

Basel, 13 June 2008

New data reveals Actemra is the first and only biologic drug to show superiority over current standard of care in rheumatoid arthritis

Two new international studies also show high remission rates in patients treated with Actemra

Basel 13 June 2008: The novel rheumatoid arthritis drug Actemra (tocilizumab) has shown superiority over the current standard of care, methotrexate (MTX), by achieving a greater reduction of signs and symptoms (e.g. swollen and tender joints) at 6 months in patients suffering from rheumatoid arthritis.¹ This positive outcome makes Actemra the first and only biologic therapy to have achieved superiority over MTX.

Furthermore, nearly three times as many patients treated with Actemra achieved disease remission (as defined by the globally recognised measure DAS28 <2.6),² the ultimate goal of treatment in this currently incurable condition.¹ The outcome is significant as RA is a debilitating long-term disease and current medicines give little hope of remission or cure – as such new treatment options are urgently needed.

William M. Burns, CEO of Roche's Pharma Division said: "The latest study data are encouraging news for patients suffering from the devastating effects of rheumatoid arthritis. As the first and only biologic treatment to demonstrate superiority to the current standard of care in early treatment for RA, we believe Actemra will offer more patients relief from their debilitating symptoms. Additionally, Actemra provides patients with a better chance for an early and durable remission."

The AMBITION study data, presented today at the European League Against Rheumatism (EULAR) congress, was designed to evaluate the efficacy and safety of Actemra (8 mg/kg) compared to MTX in patients with active RA disease. The study showed that significantly more patients receiving Actemra achieved a 20% improvement³ in their symptoms (ACR20: 70% vs. 53%) after 24 weeks of treatment.¹ No previous biologic therapy has demonstrated superiority compared to MTX in this important clinical parameter at Week 24. In addition, nearly three times as many patients taking Actemra as monotherapy achieved remission compared to those taking MTX (34% vs. 12%).¹ Notably, the patients in AMBITION had a shorter disease duration than in prior studies with Actemra. The majority of patients had not received previous therapy with MTX

and many had not been treated with any disease-modifying anti-rheumatic drugs (DMARDs).¹

“We are very encouraged by the results of the AMBITION study that shows for the first time that treatment with a single biologic agent is superior to methotrexate at six months of therapy,” said Graeme Jones, M.D., lead investigator of the AMBITION trial and Professor at the University of Tasmania in Hobart, Australia. “Overall, these compelling results further establish the efficacy and safety of Actemra in treating the chronic signs and symptoms of rheumatoid arthritis that dramatically affect the lives of patients.”

RADIATE Study Shows Actemra Effective in Difficult-to-Treat-Patients

Data from a second Actemra study, the RADIATE trial, also presented in Paris and published online this week in the *Annals of Rheumatic Diseases*, revealed that Actemra is also effective in difficult-to-treat patients who have had an inadequate response to a commonly used class of RA drugs known as anti-TNFs (anti-tumour necrosis factor therapy).⁴ Thirty percent of patients treated with Actemra in combination with MTX achieved disease remission (DAS28 <2.6) compared with 1.6% of patients who were treated with MTX alone.⁴ The study also showed that significantly more patients on Actemra achieved a reduction in their signs and symptoms following 24 weeks of treatment (ACR20: 50% vs. 10%).⁴ What made this result so remarkable was the fact that 12-18% of the study population had failed to respond to three or more prior anti-TNF therapies,⁴ leaving them with little hope of further symptom relief from these traditional treatments.

Presenting the data, Professor Paul Emery, arc Professor of Rheumatology, University of Leeds, and Principal Investigator, said, “These study results are very promising for RA patients who need a variety of treatment options, particularly when they have failed to achieve adequate pain and symptom relief with anti-TNF therapies.”

Consistent Remission Data

The remission data from both AMBITION and RADIATE studies are consistent with the results seen in previous studies in that nearly one third of patients achieved remission regardless of disease duration or previous treatment.⁵ More than 4,000 RA patients in 41 countries, including Europe and the US, have been enrolled in the clinical trial programme for Actemra, one of the largest phase III clinical trial programmes ever undertaken for a biologic therapy.

About the AMBITION Study

The Phase III AMBITION (Actemra versus Methotrexate double-Blind Investigative Trial In mONotherapy)

trial was a two-arm, randomized, double-blind, placebo-controlled study in 673 patients designed to evaluate the efficacy and safety of Actemra (8 mg/kg) compared to MTX in patients with active moderate to severe RA, including a high proportion of patients with early disease. The primary endpoint was non-inferiority followed by superiority of Actemra in ACR20 response at week 24 compared to MTX. The trial took place in 252 sites across 18 countries.

