Meissner, Dagmar {CLL~Basel}

Subject: FW: Investor update: Pegasys - Potentially a major advance in Hepatitis B treatment
Clinical studies show significantly improved efficacy over current treatments

Pegasys - Potentially a major advance in Hepatitis B treatment
Clinical studies show significantly improved efficacy over current treatments

Taipei, Taiwan - September 29, 2002

Results of a phase II study presented today at the 2002 Meeting of the Asian Pacific Association for the Study of Liver demonstrate the promise of Pegasys as an important new treatment for chronic hepatitis B (CHB) patients. Pegasys has already been approved for the treatment of chronic hepatitis C (CHC) and has been shown to provide superior efficacy when compared to conventional interferon therapy.

"All the study results we have heard today suggest that Pegasys could be a major advance in the treatment of hepatitis B," said Prof. Ming Yang Lai, one of the study authors from National Taiwan University College of Medicine, Taiwan. "Each of the currently available treatments has considerable limitations. In contrast, Pegasys appears to be a treatment that offers significantly improved efficacy, even in patients with treatment resistant disease."

In a study involving 194 patients, researchers found more than twice as many Pegasys patients responded to treatment than those using conventional interferon. 28% of patients treated with Pegasys 180µg once weekly for 24 weeks achieved the combined response of HBeAg clearance (indicating viral replication has stopped), HBV DNA suppression (indicating the virus is effectively controlled) and ALT normalization (indicating normal function of the liver). In contrast, only 12% of interferon alfa-2a patients achieved these results. Similarly, HBeAg seroconversion (loss of HBeAg and presence of anti-HBe) was achieved in 33% of patients treated weekly with Pegasys compared to 25% of patients treated with conventional interferon alfa-2a. The absence of HBeAg viral protein and the presence of HBV-neutralising antibody anti-HBe indicates that the immune system has regained control over HBV.

In the same study, Pegasys demonstrated that it is also effective in patients with difficult to treat hepatitis B - that is, those with low pre-treatment ALT levels and high pre-treatment viral load. In a study presented by Prof. Graham Cooksley, Director of Clinical Research Centre, Royal Brisbane Hospital Research Foundation, Australia, 44% of patients with difficult-to-treat HBV treated with Pegasys achieved HBeAg loss compared to 17% on conventional Interferon alfa-2a.

"As physicians, we are very encouraged by these early results with Pegasys. It is especially important to find a treatment for patients with hard-to-treat disease, because they typically respond poorly to current therapies" said Prof. Cooksley.

Lamivudine and conventional interferon alfa, the currently available standard therapies for hepatitis B in Asia, have clear limitations in terms of overall efficacy. Moreover, about 20 per cent of patients treated with lamivudine develop resistance to the drug within one year of therapy. In addition, a number of patients treated with lamivudine are required to continue therapy indefinitely. Pegasys overcomes these limitations by delivering higher efficacy within a defined treatment duration. In addition, hepatitis B virus does not develop resistance to Pegasys.

Phase III, randomized clinical trials with Pegasys are currently underway in both HBeAg positive and HBeAg negative patients.

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. The Hepatitis B virus is highly contagious and is relatively easy to transmit from one infected individual to another. It is 100 more times infectious than the HIV virus. More than two billion people have been infected by HBV and 350 million people have chronic infection, which can be easily transmitted by blood-to-blood contact, during birth, unprotected sex, and by sharing needles. For those chronically infected with HBV, treatment is the only option. Hepatitis B is the 9th leading cause of death in the world; left unchecked, it can cause liver cancer and death.

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About Pegasys

Pegasys, a new generation hepatitis therapy that is different by design, has demonstrated superior efficacy to conventional interferon combination therapy in patients infected with HCV of all genotypes. The benefits of Pegasys are derived from its new generation large 40 kilodalton branched-chain polyethylene glycol (PEG) construction, which delivers sustained therapeutic concentrations over an entire seven-day dosing interval. This results in true seven-day sustained viral suppression. In addition, Pegasys 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 a fixed 180 mcg starting dose for all patient types.

Pegasys has been approved for the treatment of chronic hepatitis C in 47 countries, including the European Union. Pegasys has also been submitted for review by regulatory authorities in the United States and Roche expects approval in monotherapy and combination later this year.

