in a sustained virological response in 50% of the patients with HCV-related cirrhosis at end of follow-up (six months after the completion of the year-long treatment).

"Given the promising results for patients with hepatitis C related cirrhosis, PEGASYS combined with ribavirin may become the new standard of care also for these difficult to treat patients," said Dr. Helbling. "We will await the final study results eagerly."

Between 20-30 per cent of individuals with chronic hepatitis C will develop cirrhosis. Of these, approximately 20 per cent will suffer from end-stage liver disease and require liver transplantation. Patients with cirrhosis caused by hepatitis C also have a much increased risk of developing hepatocellular cancer.

Extensive clinical trial evidence

PEGASYS is supported by the most extensive clinical study program ever undertaken for a hepatitis C treatment, having been studied in more than 17,000 patients ranging from those with the most difficult to treat form of the disease (genotype 1) and those with cirrhosis (scarring of the liver), to other special populations, such as in individuals co-infected with HIV and patients with end-stage renal disease.

About PEGASYS

PEGASYS, peginterferon alfa-2a (40KD), a new generation hepatitis C therapy that is different by design, is unique in providing benefit over conventional therapy in patients of all genotypes. The benefits of PEGASYS are derived from its new generation large 40 kilodalton branched-chain polyethylene glycol (PEG) construction, which allows for true seven-day viral suppression and is preferentially distributed to the liver, the primary site of infection. PEGASYS is administered once weekly in an easy-to-use pre-filled syringe with one starting dose for everyone.

PEGASYS received a unanimous positive recommendation from the European Union's Committee for Proprietary Medicinal Products (CPMP) in March that it be approved for the treatment of hepatitis C infection. PEGASYS has also been submitted for review by regulatory authorities in the United States and expects approval there later this year. PEGASYS has been approved in 20 countries since August 2001. First approved in Switzerland, PEGASYS is now also available in Argentina, Brazil, Bahrain, Belarus, Cambodia, Columbia, Costa Rica, Dominican Republic, Egypt, El Salvador, Guatemala, Kuwait, Mexico, Morocco, Peru, Russia, Syria, Uruguay and Venezuela.

About Roche

Roche is committed to the viral hepatitis disease area, having introduced Roferon-A for hepatitis C, followed by PEGASYS in hepatitis C, with studies currently being conducted on its efficacy in hepatitis B. Roche also manufactures The COBAS AMPLICOR HCV Test, v2.0 and the AMPLICOR HCV MONITOR Test, v2.0 - two tests used to detect the presence of, and quantify, HCV RNA in a person's blood. Roche's commitment to hepatitis has been further reinforced by the in-licensing of Levovirin, an alternative antiviral. Levovirin will be studied with the objective of demonstrating superior tolerability over the current standard, ribavirin.

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Investor Update

May 21, 2002

New studies highlight benefit of Xeloda in new combination treatments for colorectal cancer Xeloda shown to be effective and safe in combination with Eloxatin, Camptosar and Celebrex

Data presented on Roche's Xeloda (capecitabine), an oral tumor-activated chemotherapy approved as first-line monotherapy treatment of patients with metastatic colorectal cancer when treatment with fluoropyrimidine therapy alone is preferred, demonstrated effectiveness in several combination regimens. Combination of Xeloda with Eloxatin (oxaliplatin) showed an overall median survival at 16 months. The anti-tumor activity of Xeloda is also being studied in combination with other agents such as Camptosar (irinotecan), and Celebrex (celecoxib). The data were presented this weekend at the 38th Annual Meeting of the American Society of Clinical Oncology (ASCO).

Xeloda + Eloxatin (oxaliplatin)

Researchers led by Dr. Josep Tabernero of Hospital General d'Hebron in Barcelona, Spain, presented data from an international Phase II study of Xeloda in combination with oxaliplatin (XELOX) as first-line therapy for metastatic colorectal cancer. The results show an objective response rate of 55 percent with an additional 32 percent of patients having stable disease. In addition, 72 percent of patients treated with the combination of Xeloda and oxaliplatin (XELOX) were alive at one year. Median survival is 16 months, with 57 patients still alive. Median time to progression is currently 7.6 months, with 13 patients yet to progress and 3 patients still undergoing treatment. The 96 patients enrolled in the study received oral Xeloda and intravenous oxaliplatin.

