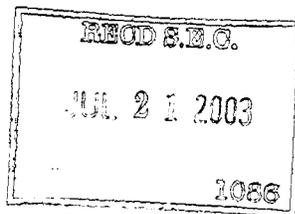




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June 30, 2003 10:32 AM



**Pegasys twice as effective as current standard therapy for Hepatitis B patients**

Published study achieves two firsts

The first study reporting on the use of PEGASYS (peginterferon alfa-2a) for the treatment of chronic hepatitis B virus (HBV) was published today in the *Journal of Viral Hepatitis*\*. The study found that PEGASYS is superior in efficacy to conventional interferon, the initial therapy recommended by a recent International Consensus Conference\*\*.

The 194 patients in the Phase II study were treated with either conventional interferon three times weekly or PEGASYS (at 90 g, 180 g or 270 g) once weekly for a 24-week-period, and were then observed with no further treatment for another 24 weeks. The study assessed what is referred to as the 'combined response' of patients. This response includes the loss of viral protein, suppression of HBV DNA levels and the normalization of the liver's function, all strong indicators of treatment efficacy.

Overall, 28% of patients who received PEGASYS for six months at the 180 g dose achieved a 'combined response.' In sharp contrast, only 12% of patients who received conventional interferon achieved a combined response.

"The viral reduction achieved with PEGASYS is substantially more pronounced than what's achieved with conventional interferon. It appears that PEGASYS enhances the patient's immune response against the virus as well as profoundly inhibiting the virus," said Prof. Graham Cooksley, the author of the study and Senior Principal Research Fellow, Clinical Research Centre, Royal Brisbane Hospital, Australia. "One reason this study was undertaken was because of the short-comings with current therapies, including nucleoside analogues, which offer less than optimal efficacy, often require long-term or continuous administration and have been associated with drug resistance."

**More profound impact on HBV than conventional interferon**

In the paper, the authors note that the beneficial effects of PEGASYS were also observed in difficult to treat patients, for example those with cirrhosis, those with low ALT or high HBV DNA levels at baseline, and those with HBV genotype C. The rapid and sustained reductions in HBeAg and HBV DNA levels indicated that PEGASYS has a more profound impact on HBV than conventional interferon alfa-2a.

**Promising seroconversion rate with Pegasys**

The paper notes that the primary treatment goal in chronic hepatitis B remains sustained suppression of HBV replication in the absence of therapy. HBeAg loss and "e" seroconversion (antibodies against the viral antigens) are indicative that this goal has been reached. Importantly, seroconversion significantly lowers a patient's risk of developing end-stage liver disease or death. "For this reason, the documented seroconversion rate of 33% in 6 months seen in this study with peginterferon alfa-2a (40KD), an agent with both antiviral and immunomodulatory properties, is eminently promising."

*dlw 7/22*

#### About Hepatitis B

Hepatitis B is a blood-borne 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 times more infectious than the HIV virus.

Despite a highly effective vaccine, 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, sex, and by sharing needles. HBV and HCV rank in the top four causes of cancer deaths in most countries in Asia and the Western Pacific rim\*\*\*. For those chronically infected with HBV, treatment is the only option.

#### About PEGASYS

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

#### About Roche

Roche is committed to the viral hepatitis disease area, having introduced Roferon-A for hepatitis B and C, followed by PEGASYS in hepatitis C and now PEGASYS is demonstrating similar superior efficacy over conventional interferon in hepatitis B. Roche has also launched its own brand of ribavirin, Copegus, to be used in conjunction with Roferon A or PEGASYS for HCV. Roche also manufactures HBV and HCV diagnostic and monitoring systems: The COBAS AMPLICOR Test, and the AMPLICOR MONITOR Test, two testing systems used to detect the presence of, and quantity of, HBV DNA or HCV RNA in a person's blood. 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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\* Cooksley, W. Graham E et al. Peginterferon alfa-2a (40KD): An advance in the treatment of HBeAg-Positive Chronic Hepatitis B. J. Viral Hepatitis. 2003;10: pages

\*\* EASL (European Association for the Study of the Liver) International Consensus Conference on Hepatitis B, 13-14 September 2002 Geneva, Switzerland, Consensus statement. Journal of Hepatology 38 (2003) 533-540.