About Roche

Headquartered in Basel, Switzerland, Roche is one of the world's leading research-orientated healthcare groups. The company's two core businesses in pharmaceuticals and diagnostics provide innovative products and services, that address prevention, diagnosis and treatment of diseases, thus enhancing people's health and quality of life. The two core businesses achieved a turnover of 13,1 billion Swiss Francs in the 1st half of 2002 and employed about 57'000 employees worldwide.

Roche is committed to the viral hepatitis disease area, having introduced Roferon-A for hepatitis C, followed by Pegasys in hepatitis C. Pegasys is also in phase III clinical development for patients infected with the HBV virus. Roche also manufactures The COBAS AMPLICORä HCV Test, v2.0 and the AMPLICOR HCV MONITORä 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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Subject: FW: Investor Update: Pivotal study shows VALCYTETM comparable to CYTOVENEÒ in preventing CMV disease among solid organ transplant recipients

Pivotal study shows VALCYTETM comparable to CYTOVENEÒ in preventing CMV disease among solid organ transplant recipients
Simpler VALCYTE dosing regimen improves patient convenience

New data presented today from a pivotal Phase III study showed that VALCYTEÒ (valganciclovir) tablets were comparable to CYTOVENEÒ (ganciclovir) capsules in the prevention of cytomegalovirus (CMV) disease in solid organ transplant recipients, with a similar safety profile. In addition, patients on VALCYTE maintained greater suppression of CMV viral load, compared to CYTOVENE. These data were presented in a late-breaker oral session today at the 42nd Annual Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) in San Diego, California, Sept. 27-30.

"This large pivotal study demonstrates that VALCYTE is comparable to CYTOVENE, the most widely used anti-CMV agent in solid organ transplantation," said Dr. Richard Freeman, Associate Professor of Surgery, Tufts University. "In addition, the once-daily dosing schedule for VALCYTE is simpler than the three times daily dosing for CYTOVENE."

"CMV is the most clinically significant infection observed following solid organ transplantation. It can affect patients in two ways - directly, by causing infectious diseases such as pneumonia and hepatitis, but also contribute to tumor development," commented Dr. Robert Rubin, Professor of Medicine, Harvard University and Massachussetts Institute of Technology.

"VALCYTE is promising, since it is an oral formulation that provides good bioavailability and may allow for safe administration of the drug for prolonged periods. This may be especially important in light of emerging evidence that CMV infection is associated with increased risk for allograft rejection."

About the phase III study
In the study, 364 CMV-negative patients at 57 sites around the world who received a solid organ transplant from CMV-positive donors were stratified by organ type (177 liver, 120 kidney, 11 kidney-pancreas, 56 heart) and randomized (2 VALCYTE: 1 CYTOVENE) to receive either VALCYTE (900 mg once-daily) or oral CYTOVENE (1000 mg three times daily). Patients began treatment within 10 days after transplantation and continued for 100 days with follow up to six months.

The study showed a low incidence of CMV disease during the first six months of treatment: 12.1 percent with VALCYTE, compared to 15.2 percent with CYTOVENE, with 29 cases reported on VALCYTE and 19 on CYTOVENE at six months. The number of patients with a measurable viral load was significantly lower in the VALCYTE group during the treatment period (2.5 percent vs. 10.4 percent), but was comparable between the two groups by six months post transplant (40 percent vs. 43 percent). In addition, acute rejection was observed less frequently with VALCYTE compared to CYTOVENE (29.7 percent vs. 36.0 percent) across all three organs studied.

The study also showed that none of the patients in the VALCYTE arm developed ganciclovir-related genotypic resistance at the CMV UL97 mutation, while two percent of patients in the CYTOVENE arm developed genotypic resistance.

Both drugs were well tolerated, with low rates of withdrawal due to adverse events: 4.9 percent of patients in the VALCYTE arm and 4.8 percent in the CYTOVENE arm withdrew due to adverse events. There was a greater incidence of neutropenia and leucopenia on the VALCYTE arm and a greater incidence of anemia in the CYTOVENE arm. The most frequent adverse events were diarrhea, tremor, graft rejection, and headache.

