



Australian Government

Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Tocilizumab

Proprietary Product Name: Actemra

Sponsor: Roche Products Pty Ltd

February 2011

TGA Health Safety
Regulation

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- The TGA is a division of the Australian Government Department of Health and Ageing, and is responsible for regulating medicines and medical devices.
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- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

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I. Introduction to Product Submission

Submission Details

<i>Type of Submission</i>	Extension of Indications
<i>Decision:</i>	Approved
<i>Date of Decision:</i>	13 January 2011
<i>Active ingredient(s):</i>	Tocilizumab
<i>Product Name(s):</i>	Actemra
<i>Sponsor's Name and Address:</i>	Roche Products Pty Ltd 4-10 Inman Road Dee Why NSW 2099
<i>Dose form(s):</i>	Concentrated solution for infusion
<i>Strength(s):</i>	80 mg/4 mL, 200 mg/10 mL and 400 mg/20 mL
<i>Container(s):</i>	Single use vial
<i>Pack size(s):</i>	Packs of 1 and 4.
<i>Approved Therapeutic use:</i>	For the treatment of moderate to severe active rheumatoid arthritis (RA) in adult patients: <ul style="list-style-type: none"> · in combination with methotrexate (MTX) or other non-biological disease-modifying anti-rheumatic drugs (DMARDs) in case of either an inadequate response or intolerance to previous therapy with one or more DMARDs; or · as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate. <p>Actemra has been shown to inhibit the progression of joint damage, as measured by X-ray, when given in combination with methotrexate.</p>
<i>Route(s) of administration:</i>	Intravenous infusion
<i>Dosage:</i>	The recommended dose of Actemra for adult patients is 8 mg/kg given once every 4 weeks.
<i>ARTG Number (s):</i>	149402, 149403, 149404

Product Background

Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disease characterized by progressive inflammatory synovitis manifested by polyarticular joint swelling. The over-production of pro-inflammatory cytokines such as tumour necrosis factor (TNF), interleukin-1 (IL-1) and IL-6 in the joints and sera of patients with RA are important mediators in the disease pathogenesis via activation of T-lymphocytes, initiating the production of acute phase reactants, and their role in stimulation of haemopoietic cells. Tocilizumab is a recombinant humanized monoclonal antibody that binds to, and inhibits signaling mediated by soluble and membrane-bound IL-6 receptors. As such, treatment with tocilizumab inhibits the pro-inflammatory functions of IL-6.

Actemra [tocilizumab (rch)] was first considered by the Australian Drug Evaluation Committee (ADEC) at its 263rd meeting held on 2-3 April 2009. There was no objection to approval of the submission for the indication which is presently approved (see below). Five controlled Phase III studies were conducted to assess the efficacy and safety of tocilizumab over 24 weeks, in one study as monotherapy, combined with methotrexate (MTX) in three studies and combined with MTX and/or other disease-modifying anti-rheumatic drugs (DMARDs) in the remaining study. All five studies were multi-centre, randomised, double-blind, controlled studies and all had an escape arm where patients with inadequate response could, at the investigator's (blinded) request, receive adjusted therapy with tocilizumab. The primary efficacy endpoint for all of the pivotal studies was a comparison of the proportion of patients in each treatment arm with an ACR 20 response at Week 24.¹ A range of other valid secondary efficacy measures were collected.

The current indication for Actemra is:

Actemra (tocilizumab) is indicated for the treatment of moderate to severe active rheumatoid arthritis (RA) in adult patients:

- § *in combination with methotrexate (MTX) or other non-biological disease modifying antirheumatic drugs (DMARDs) in case of either an inadequate response or intolerance to previous therapy with one or more DMARDs; or*
- § *as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate.*

This AusPAR describes the evaluation of an application by the sponsor (Roche Products Pty Limited) of a proposed extension of indications to include the following:

ACTEMRA (tocilizumab) has been shown to inhibit the progression of joint damage, as measured by X-ray, and to improve physical function.

Regulatory Status

The product received initial ARTG Registration in May 2009.

An approval similar to the current Australian indication in reducing the signs and symptoms of RA was obtained in Switzerland on 2 December 2008, the European Union (EU) on 16 January 2009, New Zealand on 23 July 2009, the USA on 8 January 2010, Canada on 30 April 2010 and in Japan in April 2008. It has also been marketed in Japan since June 2006 for the treatment of Castleman's disease.

A similar application for the proposed extension of indication in RA was approved by the EU on 4 June 2010. Similar applications containing the current expanded dataset have been submitted in Switzerland and the US and were expected to be submitted in Canada and New Zealand during 2010.

