

## Translation

Data from Overseas Phase III Trial (RADIATE and AMBITION)  
Demonstrates Efficacy of "Actemra<sup>®</sup>,"  
a Humanized Anti-Human IL-6 Receptor Monoclonal Antibody,  
in Rheumatoid Arthritis Patients

June 16, 2008 (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")] announced today that the humanized anti-human IL-6 (interleukin-6) receptor monoclonal antibody, Actemra<sup>®</sup> (generic name: tocilizumab -genetical recombination-), globally co-developed by Chugai and Roche, has shown efficacy as a monotherapy as well as combination therapy with methotrexate (MTX) in rheumatoid arthritis patients in a double-blinded phase III trial. RADIATE is the third overseas phase III trial and evaluated the efficacy on patients with inadequate response to anti-TNF therapies. AMBITION is the fourth overseas phase III trial and evaluated the efficacy on patients with moderate to severe rheumatoid arthritis, including many patients who have not been previously treated with MTX.. The results were presented on June 13 and 14, 2008, at The European League Against Rheumatism (EULAR) Annual Congress held in France, Paris.

### RADIATE -Trial Objective, Design and Results

**Objective:** To investigate Actemra's efficacy and safety for rheumatoid arthritis patients with inadequate response to anti-TNF therapy.

**Method:** This is a double-blinded trial evaluating 499 patients with moderate to severe active rheumatoid arthritis despite treatment with anti-TNF therapy. Patients were allocated to receive Actemra 8mg/kg, Actemra 4mg/kg, or placebo every four weeks (intravenous infusion), in combination with 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

Safety: The adverse event profile was consistent with data reported in previous studies. The overall frequency of adverse events was similar in all 3 groups.

#### **AMBITION -Trial Objective, Design and Results**

Objective: To investigate Actemra's efficacy and safety in monotherapy compared to MTX for moderate to severe rheumatoid arthritis patients who have not been treated with MTX in the past six months..

Method: This is a double-blinded trial evaluating 570 patients with moderate to severe active rheumatoid arthritis who have not been treated with MTX in the past six months and who were not determined as inadequate responders of MTX. Patients were allocated to three groups to receive either Actemra 8mg/kg every four weeks (intravenous infusion) and weekly MTX placebo, Actemra 4mg/kg every four weeks and weekly MTX placebo, or Actemra placebo every four weeks and weekly MTX (gradual increase in MTX dose).

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

Safety: The adverse event profile was consistent with data reported in previous studies. The overall frequency of adverse events was similar in both groups.

Actemra<sup>®</sup> is currently marketed in Japan under the trade name "Actemra<sup>®</sup> 200 for Intravenous Infusion" after approval as a therapy for Castleman's disease in April 2005. In April 2008, additional indications were approved in Japan for rheumatoid arthritis (including prevention of structural damage of joints), polyarticular-course juvenile idiopathic arthritis and systemic juvenile idiopathic arthritis.

Outside of Japan, Roche and Chugai are investigating Actemra<sup>®</sup> in five phase III international trials, and the OPTION trial which was the first to report in June 2007 at European League Against Rheumatism, and the TOWARD trial was the second to report in November 2007 at American College of Rheumatology. In these five trials, Actemra<sup>®</sup> is being tested in rheumatoid arthritis patients with inadequate response to DMARDs (Disease Modifying Antirheumatic Drugs), including MTX and anti-TNF therapies, and patients who have not been treated with MTX before. Roche filed Actemra with regulatory authorities in Europe and in the United States, in November 2007.

## Reference

### ***Interleukin-6 (IL-6)***

IL-6 was identified as an agent that can induce the differentiation of B cells in immune systems from cells producing antibodies. Later research revealed that IL-6 has diverse physiologic activation properties. They include proliferating and differentiating hematopoietic cells and nerve cells, as well as inflammatory reactions. IL-6 also relates to the pathologies of various immune abnormalities and inflammatory diseases, such as rheumatoid arthritis, Castleman's disease, Crohn's disease and multiple myeloma.

### ***Actemra® (humanized anti-human IL-6 receptor monoclonal antibody)***

Actemra® is a humanized antibody to the human IL-6 receptor, and was created using genome engineering technology. It controls IL-6 molecules by stopping IL-6 from binding with IL-6 receptors. Actemra® may have applications in the treatment of diseases whose pathologies apparently relate closely to IL-6.

### ***ACR response***

The ACR-20 response was developed as one of the measures of improvement in the treatment of rheumatoid arthritis by the American College of Rheumatology, with standards for a 20% response, 50% response and 70% response. An ACR-20 response is defined as a reduction in each patient of at least 20% in criteria (1) and (2) listed below, plus an improvement of at least 20% in at least three of the others.

#### Disease Activity Measure

- (1) Tender joint count
- (2) Swollen joint count
- (3) Patient's assessment of pain
- (4) Patient's global assessment of disease
- (5) Physician's global assessment of disease activity
- (6) Patient's assessment of physical function
- (7) Acute-phase reactant value