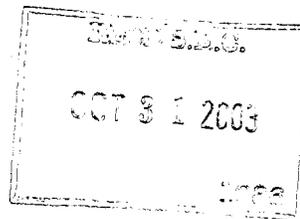


**Media Release****Roche**

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Basel, Switzerland – 28 October, 2003

**359 Patient, Phase II Clinical Study Results of MRA,  
A Beneficial Treatment for Adult Rheumatoid Arthritis**  
67<sup>th</sup> Annual Scientific Meeting of the American College of Rheumatology

**SUPPL**

Roche and Chugai Pharmaceutical Co., Ltd. (Chugai) announced today the results of a completed, large, double-blind, randomized Phase II clinical study with MRA, involving over 350 adult patients with rheumatoid arthritis (RA), which showed MRA to be a potentially effective treatment for adult RA. MRA is a humanized anti-interleukin-6 receptor antibody that inhibits the function of the cytokine interleukin-6 (IL-6). IL-6 is well recognized as playing a central role in the inflammatory response.

This large Phase II study was designed to evaluate the safety and efficacy of a range of doses of MRA given alone, and in combination with methotrexate (MTX) for the treatment of adult RA. Efficacy endpoints included Disease Activity Score (DAS) and the associated EULAR response, as well as the normalization of inflammatory markers such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) levels. A total of 359 patients with active RA, with an inadequate response to MTX, were randomized to one of seven treatment arms of intravenous infusions of MRA 8 mg/kg every 4 weeks either as monotherapy, or in combination with MTX, or MTX plus MRA placebo.

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MRA improved DAS scores and EULAR response in monotherapy and combination therapy with MTX. Efficacy was achieved at 8 mg/kg. Efficacy was also seen with 4 mg/kg doses, in combination with MTX. In addition, MRA induced favorable, dose-related changes in mean clinical and laboratory values reflective of disease improvement - both CRP and ESR. These levels became normal in both 8 mg/kg monotherapy and in 8 mg/kg combination therapy.

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MRA was well tolerated as both a mono and combination therapy and the safety profile was consistent with that expected for other biologics. To date, over 500 adult RA patients have been treated with MRA in both Europe and Japan.

Professor Sir Ravinder Maini of The Kennedy Institute of Rheumatology, London stated, "The targeted blockade of the IL-6 signal represents an additional and potentially effective treatment option for adult RA, and the results of this large Phase II clinical study demonstrate the control of signs and symptoms and inflammation and safety profile of MRA in this disease. However, more studies need to be conducted before further conclusions can be drawn."

#### **About MRA**

MRA is a humanized anti-IL-6 receptor monoclonal antibody whose novel mechanism of action may provide a new and effective form of treatment for adult RA. Phase II studies have been completed in Japan and Europe. Phase III clinical development in RA has been initiated in Japan and is under preparation in Europe and the USA. A Phase II study with MRA in systemic onset juvenile idiopathic arthritis (So-JIA) is also ongoing in Europe.

Roche and Chugai are developing MRA in collaboration with Osaka University. This co-development partnership was set up under the first licensing agreement between the two companies in 2003, where Roche will promote in all countries except Japan, South Korea and Taiwan, and the parties will co-promote in the UK, France and Germany. Other indications, such as Castleman's disease, Crohn's disease, juvenile idiopathic arthritis, and multiple myeloma, are also in clinical development.

#### **About Rheumatoid Arthritis**

RA is an autoimmune disorder of unknown cause, characterized by symmetric joint inflammation with erosive synovitis, and in some cases extra-articular involvement. Most patients experience a chronic fluctuating course of disease with joint swelling and pain that, despite therapy, may result in progressive joint destruction and ultimately lead to loss of function of joints. RA affects almost six million people around the world.