More about VALCYTE
Since VALCYTE is rapidly converted to ganciclovir after administration, adverse reactions known to be associated with CYTOVENE can be expected with VALCYTE. Both products can produce hematologic toxicity, including anemia, depressed white blood cell counts, and to a lesser extent, depreseed platelet counts. In animal studies ganciclovir was carcinogenic, teratogenic and adversely affected sperm production. In AIDS patients on certain antiretroviral regimens, didanosine (ddI) blood levels can be significantly increased when taken with VALCYTE, and the hematologic abnormalities may be exacerbated if the product is taken with AZT. Other side effects occurring with a frequency of greater than five percent include diarrhea, nausea (with or without vomiting), abdominal cramping, fever, headache and peripheral neuropathy. Kidney function can be affected, and dose adjustment is necessary with altered renal function.

About CMV

Cytomegalovirus (CMV), a member of the herpes family of viruses, infects approximately 50 to 75 percent of the U.S. adult population. In certain high-risk groups, close to 95 percent of individuals may have evidence of infection. In individuals with healthy immune systems, CMV exists in the body in a dormant state. However, among individuals with compromised immune systems - including AIDS patients and organ transplant recipients on immunosuppressant therapy - the virus can become active and cause disease. CMV is by far the most common infection in solid organ transplant recipients, with over half of the patients showing evidence of active CMV infection (viral replication). Generally, CMV occurs within the first three months of solid organ transplantation.

About Roche

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Subject: FW: Investor Update: New data shows better lipid safety profile of boosted Saquinavir vs. boosted Indinavir

New data shows better lipid safety profile of boosted Saquinavir vs. boosted Indinavir

Roche today announced results of two studies examining the lipid safety profile of twice-daily boosted saquinavir (1000 mg saquinavir with 100 mg ritonavir) for HIV. Data from the first head-to-head study of boosted protease inhibitors (the MaxCmin1 trial) revealed that boosted saquinavir (FORTOVASEÒ) led to significantly lower increases in fasting total cholesterol, LDL cholesterol and triglyceride levels than boosted indinavir (CrixivanÒ) at 48 weeks, while a separate study found no significant rises in triglycerides or cholesterol after 20 days of treatment with boosted saquinavir alone. The studies were presented at the 42nd International Conference on Antimicrobial Agents and Chemotherapy (ICAAC) and at the 4th International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV, respectively, both held this week in San Diego.

"Given the long-term nature of antiretroviral treatment, evaluating the lipid safety profiles of protease inhibitor-based regimens provides valuable information to HIV-treating physicians," said Dr. Cal Cohen, Director of Research, Community Research Initiative of New England, Boston. "It is clear from these studies that boosting twice-daily saquinavir (1000 mg) with a mini-dose of ritonavir (100 mg) allows patients to avoid the negative lipid impact of higher doses of ritonavir while maintaining maximum therapeutic benefit with saquinavir."

Results from MaxCmin1
Data from the MaxCmin1 trial, presented today at ICAAC, showed that boosted indinavir led to significantly greater increases in lipid levels at 48 weeks compared to boosted saquinavir. The study compared increases in fasting total cholesterol (17 percent vs. eight percent), LDL cholesterol (18 percent vs. three percent) and triglyceride levels (22 percent vs. nine percent) ($p<0.05$ for all three comparisons).

The final analysis of 48-week efficacy and safety data from the study were also presented. The results showed that boosted saquinavir reduced HIV to less than 50 copies/mL in a greater proportion of patients than boosted indinavir at 48 weeks (57 percent vs. 46 percent), according to the most stringent "intent-to-treat" analysis which considers dropouts as failures. Results between the two arms were comparable in the "on treatment" analysis which includes only patients who completed the treatment period (79 percent for saquinavir vs. 77 percent for indinavir). The median CD4 cell count at week 48 was 85 cells/ml in the saquinavir arm and 73 cells/ml in the indinavir arm.

Significantly more patients withdrew from the study due to non-fatal clinical adverse events in the indinavir arm than in the saquinavir arm (28 percent vs. 15 percent; P= 0.006). A total of 92 patients had at least one grade 3 (severe) and/or grade 4 (life threatening) adverse event: 62 (39 percent) in the boosted indinavir arm versus 30 (20 percent) in the saquinavir arm ($p=0.0004$). The number and type of grade 3 or 4 adverse events in the indinavir and saquinavir arms, respectively, included: cardio-pulmonary (5 and 1), renal (13 and 1), gastrointestinal (19 and 17), nervous system (8 and 4), dermatological (18 and 4), laboratory (21 and 21), and other (20 and 12).