\*\*\* Chu, CM. Natural History of Chronic Hepatitis B Virus Infection in Adults with Emphasis on the Occurrence of Cirrhosis and Hepatocellularcarcinoma. J Gastroenterol. Hepatol. 2000; 15 (suppl.):E25-30.

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# Media release



Basel, 15 July 2003

## **Roche SARS test now available**

**Test for research use only is designed to detect the virus that causes Severe Acute Respiratory Syndrome**

Roche today announced the worldwide launch of a research product designed to detect the virus that causes Severe Acute Respiratory Syndrome (SARS). The test was developed in only eight weeks, the shortest development time ever for a research product at Roche. This was made possible in part by excellent international collaboration and networking relationships with virology institutes and government agencies, including the Genome Institute of Singapore. Roche has performed preliminary studies with the product and plans additional studies at various sites in Asia, Europe, and Canada.

Roche believes the test will be an essential research tool that will help increase understanding of the epidemiology of SARS. It is based on Roche's patented real-time polymerase chain reaction (PCR) technology, which is already used worldwide in a wide variety of clinical and research applications. The SARS research product was developed using Roche's LightCycler instrument and is designed for ease of use by technicians with a variety of training levels.

Heino von Prondzynski, Head of the Diagnostics Division and Member of the Roche Executive Committee, commented: "Even if the infection rate with the SARS virus is regressive, we do not know if we will have to face another outbreak in the future. In the meantime researchers will use our product to answer questions still open about the incubation time, the point when patients are most infectious or how long the virus can survive outside the body."

The development team was based mainly at Roche's research site in Penzberg, Germany.

Supplemental work was done at outside laboratories specially designed to accommodate research involving high-risk infectious agents. Because some specimens could not be processed in Penzberg, the project team collaborated with researchers, hospitals and government agencies in the countries that represented the major SARS "hot spots."

In response to the appearance of new viral diseases, Roche Diagnostics has already set the pace for swift and proactive responses to threats from emerging pathogens. In only nine months, Roche developed a blood-screening test (investigational use only) for the detection of West Nile Virus, a mosquito-borne pathogen that can cause life-threatening illness and death and can be transmitted through infected donor blood and blood products. Roche's West Nile test is currently being evaluated at blood testing sites in the US under an Investigational New Drug (IND) application and under a similar regulatory process in Canada.

#### About SARS

Severe Acute Respiratory Syndrome (SARS) was first reported in China's Guangdong province in late 2002. SARS is a form of atypical pneumonia caused by a new strain of coronavirus. According to the World Health Organization (Cumulative Number of Reported Probable Cases of SARS from 1 November 2002 to 10 July 2003), the disease has killed more than 800 people worldwide and infected more than 8000. The majority of infections have occurred in Asia.

#### About Roche's PCR technology

Roche's patented polymerase chain reaction (PCR) technology is one of the most advanced methods in molecular diagnostics and one that earned its discoverer a Nobel Prize in Chemistry in 1993. PCR allows minute amounts of genetic material to be amplified into billions of copies (that is, to detectable levels) in only a few hours. In addition to its applications in nucleic acid fingerprinting and the diagnosis and monitoring of disease, PCR enables detection of infectious agents early in the infection cycle, often before symptoms appear. Standard immunoassay testing, by contrast, detects evidence of the body's immune response (antibodies) later in the infection cycle, leaving an increased period during which infections can be missed. Through its global licensing and scientific collaboration programs Roche has developed and encouraged the utility of PCR technology for a wide variety of clinical and research applications.

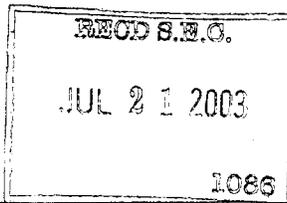
#### About Roche

Headquartered in Basel, Switzerland, Roche is one of the world's leading innovation-driven healthcare groups. Its core businesses are pharmaceuticals and diagnostics. Roche is number one in the global diagnostics market, the leading supplier of pharmaceuticals for cancer and a leader in

virology and transplantation. As a supplier of products and services for the 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 employs roughly 62,000 people in 150 countries. The Group has alliances and research and development agreements with numerous partners, including majority ownership interests in Genentech and Chugai. Roche's Diagnostics Division, the world leader in in-vitro diagnostics with a uniquely broad product portfolio, supplies a wide array of innovative testing products and services to researchers, physicians, patients, hospitals and laboratories worldwide.

