Translation

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RoACTEMRA®, a Humanized Anti-Human IL-6 Receptor Monoclonal Antibody, Approved in EU for Rheumatoid Arthritis

January 21, 2009 (Tokyo) - Chugai Pharmaceutical Co., Ltd. [Head Office: Chuo-ku, Tokyo; President Osamu Nagayama (hereafter, "Chugai")] and F. Hoffmann-La Roche Ltd. [Head Office: Basel, Switzerland. CEO: Severin Schwan (hereafter "Roche")] today announced that RoACTEMRA®, the humanized anti-human IL-6 (interleukin-6) receptor monoclonal antibody, filed with the European Medicines Evaluation Agency (EMEA) in November 2007, received approval as a treatment to improve symptoms of rheumatoid arthritis (RA).

Based on the co-development and co-promotion agreement between Chugai and Roche, Chugai will co-promote RoACTEMRA® in U.K., France and Germany, where its wholly-owned subsidiary Chugai Pharma Marketing Ltd. (Head Office: London, U.K./CEO: Alain Clergeot) has its marketing bases.

The main symptoms of RA are multiple joint inflammation and progressive joint damage, and it is reported that millions of patients suffer from RA in EU. RoACTEMRA®, the first antibody drug (humanized monoclonal antibody) originating from Japan, was created by Chugai in collaboration with Osaka University, utilizing genetic recombinant technology to produce a monoclonal antibody against the anti-IL6 receptor. It works by inhibiting biological activity of IL-6 through competitively blocking the binding of IL-6 to its receptor.

Outside of Japan, five phase III clinical trials, including extension studies in RA are going on in 40 countries involving more than 4,000 patients worldwide under co-development between Chugai and Roche. The approval was based on results and extension studies from four out of five of these trials, and the interim analysis of the remaining ongoing trial.

In Japan, 200mg preparation of Actemra® was launched in June 2005 by Chugai for Castleman's disease, following approval in April, the same year. Subsequently, it was approved for the additional indications of RA (including prevention of structural damage of joints), polyarticular-course juvenile idiopathic arthritis and systemic juvenile idiopathic arthritis in April 2008. 80mg and 400mg preparations were launched additionally in June 2008.

Chugai focuses on bone and joint diseases area as one of the strategic domains, and is committed to contribute to the treatment by providing new therapeutic options for medical professionals and patients.

The approval in the EU follows earlier approvals for the product in several countries, including Switzerland and India.

[Reference]

- **EMEA approved indication**: RoACTEMRA, in combination with methotrexate (MTX), is indicated for the treatment of adult patients with moderate to severe RA who have either responded inadequately to, or who were intolerant to, previous therapy with one or more disease modifying anti-rheumatic drugs (DMARDs) or tumour necrosis factor (TNF) antagonists. In these patients, RoACTEMRA can be given as monotherapy in cases of intolerance to methotrexate (MTX) or where continued treatment with MTX is inappropriate.

- **Outline of five phase III clinical trials**

1. OPTION Study

Objective: To investigate Actemra's efficacy and safety for rheumatoid arthritis patients with inadequate response to methotrexate (MTX) treatment.

Method: This is a double-blinded trial evaluating 623 patients with moderate to severe active rheumatoid arthritis despite long term treatment with methotrexate (MTX). Patients were allocated to receive Actemra 4mg/kg, Actemra 8mg/kg, or placebo every four weeks (intravenous infusion), in combination with weekly MTX.

Results: ACR response rates were used to determine the anti-rheumatic efficacy, and at the end of the 24 weeks (or at the last observation), Actemra group achieved statistically significantly higher response rates versus placebo.

	Actemra 8mg/kg + MTX (p value)	Actemra 4mg/kg + MTX (p value)	Placebo + MTX
Number of patients	205	213	204
ACR 20% response	58.5 (p<0.0001)	47.9 (p<0.0001)	26.5
ACR 50% response	43.9 (p<0.0001)	31.5 (p<0.0001)	10.8
ACR 70% response	22.0 (p<0.0001)	12.2 (p<0.0001)	2.0

2. TOWARD Study

Objective: To investigate Actemra's efficacy and safety for rheumatoid arthritis patients with inadequate response to DMARDs treatment.

