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Issuer	Roche Holding AG
Transaction date	03.11.2006 by an executive member of the Board of directors / member of senior management
Type of transaction	Sale of 1'100 securities amounting to CHF 158'620.00 (CHF 144.20 / security)
Type of security	Equity securities
ISIN	CH0012092048
Further transaction details	Exersale

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# Investor Update

Furnished under Rule 12g3-2(b)  
ROCHE HOLDING 82-3315



Basel, 27 October 2006

## Customising treatment with Pegasys plus Copegus improves chances for cure in Hepatitis C

### Results from two clinical trials point to innovative strategies for fast and slow

Higher fixed doses of Pegasys plus Copegus in patients with certain 'difficult-to-treat' characteristics may lead to a better chance of cure according to results presented at the 57<sup>th</sup> annual meeting of the American Association for the Study of Liver Diseases (AASLD).<sup>i</sup> It is well recognised that response rates to treatment can be significantly lower in patients who have several characteristics such as infection with genotype 1, high levels of virus in the blood, and heavy bodyweight.<sup>ii</sup> The results of a new study show that intensifying treatment with a higher fixed dose of Pegasys along with a higher dose of Copegus could yield significantly higher response rates in these difficult-to-cure patients.

"We have known for some time that certain patients have 'difficult-to-treat' characteristics and improving treatment success rates using currently available medications for these patients is an urgent need," said Michael W. Fried, M.D., University of North Carolina at Chapel Hill. "If strategies using higher fixed doses of peginterferon alfa-2a and ribavirin are validated in larger studies, these findings give us hope that more patients living with chronic hepatitis C can be cured."

#### About the higher fixed dose study

This randomised, double-blind study enrolled 188 adults with previously untreated genotype 1 chronic hepatitis C infection, high blood levels of hepatitis C (hepatitis C RNA level greater than 800,000 IU/ml) and a bodyweight of more than 85 kg. Patients received 48 weeks of treatment with Pegasys at either the standard fixed dose of 180 microg/week or a higher fixed dose of 270 microg/week, plus Copegus at the standard dose of 1200 mg/day or a higher dose of 1600 mg/day, as follows:

- peginterferon alfa-2a (40KD) 180 microg/week plus ribavirin 1200 mg/day (Group A)
- peginterferon alfa-2a (40KD) 180 microg/week plus ribavirin 1600 mg/day (Group B)
- peginterferon alfa-2a (40KD) 270 microg/week plus ribavirin 1200 mg/day (Group C)

- peginterferon alfa-2a (40KD) 270 microg/week plus ribavirin 1600 mg/day (Group D)

The rate of SVR in patients receiving the most intensive regimen (Group D) was higher than in patients receiving the standard-dose regimen (Group A) at 47 per cent versus 28 per cent. The results also highlight the important role that Copegus plays in achieving an SVR. It was the combination of a higher dose of Pegasys and a higher dose of Copegus, which seemed to act synergistically, resulting in an impressive increase in SVR (difference of 19 per cent) versus the current standard regimen.

The use of higher doses of Pegasys and Copegus was associated with a small increase in the rate of adverse events, although the number of patients stopping treatment early was similar.

A second study presented at AASLD showed that Pegasys 'super-responders' have an excellent chance of being cured following a shortened duration of therapy. Over three-quarters of hepatitis C patients with difficult-to-cure genotypes 1 and 4 who had a rapid response to treatment (virus-free at 4 weeks) went on to achieve a sustained virological response (SVR) following only 24 weeks of treatment with Pegasys (peginterferon alfa-2a (40KD)) plus Copegus (ribavirin). An SVR is indicative of a cure.

"These results show that within a month of starting therapy with Pegasys plus Copegus we can give some patients the excellent news that they are highly likely to be cured," said Dr. Peter Ferenci, lead study investigator and Professor of the Department of Internal Medicine IV, Gastroenterology and Hepatology at the University of Vienna, Austria. "These data could help patients to seek treatment and motivate them to stay on treatment. These results could change the way that patients are treated in the future."