More about MaxCmin1
The MaxCmin1 study was designed and coordinated by the Copenhagen HIV Investigator Program (CHIP). Patients from 14 countries in North and South America and Europe participated in the MaxCmin1 study. The primary objective of the study, which enrolled 317 patients, was to evaluate differences in virological failure between 1000 mg saquinavir (n=148) and 800 mg indinavir (n=158), each co-administered with a small 100 mg dose of ritonavir, at 48 weeks. (Eleven patients who were randomized did not initiate therapy.) At baseline, no difference between the study arms were observed in demographic, clinical or laboratory variables, nor in the use of any antiretroviral drug prior to inclusions or at baseline.

Fasting lipid levels with boosted Saquinavir
A separate study found no significant rises in triglycerides or total cholesterol after 20 days of treatment with twice-daily boosted saquinavir in the absence of other antiretroviral agents. In this single-center, open-label, cross-over, pharmacokinetic study, 24 healthy male volunteers were randomized to receive 10 days of treatment with either 1000 mg of saquinavir soft gel capsules (FORTOVASE) or hard gel capsules (INVIRASEÒ) with 100 mg ritonavir twice daily, and then switched to the alternate formulation of saquinavir. Fasting levels of triglycerides and cholesterol and other laboratory parameters were measured at screening and at days one, 10 and 20 of the trial, as well as during three to seven days of follow-up.

At twenty days, mean total cholesterol levels fell by 1.0 mg/dl and triglycerides rose by 1.2 mg/dl. None of these changes were considered statistically significant. There was no statistically significant change in any laboratory parameter and there were no Grade 3 or 4 laboratory toxicities during the trial. The incidence of diarrhea was significantly lower with boosted INVIRASEÒ (four of 24) than with boosted FORTOVASEÒ (15 of 24 subjects) (p

<0.01). There was no significant correlation between saquinavir drug levels and the incidence of either diarrhea or abdominal symptoms.

"Boosting" protease inhibitors
Co-administering protease inhibitors with a low dose of ritonavir is an investigational treatment strategy known as "boosting." By using low, "non-therapeutic" doses of ritonavir, the metabolism of other protease inhibitors, such as saquinavir, can be inhibited, resulting in higher and more consistent levels of the "therapeutic" protease inhibitor.

More about Saquinavir soft gel capsules (FORTOVASE)
The most frequently reported adverse events at least possibly related to treatment with saquinavir soft gel capsules and of at least moderate intensity - observed in trials evaluating the approved 1200 mg three-times-daily dosing regimen - include nausea (17.8 percent), diarrhea (15.6 percent), abdominal discomfort (13.3 percent) and dyspepsia (8.9 percent). Saquinavir soft gel capsules should not be co-administered with astemizole, terfenadine, ergot derivatives, cisapride, midazolam or triazolam, due to the potential for serious and/or life-threatening events. Concomitant use with lovastatin or simvastatin is also not recommended; caution should be exercised with other HMG-CoA reductase inhibitors metabolized by the CYP3A4 pathway. Exacerbation of chronic liver dysfunction has been reported in patients treated with saquinavir soft gel capsules. Patients should be informed that redistribution or accumulation of body fat may occur in patients receiving protease inhibitors and that the cause and long-term health effects of these conditions are not known at this time. There have also been reports of hyperglycemia, new onset or exacerbation of diabetes and of spontaneous bleeding in patients with hemophilia. Please refer to the complete product information for detailed safety information for saquinavir soft gel capsules.

More about Saquinavir hard gel capsules (INVIRASE)
Saquinavir hard gel capsules deliver the same active ingredient as saquinavir soft gel capsules, and the safety and drug interaction information provided above for saquinavir soft gel capsules also applies to saquinavir hard gel capsules. The saquinavir hard gel capsules product labeling warns that saquinavir hard gel capsules and saquinavir soft gel capsules are not bioequivalent and cannot be used interchangeably. When using saquinavir as part of an antiviral regimen saquinavir soft gel capsules is the recommended formulation. In rare circumstances, saquinavir hard gel capsules may be considered if it is to be combined with antiretrovirals, such as ritonavir, that significantly inhibit saquinavir's metabolism.

About Roche
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