The indication in the EU is:

RoActemra, in combination with methotrexate (MTX), is indicated for the treatment of moderate to severe active rheumatoid arthritis (RA) in adult patients who have either

¹ ACR responses are presented as the numerical improvement in multiple disease assessment criteria. For example, an ACR 20 response is defined as a $\geq 20\%$ improvement in (1) swollen joint count (66 joints) and tender joint count (68 joints) and (2) $\geq 20\%$ improvement in 3 of the following 5 assessments - patient's assessment of pain (VAS), patient's global assessment of disease activity (VAS), physician's global assessment of disease activity (VAS), patient's assessment of physical function as measured by the HAQ and CRP. ACR 50 and ACR 70 are similarly defined.

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 case of intolerance to MTX or where continued treatment with MTX is inappropriate. RoActemra has been shown to reduce the rate of progression of joint damage as measured by X-ray and to improve physical function when given in combination with methotrexate.

Product Information

The approved product information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

II. Quality Findings

Drug Substance (active ingredient)

Tocilizumab, also known as myeloma receptor antibody (MRA), is a recombinant humanised monoclonal antibody of the immunoglobulin (Ig) IgG1_κ (gamma 1, kappa) subclass, directed against the IL-6 receptor. It is composed of two heterodimers, each of which is composed of a heavy (H) and a light (L) polypeptide chain. The four polypeptide chains are linked intra- and inter-molecularly by disulfide bridges.

Quality Summary and Conclusions

There was no requirement for a quality evaluation in a submission of this type.

III. Nonclinical Findings

Introduction

Two new pharmacodynamic studies were provided in this submission and are reviewed below. Other nonclinical studies (pharmacodynamics and reproductive toxicity) included in the submission have already been supplied to and evaluated by the TGA in a previous submission.

Pharmacodynamics

Functional assay of competition between tocilizumab and IL-6

The competition between tocilizumab and IL-6 for IL-6 receptor (IL-6R) was determined in IL-6 dependent KT-3 cells. The cells were pre-incubated with tocilizumab at 100 µg/mL (the only concentration tested) for six hours before addition of IL-6 and further incubation for 72 hours. IL-6 dependent cell growth was observed in the presence or absence of tocilizumab. Tocilizumab completely inhibited cell growth in the presence of up to 0.32 ng/mL IL-6. Cell growth inhibition of tocilizumab was dose-dependently decreased by IL-6 at concentrations > 0.32 ng/mL. Around 50% inhibition of cell growth by tocilizumab was observed in the presence of approximately 50 ng/mL IL-6 (Figure 1). No inhibition of cell growth by tocilizumab was observed in the presence of 1000 ng/mL IL-6, indicating that IL-6 completely replaced tocilizumab from IL-6R. The study showed that IL6 and tocilizumab competitively bind to IL-6R. Measurement of culture medium showed tocilizumab was not depleted during the study.

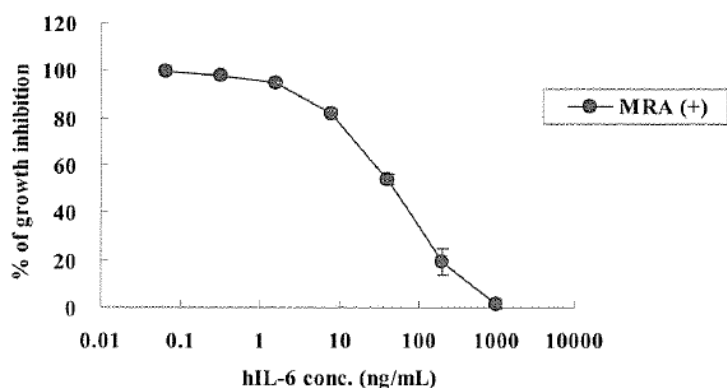


Figure 1: Competitive inhibition of KT-3 cell growth between tocilizumab (MRA, 100 µg/mL) and IL-6.

Cross-reactivity of MR16-1 with mouse tissues

MR16-1 is a rat monoclonal antibody that binds to and inhibits mouse IL-6R. The cross-reactivity of MR16-1 with mouse tissues was determined using cyrosections of tissues from normal 10-week old CD-1 mice (n=3).² The tissue sections were incubated with MR16-1 at 25 and 5 µg/mL. A large range of tissues were tested. The staining was validated using appropriate positive (recombinant mouse IL-6R resin spot slides and 7TD1 cells, a murine IL-6 dependent cell line) and negative control (recombinant human IL-6 resin spot slides) sections and antibodies (negative: RtIgG1).