A study with similar results was conducted in the U.S. led by Dr. Anthony Shields of Karmanos Cancer Institute at Wayne State University in Detroit, Michigan. The FDA is currently reviewing a new drug application (NDA) for oxaliplatin in combination with 5 fluorouracil/leucovorin for second line treatment of colorectal cancer.

Xeloda + Camptosar (irinotecan)

Researchers lead by Dr. David J. Kerr of the University of Oxford, presented results of a 33 patient Phase I/II study showing an overall response rate of 48 percent for patients treated with Xeloda and Camptosar (irinotecan). The use of Xeloda in

combination with Camptosar also stabilized the disease in 41 percent of patients. Four percent of patients had disease progression. Study participants were assigned to receive one of five increasing doses of Xeloda, and Camptosar to determine the maximum tolerated dose. The maximum tolerated dose was reached at the fourth dose level, oral Xeloda 1000 mg/m² twice daily for two weeks with one week rest, and Camptosar IV 300 mg/m² day one, with three weeks rest.

Researchers lead by Dr. Samit Hirawat of North Shore University Hospital in New York presented results on a Phase I study evaluating the safety of an every other week dosing regimen of Xeloda in combination with Camptosar for patients with metastatic colorectal cancer. Results of this study show the combination of Xeloda and Camptosar on the every other week schedule is well tolerated. Patients treated with the combination of Xeloda and Camptosar experienced mostly mild to moderate side effects (Grade 1 to 2) including anorexia, nausea, vomiting, diarrhea, and fatigue. One patient experienced Grade 3 diarrhea.

Camptosar is a topoisomerase I inhibitor anticancer agent indicated for first-line therapy in combination with 5-fluorouracil and leucovorin (5FU/LV) to treat metastatic colorectal cancer. Topoisomerase I is an enzyme essential to cancer cell division. Inhibiting this enzyme's activity kills cancer cells.

Xeloda is the first oral drug that is enzymatically converted into the cancer-fighting substance 5-FU. The enzyme thymidine phosphorylase (TP), is higher at the site of the tumor than surrounding normal tissue. This finding has not been adequately studied in the clinical setting.

Colorectal cancer is the second leading cause of cancer mortality in the United States. More than 148,300 Americans are diagnosed with colorectal cancer every year, and an estimated 56,600 people die of the disease annually.

"The results of these studies are encouraging and highlight Xeloda's possible role in combination therapy for patients with advanced and metastatic colorectal cancer," said Georges Gemayel, Vice President, National Specialty Care Business Operation, at Roche. "Furthermore, the convenience of oral dosing with Xeloda allows patients to spend less time in the hospital and more time with their loved ones, while treating and managing their disease."

Xeloda + Celebrex (celecoxib)

Data presented by Dr. E. Lin of M.D. Anderson Cancer Center and his team show that the combination of Xeloda and Celebrex (celecoxib) significantly increased the time to tumor progression to six months, versus 3 months without Celebrex, and the rate of disease stabilization to 62.5 percent, versus 22.8 percent without Celebrex, for patients with metastatic colorectal cancer. In addition, the patients treated with the combination of Xeloda and Celebrex experienced less Grade 1 to 2 hand-foot syndrome and diarrhea. The study was a retrospective analysis of 67 patients with

metastatic colorectal cancer who were either taking **Xeloda** in combination with **Celebrex** or **Xeloda** monotherapy.

Celebrex is a COX-2 specific inhibitor approved for both osteoarthritis (OA) and adult rheumatoid arthritis (RA) and for the management of acute pain. **Celebrex** is also approved for the treatment of familial adenomatous polyposis (FAP), a rare and devastating genetic disease of the colon.