#### **Additional information**

- SARS / WHO: [www.who.int/csr/sars](http://www.who.int/csr/sars)
- Genome Institute of Singapore: [gis.a-star.edu.sg](http://gis.a-star.edu.sg)
- LightCycler: [www.lightcycler-online.com](http://www.lightcycler-online.com)
- PCR technology: [www.roche-diagnostics.com/ba\\_rmd/about\\_pcr.html](http://www.roche-diagnostics.com/ba_rmd/about_pcr.html)
- Pictures: [www.roche-diagnostics.com/press\\_lounge/press\\_releases/division/division.html](http://www.roche-diagnostics.com/press_lounge/press_releases/division/division.html)



## Investor Update

July 15, 2003 3:19 PM

### **FUZEON - A revolution in HIV Care** **FUZEON establishes a new standard of care for pre-treated HIV patients**

FUZEON (enfuvirtide, formerly known as T-20), the first drug to block the HIV virus from entering the human immune cell, is revolutionizing the treatment options for pre-treated HIV patients, giving them new hope for longer and better lives.

#### Unprecedented results

World experts at the International AIDS Society (IAS), the largest international AIDS conference for 15 years to be held in France, heard today how the better than expected 24 and 48-week TORO (T-20 vs Optimized Regimen Only) 1 and TORO 2 data has confirmed that FUZEON used with an optimized regimen of available HIV medication outperformed combinations comprised of the optimized regimen without FUZEON. Patients taking FUZEON as part of their drug combination were twice as likely to achieve undetectable levels of HIV and even doubled their immune cell count increase versus those who did not take FUZEON.

#### Greatest magnitude of benefit when FUZEON is used earlier

The FUZEON containing regimen provided benefits across all sub-groups examined including patients with few or no other treatment options. However, further analyses demonstrate that in the TORO study population at 24 weeks, the greatest magnitude of benefit is achieved when FUZEON is used earlier in treatment rather than later<sup>1</sup> or when patients have a higher CD4 count ( 100 versus 100 cells/mm<sup>3</sup>).

#### Durability of response confirmed

The 48-week data from the TORO 1 and 2 studies show that the treatment benefit provided by FUZEON is maintained over longer term therapy in pre-treated patients. In addition, the duration of benefit was three times longer for patients taking a FUZEON containing regimen than for those taking the optimized regimen without FUZEON.

David Cooper, Professor of Medicine, University of New South Wales said: "The magnitude of benefit obtained by patients taking FUZEON at 24 weeks, together with the long term maintenance of benefits was remarkable, particularly given the high previous exposure to HIV medications in the patient population. The benefit from the FUZEON based regimen was greatest when used earlier, when there were a greater number of active agents to combine with FUZEON."

James Locke, a person who has been living with HIV for 18 years commented: "I have now been taking FUZEON for well over two years and still my HIV remains undetectable. FUZEON has given me back my hopes and dreams and I am now once again able to plan my future."

### 2003 - The year of FUZEON

The year 2003 marks the 20th anniversary of the discovery of the HIV virus and the approval of FUZEON in Europe and the US, heralding the start of a new era in the treatment of HIV. Developed by Roche and Trimeris Inc., FUZEON is the first in a new class of anti-HIV medication, known as 'fusion inhibitors', and represents the first new class of HIV therapy to be approved since 1996. FUZEON attacks HIV in a totally different way, compared to existing HIV medications, by blocking the fusion of HIV with human immune cells while existing drugs act once the cell is infected. As a result of the very different mechanism of action, FUZEON is active against HIV strains that have become resistant to current therapies.

### Drug supply exceeds expectations

FUZEON is one of the most structurally complex and challenging molecules ever chemically manufactured by the pharmaceutical industry at large scale, requiring more than 100 production steps. Mr. Charles Sabbah, Head of Roche Global Strategic Marketing commented: "We are now able to supply FUZEON for up to 18,000 patients by the end of the year, a significant increase over the 12-15,000 patients originally estimated. This is because supply output is continuing to steadily increase and is greater than we had projected for this point in time." Mr Sabbah added: "Physicians should now have a far greater level of confidence that they can prescribe FUZEON for those patients who will benefit from the drug and that their patients will gain access to this breakthrough medication."