Positive staining with MR16-1 was observed in the cytoplasm of mononuclear cells in lymph node and thymus (staining intensity: ± to 2+), decidual cells in placenta (1+ to 2+) and epidermal squamous epithelium in skin (± to 1+), which are known to express IL-6R. The positive staining in the tissues was not confirmed by another anti-mouse IL-6 antibody.

Nonclinical Summary and Conclusions

Tocilizumab is a recombinant, humanised IgG1 monoclonal antibody that binds to the human IL-6 receptor. It cross-reacts with IL-6 of non-human primates, for example the cynomolgus monkey, but not with rodent IL-6R. MR16-1, a rat monoclonal antibody that binds to and inhibits mouse IL-6R, was, therefore, used in reproductive toxicity studies in mice.

The cross-reactivity study showed specific binding of MR16-1 to mouse IL-6R (but not human IL-6R). Positive staining was observed only in a few mouse tissues, which are known to express IL-6R, suggesting that either the immunochemical staining was not very sensitive or low levels of IL6-1R expression in mouse tissues. Although the positive staining in the tissues was not confirmed by another anti-mouse IL-6 antibody, previously evaluated studies showed specificity of MR16-1 to mouse IL-6. The finding supports the appropriateness of the mouse as an animal model used in the reproductive toxicity studies.

In the new *in vitro* assay with tocilizumab, the recombinant antibody was shown to competitively bind to IL-6R and to functionally inhibit the growth of IL-6 dependent cells.

The new study findings do not raise any concerns concerning the registration of tocilizumab.

² CD1 (cluster of differentiation 1) is a family of glycoproteins expressed on the surface of various human antigen-presenting cells. Mice lack the group 1 CD1 molecules, and instead have 2 copies of CD1d. Thus, mice have been used extensively to characterize the role of CD1d and CD1d-dependent NKT cells in a variety of disease models.

IV. Clinical Findings

Introduction

As indicated in *Section I*, the original RA treatment indication approval in Australia was based on five controlled Phase III studies that investigated the efficacy and safety of tocilizumab over 24 weeks. The dataset demonstrated that tocilizumab was consistently effective (both in combination with MTX or as monotherapy) in reducing the signs and symptoms of moderately to severely active RA in adult patients either starting DMARD therapy de novo or requiring additional treatment following an inadequate response to prior therapy. The original application was supported with data from two dose-finding Phase II studies which identified that of the two doses assessed (4 mg/kg and 8 mg/kg), the latter was the only dose that effectively controlled inflammation throughout the one month dosing interval.

The initial submission for the indication of a reduction in signs and symptoms of RA included four 24-week Phase III studies (Studies WA17822, WA17824, WA18063 and WA18062) and a planned 24-week interim analysis of data from a 2-year Phase III study (WA17823). The current application for extension of indication in RA is supported by a single pivotal study (WA17823) which enrolled adult patients with active RA who had an inadequate response to MTX. In particular, the trial assessed the outcomes of radiographic analyses with respect to a reduction in the progression of joint damage and data on the improvement of physical function. The current application is also supported by the cumulative long-term efficacy and safety data from the open-label extension phase of Study WA17823, as well as two ongoing open-label extension studies (WA18695 and WA18696) which recruited patients from the controlled trials in the original tocilizumab registration application.

Study WA17823 had a one-year, double-blind controlled study period followed by a second year of open-label treatment with tocilizumab 8 mg/kg + MTX. The design allowed for an assessment of the efficacy of tocilizumab versus an active comparator (MTX alone) with respect to the progression of joint damage and improvement in physical function in patients with moderate to severe active RA at 12 months, as well as an assessment of the maintenance of the efficacy with continued tocilizumab therapy to 2 years. The co-primary endpoints for Study WA17823 were the change from baseline in the Total Sharp-Genant score (radiographic endpoint) and the change in physical function as evaluated by the area under the curve (AUC) for the HAQ-DI.^{3,4} Both co-primary endpoints were met in favour of

³ The mTSS (assessed using the Genant modification of the Total Sharp Scoring system) is the sum of the joint space narrowing (JSN) score plus the erosion score (ES) and has a range of 0-448. Plain x-rays of both hands and feet are obtained. A higher score represents greater structural damage. The JSN score has a range of 0-168 and is derived from evaluating 40 joints in the hands and feet which are scored from 0 (no damage) to 4. The ES has a range of 0-280 and is derived from assessing 44 hand and foot joints. Each joint is scored 0 (no damage) to 5, except the metatarsophalangeal joints of the feet which are scored 0-10.