#### **Roche Business Development and Alliance Strategy**

Roche is a distinctive alliance partner with expertise in identifying cutting-edge innovation that can lead to new and improved medicines. During the past 18 months, Roche has formed over 45 new partnerships which span a wide range of therapeutic areas and technologies, making it an industry leader. Through its alliance strategy, Roche creates value with its partners by transforming these business transactions into productive relationships. A key element of Roche's strategy is to enable

its partners to achieve their vision while maintaining their cultural identity and entrepreneurial spirit.

#### **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 65,000 people in 150 countries. The Group has alliances and R&D agreements with numerous partners, including majority ownership interests in Genentech and Chugai.

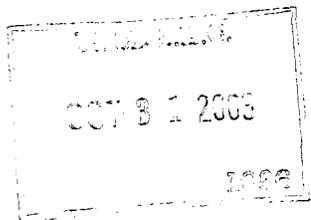
#### **About Chugai**

Chugai Pharmaceutical Co., Ltd. is one of Japan's leading research-based pharmaceutical companies with strengths in biotechnology products and in the therapeutic fields of oncology, renal diseases, cardiovascular diseases, bone/joint diseases and transplantation/infection/immunity. With pharmaceutical sales of 237 billion yen in 2002, Chugai has invested in research and development capabilities in the US and Europe, and has established sales and marketing operations in France, Germany and the UK. Chugai employs 5,867 employees worldwide.

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# Media Release



Basel, 28 October 2003

## **Pegasys found superior to current hepatitis B treatments**

**New study shows Pegasys more effective than lamivudine in most difficult-to-treat form of Hepatitis B disease**

In patients infected with the most difficult-to-treat hepatitis B virus (HBeAg negative or 'variant' HBV), Pegasys is more effective than lamivudine and the addition of lamivudine to Pegasys does not provide additional efficacy, according to results presented at a conference\* today.

This Phase III study, conducted in 13 countries, is the largest multinational study of pegylated interferon in patients with 'variant' hepatitis B virus and it is the first large-scale head-to-head study to compare Roche's pegylated interferon against lamivudine. Lamivudine is the most commonly used therapy for infections with the hepatitis B virus.

"With Pegasys, we have for the first time a hepatitis B therapy which can produce a high sustained treatment response, and this is extremely encouraging to physicians looking for treatment solutions," said Professor Patrick Marcellin, Hepatologist from the Hôpital Beaujon, Clichy, France and the lead investigator for the study. "What is also important is that with Pegasys we have a defined treatment period, which is what most patients want."

"These are highly encouraging results for physicians and patients in the fight against this serious liver infection," said William M. Burns, Head of the Pharmaceutical Division at Roche. "Based on these extremely positive results, we plan to file Pegasys in hepatitis B with health authorities next year."

### **About the study**

The 537 patients enrolled in the study, all of whom had HBeAg negative HBV and raised blood levels of ALT, a specific liver enzyme serving as a marker for liver inflammation, were treated for 48 weeks with either Pegasys 180 µg once weekly plus placebo, lamivudine 100 mg once daily or a combination of the two. They were then observed for a further 24 weeks with no treatment. The treatment was considered effective if ALT levels fell to normal and viral DNA levels, a measure for the concentration of virus in the bloodstream, were reduced below 20,000 copies/ml at the end of the follow-up period.

### **Viral load and ALT levels significantly impacted**

At the end of the follow-up period, the study found for the two primary endpoints that:

- 42.9% of patients treated with Pegasys monotherapy reduced their hepatitis B viral DNA to less than 20,000 copies per/ml compared to only 29.3% of those treated with lamivudine. This result is statistically highly significant. The combination of Pegasys and lamivudine yielded a reduction in hepatitis B viral DNA in 44.1% of patients, demonstrating that the addition of lamivudine to Pegasys does not improve the treatment outcome.
- In addition Pegasys had a better impact on ALT than lamivudine: 59.3 per cent of patients treated with Pegasys had their elevated ALT levels return to normal; compared to only 44.2% of lamivudine-treated patients. The combination of Pegasys and lamivudine (59.8%) was not statistically different to Pegasys alone.