### Notes to Editors:

#### Study Design

TORO 1 (T-20 vs. Optimised Regimen Only) and TORO 2 are randomised, open-label trials that enrolled approximately 1,000 patients at 112 centres internationally. Patients in the trials were treatment-experienced and/or had documented resistance to each of the three classes of currently available antiretrovirals. In addition, each patient was required to have a HIV level of greater than 5,000 copies/mL.

At entry, genotypic and phenotypic resistance testing was used to aid in the selection of an antiretroviral regimen, consisting of three to five drugs, including if appropriate, up to two newly approved or investigational drugs. After selection of the regimen, patients were randomised 2:1 to receive either the regimen in combination with FUZEON or the regimen alone. Patients randomized to FUZEON receive FUZEON administered as one 90 mg subcutaneous self-injection twice-daily.

### Safety of FUZEON

FUZEON is administered as a twice-daily subcutaneous injection. Local injection site reactions were the most frequent adverse events associated with the use of FUZEON. In the TORO studies, 98 percent of patients had at least one local injection site reaction over the course of 48 weeks. In this treatment-experienced patient population, 4 percent of patients at 48 weeks discontinued treatment with FUZEON as a result of injection site reactions.

An increased rate of some bacterial infections, primarily pneumonia, was seen in patients treated with FUZEON. It is unclear if this increased incidence is related to FUZEON use. The addition of FUZEON to background antiretroviral therapy generally did not increase the frequency or the severity of the majority of adverse reactions. The majority of adverse reactions were of mild or moderate intensity. Hypersensitivity reactions have occasionally been associated with FUZEON therapy and in rare cases have recurred on re-challenge.

#### FUZEON indication in the European Union

The indication for FUZEON in the European Union is for "use in combination with other antiretroviral medicinal products for the treatment of HIV-1 infected patients who have received treatment with and failed on regimens containing at least one medicinal product from each of the following antiretroviral classes, protease inhibitors, non-nucleoside reverse transcriptase inhibitors and nucleoside reverse transcriptase inhibitors, or who have intolerance to previous antiretroviral regimens. In deciding on a new regimen for patients who have failed an antiretroviral regimen, careful consideration should be given to the treatment history of the individual patient and the patterns of mutations associated with different medicinal products. Where available, resistance testing may be appropriate."

#### Resistance to HIV drugs

It is estimated that in a single untreated person the virus can mutate to form around a billion new and potentially different versions of HIV every day. The incidence of drug resistant HIV among already treated patients is increasing at a disturbing rate. It was recently reported in one study that up to 50 percent of patients in North America are infected with a strain of the virus that has developed resistance to one or more anti-HIV drug.

#### Roche in HIV

Roche is at the forefront of efforts to combat HIV infection and AIDS, committed since 1986 to groundbreaking research and development of innovative new drugs and diagnostic technology. Saquinavir was the first Protease Inhibitor (PI) and was first introduced by Roche in 1995 in the US.

As a consequence of Roche's continuous research and development, the combination of boosted saquinavir with ritonavir (1000/100 mg twice daily) has shown encouraging results in the MaxCmin 1 trial with high efficacy and an excellent safety and tolerability profile. Saquinavir/r was approved in the EU in August 2002. Viracept (nelfinavir), a leading PI is supplied by Roche outside the US and Canada. In first-line HIV therapy, Viracept delivers consistent long-term efficacy and safety. When used first line, Viracept also allows the subsequent use of both NNRTIs and other PIs for most patients due to its unique resistance pattern. FUZEON received approval from the US Food and Drug Administration (FDA) in March 2003, and from the European Commission and Switzerland in May 2003. T-1249 is being co-developed by Roche and Trimeris.

The viral load measurements in the clinical trials for FUZEON were performed using the AMPLICOR HIV-1 MONITOR TEST, version 1.5. This test from Roche Diagnostics is considered to be a highly sensitive measurement of the amount of HIV circulating in a patient's blood ("viral load"). With a limited number of treatment regimens available, the accurate monitoring of viral load levels is essential to establish and monitor the effectiveness of therapeutic regimens and assess the potential onset of drug resistance.