⁴ The HAQ-DI is a patient reported questionnaire used to provide an assessment of the impact of the disease and its treatment on physical function. The tool assesses the degree of difficulty experienced by the individual in 8 domains of daily living activities using 20 questions. The domains include dressing and grooming, arising, eating, walking, hygiene, reach, grip and common daily activities, with each domain (activity) consisting of 2 or 3 items. For each question, the level of difficulty is scored from 0 to 3 with 0 = "without any difficulty", 1 = "with some difficulty", 2 = "with much difficulty" and 3 = "unable to do". If the maximum score equals 0 or 1, but a device related to that activity was used or help from another person was provided for the activity, then the activity score is increased to 2. However, if the activity score was already 2 and a device related to that activity was used or help from another person was provided, the

tocilizumab therapy. Treatment with tocilizumab 8 mg/kg in combination with MTX resulted in > 80% inhibition in the progression of joint damage which was supported by changes in both erosion and joint space narrowing scores at Week 104. There was also a significant improvement in physical function at 1 and 2 years as assessed by the AUC for the change from baseline in HAQ-DI. Compared with patients treated with placebo infusions + MTX, a significantly higher proportion of patients who received tocilizumab 8 mg/kg + MTX achieved the clinically important difference for the change in HAQ-DI of 0.30 by Week 52. This response was maintained for up to 104 weeks of observation.

In the RA clinical trial program, a total of 2644 subjects have received at least part of one infusion of tocilizumab (774 patients on 4 mg/kg and 1870 subjects on 8 mg/kg) in a controlled setting as of the data cut-off date (6 February 2009). Regarding duration of follow-up following drug exposure in the “All Control” population, 1555 patients had received control treatment (exposure of 717.4 patient-years) compared to 500.1 and 1013.2 patient-years of total exposure for tocilizumab 4 mg/kg and 8 mg/kg, respectively. In all but one of the earlier studies (WA17824), which was part of the original submission, all patients continued to receive concurrent DMARDs (usually MTX) with tocilizumab. Up to the cut-off date for this submission (11 April 2009), 4009 patients comprised the “All Exposure” population (that is, received at least one dose of tocilizumab, either in a controlled or open-label setting) dataset for the assessment of safety, with over 1000 of these patients receiving treatment for at least 156 weeks (3 years). This population provides a total of 8579.7 patient years of exposure and 9414.3 patient-years of observation following treatment with tocilizumab. Overall this represents a 3-fold increase in exposure to tocilizumab since the original registration application, providing a significantly larger database for the evaluation of safety, including relatively uncommon events. The safety profile of tocilizumab 8 mg/kg is well characterized in treatment durations of up to 3 years. In general, the majority of adverse events noted during the clinical trial program are mild to moderate in severity, reversible and usually not treatment limiting. As with all biological DMARDs used for the treatment of patients with severe RA, vigilance for serious infections is a key aspect of management. Some adverse events that require special consideration include an increased frequency of elevations in serum transaminases and neutropenia when tocilizumab is combined with MTX, a low risk of significant acute infusion reactions and gastrointestinal perforations, and a minor sustained elevation in serum cholesterol concentrations. However, to date, there does not appear to be an increase (beyond expectations for the treatment population) in the rates of malignancy or other serious adverse events (such as cardiovascular disease) with continued treatment with tocilizumab 8 mg/kg.

Apart from the current pivotal study (WA17823), the other four Phase III clinical trials involved in the original licensing submission for tocilizumab in RA have been published in peer reviewed journals. In all but one of the controlled studies in the original dataset, the primary efficacy comparison for clinical endpoints (ACR 20 response rate) was made following 24 weeks of observation. However, patients continued to be followed-up in open-label extension protocols in which patients were eligible to receive additional doses of tocilizumab. The design of the new pivotal study (WA17823) was discussed with regulatory authorities in Europe prior to the study commencement and was considered to adequately address the proposed variations in indication for tocilizumab. The endpoints used in the pivotal study were consistent with those recommended by the European League against

score for that activity remains 2. A total score of between 0 and 3 is obtained from the mean of each activity. A change from baseline in the HAQ-DI of at least -0.22 units has been specifically defined for RA in peer-reviewed literature to be the smallest measurable reduction that is clinically significant.

Rheumatism (EULAR), the American College of Rheumatology (ACR) and various regulatory agencies at the time of their conduct.