#### About the 'super-responder' study

In this study, patients received Pegasys 180 microg once weekly plus a 1000-1200 mg daily dose of Copegus. After 4 weeks of treatment, virus levels in the blood were measured to identify the 'super-responders'. 'Super-responders' (patients who were virus-free at week 4) were treated for only another 20 weeks, receiving a total of 24 weeks of therapy. All other patients continued on treatment and were reassessed at week 12. Those who had an early virological response (EVR; undetectable viral load or a drop in viral load to less than one per cent of pre-treatment viral load at week 12) were randomised to receive either 48 or 72 weeks of therapy. Those who did not have an EVR continued treatment for 72 weeks.<sup>iii</sup>

#### Results:

- 77 per cent of 'super-responders' in the study achieved an SVR.

- Among those who had an EVR, SVR rates were similar (56 per cent of patients treated for 48 weeks achieved an SVR compared with 43 per cent treated for 72 weeks).
- Patients who did not have an EVR were highly unlikely to achieve an SVR (4 per cent even after 72 weeks of treatment).

“These two clinical trials underscore Roche’s commitment to finding better treatment solutions with Pegasys, the cornerstone of hepatitis C therapy,” said Claire Steers, Pegasys Life Cycle Leader at Roche. “It is this ongoing commitment that has led to Pegasys being indicated for the treatment of hepatitis C in the broadest range of patients, including difficult-to-cure patients such as those with HIV-HCV co-infection and cirrhotic patients.”

#### About Hepatitis C

Hepatitis C, the most common chronic blood-borne infection, is transmitted primarily through blood or blood products. Hepatitis C chronically infects 170 million people worldwide,<sup>iv</sup> with an additional three to four million people newly infected each year. It is a leading cause of cirrhosis, liver cancer and liver failure.

#### About Pegasys

Pegasys, the market leader worldwide in hepatitis C therapy, provides significant benefit over conventional combination interferon therapy in hepatitis C patients of all genotypes. The benefits of Pegasys are derived from its 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. Pegasys is the only pegylated interferon available as a ready-to-administer solution. Each weekly subcutaneous injection contains 180microg of pegylated interferon alfa-2a (40KD), which is the approved dose for all patients, regardless of body weight.

#### About Roche

Headquartered in Basel, Switzerland, Roche is one of the world’s leading research-focused healthcare groups in the fields of pharmaceuticals and diagnostics. As a supplier of innovative products and services for the early detection, prevention, diagnosis and treatment of disease, the Group contributes on a broad range of fronts to improving people’s health and quality of life. Roche is a world leader in diagnostics, the leading supplier of medicines for cancer and transplantation and a market leader in virology. In 2005 sales by the Pharmaceuticals Division totalled 27.3 billion Swiss francs, and the Diagnostics Division posted sales of 8.2 billion Swiss francs. Roche employs roughly 70,000 people in 150 countries and has R&D agreements and strategic alliances with numerous partners, including majority ownership interests in Genentech and Chugai. Additional information about the Roche Group is available on the Internet

(www.roche.com).

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#### References:

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- i Fried M, Jensen D, Rodriguez-Torres M, et al. Improved sustained virological response (SVR) rates with higher, fixed doses of peginterferon alfa-2a (40KD) (PEGASYS®) plus ribavirin (RBV)(COPEGUS®) in patients with "difficult-to-cure" characteristics. In: American Association for the Study of Liver Diseases; 2006; Boston, Massachusetts 2006.
  - ii Fried MW, Shiffman ML, Reddy KR, et al. Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. N Engl J Med 2002;347(13):975-82.
  - iii Ferenci P, Laferl H, et al. Customizing treatment with peginterferon alfa-2a (40KD) (PEGASYS®) plus ribavirin (COPEGUS®) in patients with HCV genotype 1 or 4 infection. Interim results of a prospective randomized trial.
  - iv Global surveillance and control of hepatitis C. Report of a WHO Consultation organized in collaboration with the Viral Hepatitis Prevention Board, Antwerp, Belgium. J Viral Hepat 1999;6(1):35-47.

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Basel, 27 October 2006

## Roche's oral polymerase inhibitor shows strong antiviral activity in chronic hepatitis C patients

R1626 demonstrates greatest hepatitis C viral load reduction of all polymerase inhibitors

Roche's new investigational drug for hepatitis C has been shown to have a strong antiviral effect. The drug, which is known as R1626, has achieved clinically significant reductions in viral load in chronic hepatitis C patients infected with the difficult-to-cure genotype 1 virus.<sup>i</sup> Furthermore, the drop in hepatitis C viral load achieved in patients receiving R1626 is the largest seen for this class of antiviral treatments called polymerase inhibitors. These findings were announced today at the annual meeting for the 57<sup>th</sup> American Association for the Study of the Liver (AASLD) in Boston.