### **Patients typically relaps after treatment is stopped**

HBeAg negative HBV, also known as 'variant' or 'pre-core mutant' hepatitis B, is caused by a genetic mutation to the virus. Patients infected with the HBeAg negative HBV are more likely to have severe destructive inflammatory changes to their liver and fibrosis when they first see their physician than those infected with the HBeAg positive disease. Patients typically relapse after treatment is stopped. HBeAg negative HBV accounts for approximately 40 per cent of cases in the US and over 80 per cent of cases in Southern Europe.

"We have shown previously that Pegasys is an effective treatment for the more common HBeAg-positive strain of HBV," said Professor Graham Cooksley, Senior Principal Research Fellow, Clinical Research Centre, Royal Brisbane Hospital, Australia. "These results mean we can now also use Pegasys with confidence to treat patients with the more challenging HBeAg negative strain of the disease."

### **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 among the top four causes of cancer deaths in most countries in Asia and the Western Pacific rim.<sup>4</sup> 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 180 mcg of pegylated interferon alfa-2a which is the approved dose for all patients, regardless of body weight.

### **Roche in hepatitis**

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 also demonstrates superior efficacy over current treatments: conventional interferon and lamivudine 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.

## 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 65,000 people in 150 countries. The Group has alliances and R&D agreements with numerous partners, including majority ownership interests in Genentech and Chugai.

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\* 54th American Association for the Study of Liver Diseases (AASLD) Annual Meeting

## NOTES TO THE EDITOR:

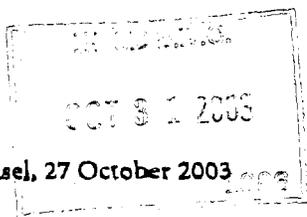
- New guidelines on HBV were recently developed by the European Association for the Study of Liver (EASL).<sup>iii</sup> Conventional interferon monotherapy was recommended as the first therapeutic approach when treating these patients. The EASL Jury noted however, that the optimal treatment of hepatitis B will require regular revision in light of new data.

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<sup>i</sup> 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;10:298-305

<sup>ii</sup> Chu, CM. Natural History of Chronic Hepatitis B Virus Infection in Adults with Emphasis on the Occurrence of Cirrhosis and Hepatocellular carcinoma. *J Gastroenterol. Hepatol*. 2000;15 (suppl.):E25-30.

<sup>iii</sup> EASL International Consensus Conference on Hepatitis B. 13-14 September, 2002: Geneva, Switzerland. Consensus statement (short version). *J Hepatol*, 2003.38:533-40.



Basel, 27 October 2003

## **Phase II clinical study of MRA shows significant clinical benefit to children with systemic-onset Juvenile Idiopathic Arthritis**

**67<sup>th</sup> Annual Scientific Meeting of the American College of Rheumatology**

F. Hoffmann-La Roche (Roche) and Chugai Pharmaceutical Co., Ltd. (Chugai) announced today new Phase II data which indicate that treatment with MRA provides significant clinical benefit to children suffering from systemic-onset juvenile idiopathic arthritis (So-JIA). MRA is a humanized anti-interleukin-6 receptor antibody that inhibits the function of the cytokine interleukin-6 (IL-6). IL-6 is well recognized as playing a central role in the disease process of So-JIA.

This open, early Phase II dose-escalation clinical trial was designed to investigate the safety and efficacy of MRA in 11 children with active So-JIA. All the children were administered an initial intravenous dose of 2 mg/kg of MRA, followed by increased doses up to 8mg/kg depending on their levels of C-reactive protein (CRP), a marker of the disease activity.

MRA rapidly reduced the disease activity of So-JIA in 10 of 11 children. A 70% reduction of disease activity, as defined by a standard set of criteria, was achieved in 1 out of 3 children receiving 3 doses of 2mg/kg, in 3 out of 5 receiving 4mg/kg, and in all 3 children receiving 8mg/kg. The analysis of this data demonstrated a rapid improvement of clinical manifestations such as fever, rash, arthritis, and fatigue.

No children withdrew from the trial because of disease flare or adverse events.