About **Xeloda**

Xeloda is indicated as first-line treatment of patients with metastatic colorectal cancer when treatment with fluoropyrimidine therapy alone is preferred. Combination chemotherapy has shown a survival benefit compared to 5-FU/LV alone. A survival benefit has not been demonstrated with **Xeloda** monotherapy as with the combination chemotherapy in colorectal cancer. Use of **Xeloda** instead of 5-FU/LV combinations has not been adequately studied to assure safety or preservation of the survival advantage.

Xeloda (capecitabine) in combination with **Taxotere** (docetaxel) are indicated for the treatment of metastatic breast cancer after failure of anthracycline therapy. **Xeloda** is also indicated for the treatment of patients with metastatic breast cancer resistant to both paclitaxel and an anthracycline-containing chemotherapy regimen or resistant to paclitaxel and for whom further anthracycline therapy is not indicated. Resistance is defined as progressive disease while on treatment, with or without an initial response, or relapse within six months of completing treatment with an anthracycline-containing adjuvant regimen.

Xeloda is covered by Medicare.

To further improve patient safety, Roche submitted data from a clinical trial that confirmed an interaction between **Xeloda** and warfarin. To heighten physicians' awareness, Roche has agreed with the FDA to make the **Xeloda** and warfarin interaction information more prominent in a black box warning statement and support an ongoing program for physician and patient awareness of the potential interaction between **Xeloda** and coumarin derivative anticoagulants, such as warfarin.

Xeloda Safety Information

Xeloda is contraindicated in patients with severe renal impairment and those with hypersensitivity to 5-fluorouracil. For patients with moderate renal impairment dose reduction is required.

Patients receiving concomitant capecitabine and oral coumarin-derivative anticoagulant therapy should have their anticoagulant response (INR or prothrombin time) monitored frequently in order to adjust the anticoagulant dose accordingly. A clinically important **Xeloda**-warfarin drug interaction was demonstrated in a clinical pharmacology trial. Altered coagulation parameters and/or bleeding, including death,

have been reported in patients taking Xeloda concomitantly with coumarin-derivative anticoagulants such as warfarin and phenprocoumon. Post-marketing reports have shown clinically significant increases in prothrombin time (PT) and INR in patients who were stabilized on anticoagulants at the time Xeloda was introduced. These events occurred within several days and up to several months after initiating Xeloda therapy and, in a few cases, within one month after stopping Xeloda. These events occurred in patients with and without liver metastases. Age greater than 60 and a diagnosis of cancer independently predispose patients to an increased risk of coagulopathy.

Xeloda can induce diarrhea, sometimes severe. Patients with severe diarrhea should be carefully monitored and given fluid and electrolyte replacement if they become dehydrated. Incidence of grade 3 or 4 treatment-related adverse events and serious adverse events are greater in patients \geq 60 years of age receiving Xeloda in combination with docetaxel. Xeloda may cause fetal harm if given during pregnancy. Patients taking phenytoin concomitantly with Xeloda should be carefully monitored for plasma phenytoin levels; phenytoin dose may need to be reduced. Grade 3 and Grade 4 adverse events (\approx 5% of patients) are hand-foot syndrome, diarrhea, nausea, vomiting, stomatitis, abdominal pain, fatigue, decreased appetite, dehydration, venous thrombosis and dermatitis.

As with any cancer therapy, there is a risk of side effects, and these are usually manageable and reversible with dose modification or interruption. Visit <http://www.xeloda.com> or call Roche at 800-526-6367 for full prescribing information.

Xeloda is a registered trademark of Hoffmann-La Roche Inc.

About Roche

Headquartered in Basel, Switzerland, Roche is one of the world's leading research-oriented healthcare groups in the fields of pharmaceuticals, diagnostics and vitamins. Roche's products and services address prevention, diagnosis and treatment of diseases, thus enhancing well-being and quality of life. Roche sells its products in over 170 countries.

Eloxatin (oxaliplatin) is manufactured by Sanofi.
Celebrex (celecoxib) is manufactured by Pharmacia Corporation.
Camptosar (irinotecan) is manufactured by Pharmacia Corporation.

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