Roche is a committed partner of the Accelerating Access Initiative to increase access to HIV care in sub-Saharan Africa and the world's Least Developed Countries. For more information on Roche policy and pricing of HIV protease inhibitors for these regions and research in HIV, visit [www.roche-hiv.com](http://www.roche-hiv.com).

#### About Roche

Headquartered in Basel, Switzerland, Roche is one of the world's leading innovation-driven healthcare groups. Its core businesses are pharmaceuticals and diagnostics. Roche is number one in the global diagnostics market and is the leading supplier of pharmaceuticals for cancer and a leader in virology and transplantation. As a supplier of products and services for the 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 employs roughly 62,000 people in 150 countries. The Group has alliances and research and development agreements with numerous partners, including majority ownership interests in Genentech and Chugai.

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#### About Trimeris

Trimeris, Inc. (Nasdaq: TRMS) is a biopharmaceutical company engaged in the discovery, development and commercialization of novel therapeutic agents for the treatment of viral disease. The core technology platform of fusion inhibition is based on blocking viral entry into host cells. FUZEON, recently approved in the U.S. and the European Union, is the first in a new class of anti-HIV drugs called fusion inhibitors. Trimeris' second fusion inhibitor product candidate, T-1249, has received fast track status from the FDA and is in Phase I/II clinical testing. Trimeris is developing FUZEON and T-1249 in collaboration with F. Hoffmann-La Roche Ltd. For more information about Trimeris, please visit the company's website at [www.trimeris.com](http://www.trimeris.com).

#### Trimeris Safe Harbor Statement

This document and any attachments may contain forward-looking information about the Company's financial results and business prospects that involve substantial risks and uncertainties. These statements can be identified by the fact that they use words such as "expect," "project," "anticipate," "intend," "plan," "believe" and other words and terms of similar meaning. Among the factors that could cause actual results to differ materially are the following: there is uncertainty regarding the success of research and development activities, regulatory authorisations and product commercialisations; the results of our previous clinical trials are not necessarily indicative of future clinical trials; and, our drug candidates are based upon novel technology, are difficult and expensive to manufacture and may cause unexpected side effects. For a detailed description of these factors, see Trimeris' Form 10-K filed with the Securities and Exchange Commission on March 27, 2003 and its periodic reports filed with the SEC.

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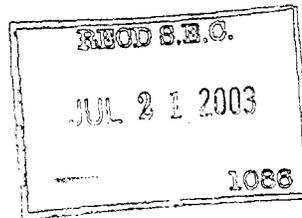
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## Media Release



Basel, 18. July, 2003

### **European Commission recognizes Roche's pivotal trial in new Pegasys label for Hepatitis C**

**Label changes set to benefit patients as it relates treatment recommendations to viral genotype**

Roche announced today that the European Commission has approved a new label for Pegasys (peginterferon alfa 2-a (40KD)) in Europe, as a result of Roche's pivotal study<sup>1</sup> that demonstrates that the duration of combination therapy and dose of Copegus (ribavirin) for chronic hepatitis C patients depends on viral genotype. This decision is set to benefit patients as they will only continue on therapy for as long as needed to obtain benefit, depending on genotype.

The EC recommends that patients infected with genotype 1 should receive 12 months of therapy with standard dose Copegus (ribavirin), while patients with genotype 2/3 only need 6 months of therapy and a lower dose of Copegus. The decision was based on the unanimous positive opinion adopted by the Committee for Proprietary Medicinal Products on 24 April 2003.

"We are pleased that the European Commission has approved the label to reflect this new and important data on how best to treat hepatitis C patients who are prescribed Pegasys and Copegus," said William M Burns, Head of Roche's Pharmaceutical Division. "It's not only a competitive label but one that provides benefits to patients."

Another change to the label is that Pegasys combination therapy no longer requires a patient to have a biopsy confirming the extent of liver disease prior to starting treatment. This is particularly helpful to patients. Pegasys combination treatment is also the only pegylated interferon hepatitis C treatment in Europe that is indicated for patients with compensated cirrhosis, an advanced stage of liver disease that can lead to liver cancer and the need for liver transplantation.