These preliminary Phase II data show that MRA achieves a marked improvement of symptoms in children with active So-JIA and a normalization of acute phase reactants such as CRP as markers of inflammation. However, additional large-scale clinical trials need to be conducted before further

conclusions can be drawn.

#### **About MRA**

MRA is a humanized anti-IL-6 receptor monoclonal antibody whose novel mechanism of action may provide a new and effective form of treatment also for adult RA. Phase II studies have been completed in Japan and Europe. Phase III clinical development in RA has been initiated in Japan and is under preparation in Europe and the USA. An early Phase II study with MRA in systemic onset juvenile idiopathic arthritis (So-JIA) is also ongoing in Europe.

Roche and Chugai are developing MRA in collaboration with Osaka University. This co-development partnership was set up under the first licensing agreement between the two companies in 2003, where Roche was granted the right to promote in all countries except Japan, South Korea and Taiwan, and the parties would co-promote in the UK, France and Germany. Other indications, such as Castleman's disease, Crohn's disease, and multiple myeloma are also in clinical development.

#### **About Juvenile Idiopathic Arthritis**

Systemic-onset juvenile idiopathic arthritis (So-JIA) is a severe, steroid-dependent disorder, sometimes progressing to a fatal disease. Elevated serum IL-6 may play an important role in the clinical signs and symptoms of this disease. Approximately 20% of patients with juvenile rheumatoid arthritis suffer from So-JIA.

#### **Roche Business Development and Alliance Strategy**

Roche's innovation strategy is based on strong in-house research with centres in Japan, Europe and the USA and strategic alliances with Genentech and Chugai. Complementing and strengthening the Group's dynamic R&D capabilities are over 80 scientific and commercial collaborations with biotech companies and universities in clearly defined focus areas. In the past 18 months, Roche has formed over 45 new partnerships, which span a wide range of therapeutic areas and technologies, making it an industry leader. A key element of this strategy is to enable its partners to achieve their vision while maintaining their cultural identity and entrepreneurial spirit.

#### **About Roche**

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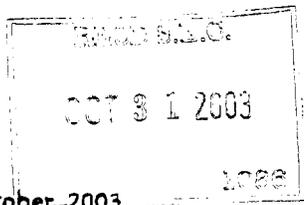
prevention, diagnosis and treatment of disease, Roche contributes on a broad range of fronts to improving people's health and quality of life. Roche employs roughly 62,000 people in 150 countries. Roche has alliances and research and development agreements with numerous partners, including majority ownership interests in Genentech and Chugai. For more information, access our website at [www.roche.com](http://www.roche.com).

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Basel, 27 October 2003

## Long-term data shows MabThera to be a highly promising treatment for Rheumatoid Arthritis (RA)

Extended data from phase II study shows RA patients continue to respond to MabThera for up to 48 weeks

Roche, Genentech and IDEC Pharmaceuticals Inc. today announced positive results from an extended Phase II study showing that a single, short course of treatment (two doses) with MabThera (rituximab) significantly improved symptoms in patients with severe rheumatoid arthritis (RA) for up to 48 weeks\*. In the study, investigators followed up with patients who had completed a 24-week clinical trial, in order to assess duration of response with MabThera beyond the initial endpoint of 24 weeks. Participants in the 24 week, four arm, placebo controlled trial were randomized to receive MabThera alone or in combination with cyclophosphamide or methotrexate (MTX), as compared to patients receiving MTX alone.

At 48 weeks, patients receiving the combination of MabThera and MTX had the greatest improvement in symptoms:

- 65% of patients showed at least a 20% improvement in symptoms
- 35% showed at least a 50% improvement
- 15% showed at least a 70% improvement.

"These data indicate that selectively targeting B cells is a promising and innovative potential therapeutic approach for the treatment of rheumatoid arthritis," said Professor Paul Emery, Leeds General Infirmary, UK, one of the trial's key investigators. "With just two doses of MabThera, patients continued to respond to treatment for up to 48 weeks."