In the AMBITION study, 70%, 44% and 28% of patients in the ACTEMRA (8 mg/kg) monotherapy arm achieved ACR20, ACR50 and ACR70 compared, respectively, with 53%, 34% and 15%, respectively, of patients treated with MTX alone.¹ Disease remission (DAS28 <2.6) was demonstrated in 34% of Actemra patients compared with 12% of patients in the control group.¹

About the RADIATE study

The Phase III RADIATE (Research on Actemra Determining efficacy after Anti-TNF FailurEs) study was a three-arm, randomised, double-blind, placebo-controlled study of the safety and reduction of signs and symptoms during treatment with Actemra (8mg/kg or 4mg/kg) in combination with MTX, in patients with moderate to severe active RA who had an inadequate response to at least one anti-TNF therapy. Traditionally this patient group have more refractory disease and prove more difficult to treat. The study involved treating 499 patients randomised across three treatment groups and was conducted at 128 trial sites in 13 countries. Each group of patients either received 8mg/kg or 4mg/kg Actemra, or placebo in addition to 10-25mg MTX weekly.

In the RADIATE study, 50%, 29% and 12% of RA patients treated with ACTEMRA (8 mg/kg) plus MTX achieved ACR20, ACR50 and ACR70, respectively, compared with 10%, 4% and 1%, respectively, of patients treated with placebo infusions plus MTX weekly.⁴ Treatment with Actemra and MTX showed significant clinical benefits even in patients who received three anti-TNFs therapies that failed. Furthermore, disease remission (DAS28 <2.6) was demonstrated in 30% of Actemra patients compared with 1.6% of patients in the control group.⁴

About Actemra

Actemra is the result of research collaboration by Chugai and is being co-developed globally with Chugai. Actemra is the first humanized interleukin-6 (IL-6) receptor-inhibiting monoclonal antibody. An extensive clinical development program of five Phase III trials was designed to evaluate clinical findings of Actemra. The five studies have reported meeting their primary endpoints. Actemra is awaiting approval in the United

States and Europe. In Japan, Actemra was launched by Chugai in June 2005 as a therapy for Castleman's disease; in April 2008, additional indications for rheumatoid arthritis, polyarticular-course juvenile idiopathic arthritis and systemic-onset juvenile idiopathic arthritis were also approved in Japan.

Actemra is generally well tolerated. The overall safety profile of Actemra is consistent across all global clinical studies. The most common, non-serious, adverse events reported are upper respiratory tract infection, nasopharyngitis, headache and hypertension. As with other biological disease modifying anti-rheumatic drugs (DMARDs), serious infections and hypersensitivity reactions including a few cases of anaphylaxis, have been reported in some patients treated with Actemra. Increases in liver transaminases (ALT and AST) were seen in some patients; these increases were generally mild and reversible, with no hepatic injuries or any observed impact on liver function.

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 the world's biggest biotech company and an innovator of products and services for the early detection, prevention, diagnosis and treatment of diseases, the Group contributes on a broad range of fronts to improving people's health and quality of life. Roche is the world leader in in-vitro diagnostics and drugs for cancer and transplantation, and is a market leader in virology. It is also active in other major therapeutic areas such as autoimmune diseases, inflammatory and metabolic disorders and diseases of the central nervous system. In 2007 sales by the Pharmaceuticals Division totalled 36.8 billion Swiss francs, and the Diagnostics Division posted sales of 9.3 billion francs. Roche has R&D agreements and strategic alliances with numerous partners, including majority ownership interests in Genentech and Chugai, and invested over 8 billion Swiss francs in R&D in 2007. Worldwide, the Group employs about 79,000 people. Additional information is available on the Internet at www.roche.com.

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References

¹ Jones, G. *et al.* Tocilizumab monotherapy is superior to methotrexate monotherapy in reducing disease activity in patients with rheumatoid arthritis: The AMBITION study. Presented at EULAR, 13 June 2008.

² The Disease Activity Score (DAS28) is a combined index that measures disease activity in patients with RA. It combines information from 28 tender and swollen joints (range 0-28), erythrocyte sedimentation rate, and a general health assessment on a visual analog scale. The level of disease activity is interpreted as low ($DAS28 \leq 3.2$), moderate ($3.2 < DAS28 \leq 5.1$) or high ($DAS28 > 5.1$). $DAS28 < 2.6$ corresponds to being in remission according to the criteria of the American Rheumatism Association (ARA).

³ The ACR response is a standard assessment used to measure patients' responses to anti-rheumatic therapies, devised by the American College of Rheumatology (ACR). It requires a patient to have a defined percentage reduction in a number of symptoms and measures of their disease. For example, a 20, 50, or 70% level of reduction (the percentage of reduction of RA symptoms) is represented as ACR20, ACR50 or ACR70. An ACR70 response is exceptional for existing treatments and represents a significant improvement in a patient's condition.

⁴ Emery, P. *et al.* Tocilizumab significantly improves disease outcomes in patients with rheumatoid arthritis whose anti-TNF therapy failed: The RADIATE study. Presented at EULAR, 13 June 2008.

⁵ Disease remission ($DAS28 < 2.6$) was achieved in one in three patients treated with ACTEMRA plus DMARDS in the TOWARD (Tocilizumab in cOmbination With traditional DMARD therapy) trial presented at the ACR 2007; similar results were also seen in the OPTION (TOcilizumab Pivotal Trial in Methotrexate Inadequate respONDers) study published under Smolen, J. Effect of interleukin-6 receptor inhibition with tocilizumab in patients with rheumatoid arthritis (OPTION study): a double-blind, placebo-controlled, randomised trial, *The Lancet*; Volume 371, Issue 9617, Pgs 998-1006.