### **Excellent Treatment Outcomes**

The clinical results examined by the Committee demonstrate that Pegasys, when combined with Copegus, provides some of the highest sustained virological responses (SVR) ever seen in chronic hepatitis C. New SVR rates included in the label include several firsts.

- Overall, up to 63% of hepatitis C patients treated with Pegasys combination therapy achieve a SVR – the highest virological response rate included in a European label.
- For Pegasys patients infected with genotype 1, that is the most common yet one of the most difficult-to-treat genotypes, 52% of patients achieved a SVR – the highest response included in a label for a hepatitis C treatment in Europe.
- For Pegasys patients infected with the genotype 2/3 viruses, 80% of patients achieved a SVR when treated for 24 weeks and a low daily dose of 800 mg of Copegus.

Pegasys is the only pegylated interferon with which prospective research has been undertaken that provides for the customization of therapy according to genotype, and has had the data reviewed and accepted by regulatory authorities. In fact, this seminal research has now been reflected in the US NIH Consensus Conference on the Management of Hepatitis C and it is affirmation of the importance of genotype. A patient's genotype is the most important factor influencing the outcome of treatment.

### **Roche in Hepatitis**

Roche is committed to the viral hepatitis disease area, having first introduced Roferon-A for hepatitis B and then C, followed by Pegasys in hepatitis C. Pegasys is also in phase III clinical development for patients infected with the HBV virus. Roche manufactures and sells the Amplicor HCV Test (v2.0) and the Amplicor HCV Monitor Test (v2.0) - two tests used to detect and quantitate the amount of HCV RNA in a person's blood. The company's commitment to hepatitis is 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.

### **About Roche**

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and treatment of disease, the Group contributes on a broad range of fronts to improving people's health and quality of life. Roche employs roughly 62,000 people in 150 countries. The Group has alliances and research and development agreements with numerous partners, including majority ownership interests in Genentech and Chugai.

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**Notes to the editor:**

- Pegasys was first approved in European Union, just over one year ago, on June 20<sup>th</sup>, 2002.
- Pegasys and Copegus have now been approved in over 80 countries, with the latest approval in Australia in June, 2003.
- A SVR denotes that a patient has remained viral negative six months after completing therapy and is considered virus free or 'cured'.
- A biopsy is used to confirm the extent of liver damage (fibrosis).

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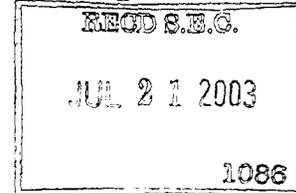
<sup>4</sup> Hadziyannis, S. et al. "Peginterferon Alfa-2A (40 KD) (PEGASYS) in Combination with Ribavirin ): Efficacy and Safety Results from a Phase III, Randomized, Double-Blind, Multicentre Study Examining Effect of Duration of Treatment and RBV Dose". EASL, 2002.

# Media Release



**Embargoed Until 2:00 pm Eastern Time, 8:00 pm CET,  
Thursday, July 17, 2003**

Basel, 17 July 2003



## **Roche Researchers Discover Potential New Treatment for Type 2 Diabetes Researchers Identify New Class of Drugs**

Tomorrow's issue of *Science* reports that researchers at Roche have discovered a new class of drugs which, in preclinical studies, increase the efficiency of an enzyme critical to maintaining the normal balance of glucose in the body. This discovery represents a potential new treatment for the more than 135 million people who are afflicted with type 2 diabetes worldwide.

Patients with type II diabetes have too little insulin and produce too much glucose. "The glucokinase (GK) enzyme is the body's first step in breaking down or metabolizing glucose," explained Joseph Grippo, Ph.D., Roche vice president, Metabolic Diseases. "When the enzyme is functioning normally, GK helps the body maintain glucose levels by controlling the release of insulin from the pancreas as well as the disposal of glucose in the liver."

Grippo and his team of scientists identified and developed a new class of drugs - called glucokinase activators (GKAs) - that increase the efficiency, or activate, this pivotal enzyme, and in doing so lowers blood sugar in preclinical models of type 2 diabetes.