Method: This is a double-blinded trial evaluating 1,216 patients with moderate to severe active rheumatoid arthritis despite treatment with DMARDs. Patients were allocated to receive Actemra 8mg/kg, or placebo every four weeks (intravenous infusion), in combination with traditional DMARDs.

Results: ACR response rates were used to determine the anti-rheumatic efficacy, and at the end of the 24 weeks (or at the last observation), Actemra group achieved statistically significantly higher response rates versus placebo.

	Actemra 8mg/kg + MTX	Placebo + MTX	p value
Number of patients	803	413	
ACR 20% response	60.8	24.5	p<0.0001
ACR 50% response	37.6	9.0	p<0.0001
ACR 70% response	20.5	2.9	p<0.0001

3. RADIATE Study

Objective: To investigate Actemra's efficacy and safety for rheumatoid arthritis patients with inadequate response to an anti-tumor necrosis factor (anti-TNF) agent.

Method: This is a double-blinded trial evaluating 498 patients with moderate to severe active rheumatoid arthritis despite treatment with anti-TNF agent. Patients were allocated to receive Actemra 4mg/kg, Actemra 8mg/kg, or placebo every four weeks (intravenous infusion), in combination with weekly MTX.

Results: ACR response rates were used to determine the anti-rheumatic efficacy, and at the end of the 24 weeks (or at the last observation), Actemra group achieved statistically significantly higher response rates versus placebo.

	Actemra 8mg/kg + MTX (p value)	Actemra 4mg/kg + MTX (p value)	Placebo +MTX
Number of patients	170	161	158
ACR 20% response	50.0 (p<0.0001)	30.4 (p<0.0001)	10.1
ACR 50% response	28.8 (p<0.0001)	16.8 (p<0.0001)	3.8
ACR 70% response	12.4 (p=0.0002)	5.0 (p=0.1005)	1.3

4. AMBITION Study

Objective: To investigate efficacy and safety of Actemra monotherapy versus methotrexate in rheumatoid arthritis patients.

Method: This is a double-blinded trial evaluating 673 patients with moderate to severe active rheumatoid arthritis. Patients were allocated to receive Actemra 8mg/kg every four weeks (intravenous infusion) plus weekly MTX placebo, or Actemra placebo very four weeks plus weekly MTX.

Results: ACR response rates were used to determine the anti-rheumatic efficacy, and at the end of the 24 weeks (or at the last observation), Actemra monotherapy group achieved non-inferiority followed by statistically significantly higher response rates versus placebo.

	Actemra 8mg/kg	MTX	p value
Number of patients	286	284	
ACR 20% response	70	53	p<0.0001
ACR 50% response	44	34	p=0.0023
ACR 70% response	28	15	p=0.0002

5. LITHE Study

Objective: To investigate Actemra's efficacy with respect to prevention of joint damage, and safety for rheumatoid arthritis patients with inadequate response to methotrexate (MTX) treatment.

Method: This is a double-blinded trial evaluating 1,170 patients with moderate to severe active rheumatoid arthritis despite treatment with methotrexate (MTX). Patients were allocated to receive Actemra 4mg/kg, Actemra 8mg/kg, or placebo every four weeks (intravenous infusion), in combination with weekly MTX.

1-year result: Changes from baseline in Genant-modified Sharp score and the area under the curve (AUC) in the Health Assessment Questionnaire Disability Index (HAQ-DI) at week 52 were observed. Also, ACR response rates were used to determine the anti-rheumatic efficacy.

Mean joint erosion, joint space narrowing and total Genant-modified sharp scores showed significant inhibition of radiographic progression from baseline and mean change from baseline in HAQ-DI significantly decreased in Actemra groups compared with control. Also, ACR response rates in the Actemra groups were statistically higher than those in the control arm.

* LITHE study is ongoing, while the 1-year analysis was included in the submission data.

- **Safety profile**

The overall safety profile observed in the global studies of Actemra is consistent and Actemra is generally well tolerated. The serious adverse events reported in ACTEMRA global clinical studies included serious infections and hypersensitivity reactions including a few cases of anaphylaxis. The most common adverse events reported in clinical studies were upper respiratory tract infection, nasopharyngitis, headache, hypertension and transient increases in liver function tests (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.