

## ACTEMRA in Rheumatoid Arthritis

### What is ACTEMRA?

ACTEMRA (tocilizumab, RoACTEMRA within the EU) is the first in a new class of treatments for rheumatoid arthritis (RA) which target IL-6<sup>i</sup>, a chemical messenger in the body responsible for the painful and persistent inflammation that people with RA suffer.<sup>ii</sup>

Excess levels of IL-6 are produced in the joints of people with RA. This not only leads to inflammation and long-term joint damage, but can also cause other complications such as anaemia and fatigue.<sup>iii</sup> ACTEMRA blocks the activity of IL-6 and reduces its impact.<sup>1</sup> This prevents a worsening of RA, both in the joints and throughout the body.<sup>1</sup>

### ACTEMRA Phase III clinical trials

The Phase III clinical trial programme for ACTEMRA consists of five trials, designed to investigate the safety, efficacy and tolerability of ACTEMRA.<sup>iv,v,vi,vii,viii</sup> More than 4,000 patients across 41 countries have been involved in the trials, and over 2,500 of those patients participating in the Phase III OPTION, TOWARD, RADIATE and AMBITION trials entered the long-term extension studies (GROWTH95; GROWTH96).

These extension studies reinforce the long-term efficacy of ACTEMRA in RA across all patient types, having demonstrated that up to 56% of patients with active RA treated with ACTEMRA for over two years will achieve disease remission (as defined by DAS28 <2.6).<sup>ix,x</sup>

Below is an overview of the key results from each of the five trials.

In the **OPTION** (TOcilizumab Pivotal Trial in Methotrexate Inadequate respONDers)<sup>iv</sup> trial, over 40% of people treated with ACTEMRA plus methotrexate (MTX) achieved a 50% reduction in symptoms versus MTX alone, with 22% of patients achieving a 70% reduction in symptoms. In addition, disease remission was demonstrated in 28% of those treated with ACTEMRA vs 1% for MTX alone.

In the **TOWARD** (Tocilizumab in c**O**mbination **W**ith traditional **DMARD** therapy)<sup>v</sup> trial, at 24 weeks, significantly more people achieved a 20%, 50% and 70% (ACR20, ACR50 and ACR70)<sup>8</sup> reduction of symptoms with ACTEMRA plus Disease Modifying Anti-Rheumatic Drugs (DMARDs) compared to the control group. ACR20, ACR50 and ACR70 was achieved in 61%, 38% and 21% respectively amongst those treated with ACTEMRA plus DMARDs, versus 25%, 9% and 3% respectively, in those treated with placebo plus DMARDs. Disease remission was demonstrated in 30% of people treated with ACTEMRA compared with 3% of those treated with DMARDs alone.

In the **RADIATE** (**R**esearch on **ACTEMRA** **D**etermining efficacy after **Anti-TNF** **F**ailur**Es**)<sup>vi</sup> trial, 30% of those treated with ACTEMRA and MTX achieved disease remission compared with nearly 2% for MTX alone and a greater proportion of those treated with ACTEMRA plus MTX achieved a significant improvement in disease signs and symptoms (ACR scores) following 24 weeks of treatment, compared to those treated with placebo plus MTX.

Results from the **AMBITION** (**ACTEMRA** versus **M**ethotrexate double-**B**lind **I**nvestigative **T**rial **I**n **m**ONotherapy)<sup>vii</sup> trial revealed that ACTEMRA is the only product to have proven superiority to MTX in monotherapy in achieving a 20%, 50% and 70% (ACR20, ACR50 and ACR70)<sup>xi</sup> response (at 6 months). In addition, the trial, which included a high proportion of patients with early disease, demonstrated that 40% of patients treated with ACTEMRA monotherapy who had no prior treatment with DMARDs achieved DAS28 remission at week 24, compared to those treated with MTX alone.