He said the GKA compound is unique because it stimulates the pancreas to release more insulin and also keeps the liver from producing too much glucose. Currently many diabetic patients are given two medications to achieve this dual action: sulfonylureas and metformin. Both of these drugs were discovered over 25 years ago, and are still used as first-line anti-diabetes treatments.

"By being able to activate the GK enzyme, we may be able to provide a mechanism to improve both defects commonly found in type 2 diabetes, namely insulin release and hepatic [liver] glucose

metabolism," said Joseph Grimsby, Ph.D., Roche's preclinical GKA project leader and primary author of the *Science* article, *Allosteric Activators of Glucokinase: Potential Role in Diabetes Therapy*.

"Roche's discovery and preclinical findings support the important role GK plays as a glucose sensor and suggest that pharmacological activation of GK activity could have important clinical benefits in type 2 diabetes," added Franz Matschinsky, M.D., of the Department of Biochemistry and Diabetes Center, University of Pennsylvania School of Medicine, and editor-in-chief of *Diabetes*. He also contributed to the *Science* paper.

#### **Rationale**

Roche's interest in the GK enzyme followed a key discovery made in 1992 that showed a small subset of diabetes, known as maturity onset diabetes of the young type 2 (MODY2), is caused by mutations in the GK gene.

Preclinical findings provided strong biological rationale for considering GK as a target for drug discovery efforts. The Roche team screened 120,000 compounds and found one that seemed to activate GK. An important test with this early compound proved that GK activation works, giving the green light to move additional generations of GKA compounds through the Roche pipeline.

Even though there is much work ahead, confidence is strong that this new class of glucose activators could play an important role as hypoglycemic agents in the treatment of type 2 diabetes. Type 2 diabetes is such a huge unmet medical need. It is predicted that 300 million people will be diagnosed with this serious disease by 2025. "It is quite rare and very exciting to be involved in a drug with this kind of potential to dramatically impact the lives of patients," added Grimsby.

"The GK enzyme is pivotal as a key controller of glucose homeostasis (balance) in all people, so being able to activate this natural control point has enormous potential for all patients with type 2 diabetes," said Grippo.

#### **Roche Diabetes Care**

Roche has a strong commitment to diabetes care, with products and services that help people better manage their disease, including a leading weight loss medication indicated for obese. Along with its breakthrough pharmaceutical research with the new class of GKA drugs, Roche has several other anti-diabetes medications in clinical trials.

In addition, Roche Diagnostics is the global leader in diabetes care, and a pioneer in the development of blood glucose monitoring systems. With total annual sales of 2,511 million Swiss Francs and a growth rate of 14% in local currencies (2002), Roche Diabetes Care is the market leader in its segment. Its main products are the Accu-Chek™ family of blood glucose meters and test strips, including Accu-Chek Compact, Accu-Chek Advantage and Accu-Chek Active. For more information on Roche Diagnostics, visit their website - <http://www.roche-diagnostics.com/>

#### **Roche Innovation**

Roche's commitment to innovation, research and development has been its key to scientific and commercial success for more than a century. To ensure we maintain a level of innovation, the company currently has a very strong development portfolio, which includes both Roche discoveries and compounds from our many alliance deals. In fact, Roche led the pharmaceutical industry in this area in 2002. Roche's pipeline includes compounds to alleviate conditions such as arthritis, ovarian cancer, stress urinary incontinence, asthma, and depression, along with a host of other disease areas.

#### **About Roche**

Headquartered in Basel, Switzerland, Roche is one of the world's leading innovation-driven healthcare groups. Its core businesses are pharmaceuticals and diagnostics. Roche is number one in the global diagnostics market, the leading supplier of pharmaceuticals for cancer and a leader in virology and transplantation. As a supplier of products and services for the 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 employs roughly 62,000 people in 150 countries. The Group has alliances and R&D agreements with numerous partners, including majority ownership interests in Genentech and Chugai.

#### **Additional Information**

Influencing the body's regulatory mechanisms in order to treat type 2 diabetes

<http://www.roche.com/pages/downloads/science/pdf/rtdcinannh02.pdf>

Roche Health Kiosk:

[http://www.health-kiosk.ch/hkiosk/english/html/1/g\\_1\\_start.html](http://www.health-kiosk.ch/hkiosk/english/html/1/g_1_start.html)