"The results from this phase I study show us that the polymerase inhibitor R1626 is very effective in inhibiting hepatitis C viral replication. In fact, the drop in hepatitis C virus is the best that we have seen with all the polymerase inhibitors studied so far," said Dr. Stuart Roberts, Director of Gastroenterology at Alfred Hospital in Melbourne, Australia and lead investigator of the study. "Adding R1626 to current therapies could potentially improve cure rates in hepatitis C."

As a result of these outstanding virological results, Roche has commenced a phase II trial to evaluate how well R1626 works in combination with the current standard of care, Pegasys (peginterferon alfa-2a (40KD)) and Copegus (ribavirin).

### About the study presented at AASLD

In this phase I study, 47 patients with genotype 1 hepatitis C were randomised to receive either oral treatment with R1626 twice daily or placebo for 14 days with 14 days of follow up. The final results presented at AASLD included patients who received the higher doses of R1626 at 3,000 mg or 4,500 mg twice a day.

### The study found:<sup>ii</sup>

- Clinically significant reductions in serum hepatitis C virus RNA (a measure of how much virus is in the blood) of 1.2, 2.6 and 3.7 log reduction with R1626 at the doses of 1,500 mg, 3,000 mg and 4,500 mg, respectively.

- R1626 at all doses tested had a good safety profile and no patient was prematurely withdrawn. Reversible mild to moderate haematological changes were observed with increasing doses.

#### **Defining treatment for a new generation**

“Roche is fully committed to developing the best treatment options so that as many patients as possible have the best chance for a cure,” said Dr Friederike Zahm, Life Cycle Leader for R1626 at Roche in Basel, Switzerland. “The development of R1626, ongoing research with Pegasys and extensive partnerships with other companies such as InterMune, Pharmasset and Maxygen underscores our long-term commitment to finding effective therapies to benefit patients with chronic hepatitis C.”

#### **About the phase IIa R1626 clinical trial**

Roche have commenced a multicentre phase II trial that is enrolling patients with genotype 1 chronic hepatitis C who have not previously received treatment. Patients are randomised into four treatment groups assessing R1626 with Pegasys or Pegasys plus Copegus, versus the standard of care. Following the first 4 weeks of treatment, all patients will receive Pegasys 180 microg subcutaneously every week plus Copegus 1,000-1,200 mg daily for another 44 weeks, making the total treatment duration of 48 weeks.

The objectives of the study are to evaluate the 4 week safety and antiviral effect of combining R1626 with Pegasys and/or Copegus. The study is currently enrolling patients in the US. Patients and healthcare providers interested in the trial can find more information at [www.roche-trials.com](http://www.roche-trials.com).

#### **About Hepatitis C**

Hepatitis C, the most common chronic blood-borne infection, is transmitted primarily through blood or blood products. Hepatitis C chronically infects 170 million people worldwide,<sup>iii</sup> with an additional three to four million people newly infected each year. It is a leading cause of cirrhosis, liver cancer and liver failure, despite being potentially curable. The future of hepatitis C therapy is likely to involve combinations of new small-molecule antiviral drugs and pegylated interferon-based treatment, like Pegasys.

#### **About Roche**

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#### References:

<sup>i</sup> Roberts S, Cooksley G, et al. Results of a Phase 1B, Multiple Dose Study of R1626, a Novel Nucleoside Analog Targeting HCV Polymerase in Chronic HCV Genotype 1 Patients. Presented at the American Association for the Study of the Liver (AASLD). Oct 30, 2006.

<sup>ii</sup> Roberts S, Cooksley G, et al. Results of a Phase 1B, Multiple Dose Study of R1626, a Novel Nucleoside Analog Targeting HCV Polymerase in Chronic HCV Genotype 1 Patients. Presented at the American Association for the Study of the Liver (AASLD). Oct 30, 2006.

<sup>iii</sup> Global surveillance and control of hepatitis C. Report of a WHO Consultation organized in collaboration with the Viral Hepatitis Prevention Board, Antwerp, Belgium. J Viral Hepat 1999;6(1):35-47.

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