

Translation

Data from Overseas Phase III Trial (LITHE) of "Actemra[®]," a Humanized Anti-Human IL-6 Receptor Monoclonal Antibody, Demonstrates Efficacy in Preventing Structural Joint Damage in Rheumatoid Arthritis Patients

October 27, 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[®] (generic name: tocilizumab -genetical recombination-), co-developed by Chugai and Roche, has shown efficacy in inhibiting structural joint damage as a combination therapy with methotrexate (MTX) in rheumatoid arthritis patients in a double-blinded phase III trial. LITHE trial is the fifth overseas phase III trial and evaluated the efficacy on patients with inadequate response to MTX. The one-year result, which is one of the endpoints of this two-year study, will be presented on October 28, 2008, at American College of Rheumatology (ACR) Annual Congress held in San Francisco, USA.

LITHE -Trial Objective, Design and Results

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

Method: This is a double-blinded trial evaluating 1,196 patients with moderate to severe active rheumatoid arthritis despite treatment with MTX. Patients were allocated to receive Actemra 8mg/kg, Actemra 4mg/kg, or placebo every four weeks (intravenous infusion), in combination with MTX.

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.

Results: 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.

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, and did not change from 6 to 12 months.

Actemra[®] is currently marketed in Japan under the trade name "Actemra[®] 200 for Intravenous Infusion" after approval as a therapy for Castleman's disease in April 2005 and launch in June 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[®] in five phase III international trials. OPTION[®] trial was the first to report in June 2007 at European League Against Rheumatism, TOWARD trial was the second to report in November 2007 at American College of Rheumatology, and RADIATE and AMBITION trials were the fourth and fifth to report in June 2008 at European League Against Rheumatism. In these five trials, Actemra[®] is being tested as monotherapy and in combination with DMARDs in rheumatoid arthritis patients with inadequate response to DMARDs, 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, and is currently under review.

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.

Genant-modified Sharp score

Genant-modified Sharp score assesses structural damage by measuring erosions in 14 sites in hand and wrist and 13 sites in foot using x-ray.

Health Assessment Questionnaire Disability Index

Health Assessment Questionnaire (HAQ) is a questionnaire to be answered by patients to measure the functional disability of patients who suffer chronic diseases, and focuses on physical disability with less influence by social, psychological and economic factors. HAQ consists of 20 questions related to daily activities and patients report the amount of difficulty they have in performing these activities. Disability Index is assessed from the results of the questionnaire, to measure the degree of functional disability.

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