**LITHE** (Toci**L**izumab safety and **T**HE prevention of structural joint damage)<sup>8</sup> trial data confirms ACTEMRA's efficacy in preventing the progression of joint destruction. At 1 year, patients treated with ACTEMRA (8mg/kg) had 3 times less progression of joint damage (measured by Total Sharp Score) compared to those treated with MTX alone. The data also demonstrated that significantly more patients treated with ACTEMRA achieved remission at 6 months compared to those treated with MTX alone (33% vs. 4%), and these rates continued to increase over time to 1 year (47% vs. 8%). Recent results from LITHE reveal that these benefits are maintained or improved at 2 years. ACTEMRA was also shown to improve the patients' ability to perform normal daily activities, as assessed by the Health Assessment Questionnaire (HAQ).<sup>xii</sup>

## Approval of ACTEMRA

RoACTEMRA was approved in the European Union in January 2009 for the treatment of RA in patients who have either responded inadequately to, or who were intolerant to, previous therapy with one or more DMARDs or TNF inhibitors. It is also approved for use in several other countries, including India, Brazil, Switzerland and Australia.

ACTEMRA was first approved in Japan, and launched by Chugai in June 2005 as a therapy for Castleman's disease. In April 2008, additional indications for RA, juvenile idiopathic arthritis and systemic-onset juvenile idiopathic arthritis were also approved in Japan.

ACTEMRA is the result of research collaboration by Chugai and is being co-developed globally with Chugai.

## References:

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- <sup>i</sup> Sebba A. Tocilizumab: The first interleukin-6-receptor inhibitor. *American Journal of Health-System Pharmacy* 2008;65(15):1413-1418
- <sup>ii</sup> Lipsky PE. Interleukin-6 and rheumatic diseases. *Arthritis Res Ther* 2006; 8 (Suppl 2):S4
- <sup>iii</sup> Yoshizaki K, Nishimoto N, Mihara M, Kishimoto T. Therapy of rheumatoid arthritis by blocking IL-6 signal transduction with a humanized anti-IL-6 receptor antibody. *Springer Semin Immunopathol* 1998;20:247-259
- <sup>iv</sup> Smolen JS, Beaulieu A, Rubbert-Roth A *et al.* Effect of interleukin-6 receptor inhibition with tocilizumab in patients with rheumatoid arthritis (OPTION study): a double-blind, placebo-controlled, randomised trial. *The Lancet* 2008;371(9617):987-997
- <sup>v</sup> Genovese MC, McKay JD, Nasonov EL *et al.* Interleukin-6 receptor inhibition with tocilizumab reduces disease activity in rheumatoid arthritis with inadequate response to disease-modifying antirheumatic drugs: The tocilizumab in combination with traditional disease-modifying antirheumatic drug therapy (TOWARD) study. *Arthritis & Rheumatism* 2008;58(10):2968-2980
- <sup>vi</sup> Emery P, Keystone E, Tony H *et al.* Tocilizumab significantly improves disease outcomes in patients with rheumatoid arthritis whose anti-TNF therapy failed: The RADIATE study. Presented at the European League Against Rheumatism (EULAR) congress, 11-14 June 2008, Paris
- <sup>vii</sup> Jones, G. *et al.* Comparison of tocilizumab monotherapy versus methotrexate monotherapy in patients with moderate to severe rheumatoid arthritis: The AMBITION study. *ARD Online First*, published March 17, 2009
- <sup>viii</sup> Kremer, J. *et al.* Tocilizumab inhibits structural joint damage, improves physical function, and increases DAS28 remission rates in RA patients who respond inadequately to methotrexate: The LITHE Study. Abstract presented at EULAR 2009
- <sup>ix</sup> 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).
- <sup>x</sup> Efficacy of Tocilizumab (TCZ) in Rheumatoid Arthritis (RA): Interim analysis of long-term extension trials of up to 2.5 years. Smolen J *et al.* Abstract presented at EULAR 2009
- <sup>xi</sup> 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
- <sup>xii</sup> HAQ, or the Health Assessment Questionnaire Disability Index, is a patient self-report functional status (disability) measurement used to assess the patient's functional ability and discomfort during the past week. It is a commonly used instrument in many disease areas, including RA