### About the Study

The study included 161 patients with active, long-standing RA (mean 10.4 years) who had not responded or responded inadequately to multiple other therapies. Patients were randomized into one of four treatment groups. The first group continued receiving methotrexate (MTX) alone ( $\geq 10$  mg weekly), the second group received MabThera alone (2 infusions of 1g), the third group received MabThera (2 infusions of 1g) in combination with cyclophosphamide (2 infusions of 750 mg) and the fourth group received MabThera (2 infusions of 1g) in combination with MTX ( $\geq 10$  mg weekly). Each group also received a 17-day course of corticosteroids (total dose of 960 mg). MabThera was infused intravenously on days one and 15 of the study – no further treatment with MabThera was given.

Results from the other three arms of the study include:

- MTX alone: 20% of patients experienced a 20% improvement in symptoms and 5% experienced 50% improvement; none experienced 70% improvement
- MabThera alone: 30% experienced 20% improvement, 13% experienced 50% improvement and 8% experienced 70% improvement
- MabThera and cyclophosphamide: 44% experienced 20% improvement, 22% experienced 50% improvement and 10% experienced 70% improvement

According to the investigators, the study's safety profile indicates that all three MabThera regimens were well tolerated with similar levels and type of adverse events compared to MTX alone. A large proportion of events were reported during the initial 15 days, with many associated with the first MabThera infusion. The majority of events were of mild to moderate in intensity. At week 48, the incidence and types of events, including infections, were evenly balanced between all groups.

### Ongoing Studies

Based on these exciting phase II results, Roche has initiated pivotal trials evaluating MabThera in the treatment of RA, including a phase III study for patients who have had an inadequate response to anti-TNF therapies (REFLEX) and a phase IIb study for patients who have had an inadequate response to DMARDs (DANCER) Both of these trials are currently enrolling patients.

### About MabThera

MabThera (rituximab) is a therapeutic antibody that selectively targets B cells, which are thought to play a key role in the inflammatory cascade of RA – a series of reactions inflaming the synovia and leading to the cartilage loss and bone erosion that is characteristic of the disease.

MabThera is currently indicated for use in the treatment of the most common form of blood cancer, non-Hodgkin's lymphoma (NHL) and marketed by Roche and Genentech, and was developed by IDEC and Genentech. MabThera/ Rituxan is marketed in Europe as MabThera and in the US, Canada and Japan as Rituxan. Approx. 300,000 patients have received MabThera to date.

#### About rheumatoid arthritis

RA affects almost 6 million people around the world, up to 2 million of which are in Europe, and is a debilitating disease that hinders the daily activities of sufferers. RA is characterized by inflammation of multiple joints, cartilage loss and bone erosion, which leads to joint destruction and ultimately reduced joint function. Additionally, since RA is a systematic disease, it can have effects in other tissues, such as lungs, eyes and bone marrow. After ten years of RA, fewer than 50% of patients can continue to work or function normally on a day to day basis.

#### About Roche

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#### About Genentech

Genentech is a leading biotechnology company that discovers, develops, manufactures and commercializes biotherapeutics for significant unmet medical needs. Fifteen of the currently approved biotechnology products originated from or are based on Genentech science. Genentech manufactures and commercializes ten biotechnology products in the United States. The company has headquarters in South San Francisco, California and is traded on the New York Stock Exchange under the symbol DNA. For press releases and additional information about the company, please visit <http://www.gene.com>.

### **About IDEC**

IDEC Pharmaceuticals focuses on the commercialization and development of targeted therapies for the treatment of cancer and autoimmune diseases. IDEC's antibody products act chiefly through immune system mechanisms, exerting their effect by binding to specific, readily targeted immune cells in the patient's blood or lymphatic systems. IDEC is headquartered in San Diego, California, and is traded on the NASDAQ National Market System under the stock symbol, IDPH.

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\* The study was presented during an oral session at the annual scientific meeting of the American College of Rheumatology (ACR) Meeting, October 24-28.