Pharmacodynamics

There was very little new information regarding the pharmacodynamics (PD) of tocilizumab in this submission. Within Study WA17823, the mean concentration of Rheumatoid Factor (RF) decreased from baseline by 38% at Week 24 with both doses of tocilizumab + MTX (272 IU/mL to 169 IU/mL; n=321 for 8 mg/kg and 307 IU/mL to 202 IU/mL; n=307 for 4 mg/kg) compared to patients receiving placebo infusions + MTX where RF levels declined by 22.5% (294 IU/mL to 228 IU/mL; n=215). Changes from baseline to Week 24 in the median RF concentrations followed a similar trend. The median baseline concentrations were 113, 108 and 114 IU/mL for placebo + MTX, tocilizumab 4 mg/kg + MTX and tocilizumab 8 mg/kg + MTX treatment groups, respectively. The corresponding median 24-week levels of RF were 97 IU/mL (14% lower) for placebo + MTX, 67 IU/mL (38% less) for tocilizumab 4 mg/kg + MTX and 72 IU/mL (37% lower) for tocilizumab 8 mg/kg + MTX.

At Week 24, the proportion of subjects whose RF status changed from positive to negative (determined by a concentration $>$ or $<$ 15 IU/mL) decreased slightly for both doses of tocilizumab, but more so with the 8 mg/kg dosing arm, (80.7% [322/399] at baseline and 77.2% [237/307] at Week 24 for 4 mg/kg + MTX; and 82.9% [330/398] at baseline and 73.2% [235/321] at Week 24 for 8 mg/kg + MTX) compared to patients receiving MTX alone where the percentage of subjects who remained RF positive remained relatively constant (81.7% [321/393] at baseline and 81.9% [176/215] at week 24).

Other biochemical markers known to correlate with RA disease activity and progression show that tocilizumab treatment results in significant decreases in the mean concentrations of C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), both markers of inflammation, relative to the declines observed in patients receiving placebo infusions + MTX. This information is considered in the efficacy section of this report.

This submission did not contain any PD information in relation to biochemical markers of cartilage and bone matrix turnover (such as assessments of urinary levels of collagen, telopeptides or pyridinolines) which may have supported the biological plausibility of tocilizumab in its claim of inhibiting structural joint damage in RA. Furthermore, pre-clinical data indicates that IL-6 can indirectly stimulate osteoclastic activity and bone resorption, and by altering the balance between osteoclastic and osteoblastic activity has the potential to change the dynamics of bone modeling.

Pharmacokinetics

The pharmacokinetics (PK) of different tocilizumab dosing regimens used for the treatment of RA patients were presented in the original licensing application. The main differences in PK between the 4 mg/kg and 8 mg/kg dosing regimens (given by one hour infusion) is that the area under the plasma concentration time curve (AUC), the minimal plasma concentration (C_{\min}) and the maximal plasma concentration (C_{\max}) appear to increase in a dose proportional relationship over the limited dose range.

Key PK parameters of tocilizumab at a dose of 8 mg/kg given every 4 weeks for 24 weeks are:-

- Effective elimination half-life at steady state ranges from 8-14 days,
- Steady state is achieved after the first dose for C_{\max} values, after 8 weeks for AUC and after 20 weeks for trough concentrations (C_{\min}),

- Clearance is small (~12.5 mL/hr) which is consistent with a IgG antibody with minimal contribution by biliary or renal elimination, that is, elimination is largely dependent upon redistribution and non-specific IgG clearance pathways, and
- AUC, C_{min} and C_{max} all increase with increasing body weight but at a patient body weight > 100 kg the increases in these parameters is higher than mean predicted values obtained from population PK analysis (hence, doses > 800 mg per infusion are not recommended for subjects > 100 kg).

In Study WA17823, pharmacokinetic sampling was a secondary endpoint to be explored in a consenting subset of the overall study population. Trough concentrations of tocilizumab were assessed if the previous two doses of tocilizumab were unchanged and if the time elapsed from the last tocilizumab dose was 28 +/- 3 days. In total, 841 patients provided PK samples as per the trial protocol. The mean age of the patients was 53 (range: 19-85) years. Most were female (82.8%, 696/841). The mean patient weight was 71.6 kg (standard deviation [SD] 15.9; range: 34.5-148 kg). The mean trough tocilizumab concentrations for those receiving 4 mg/kg appear to decline after Week 24 (that is, during the mid-study testing intervals of Weeks 52 and 80) before returning to baseline at study conclusion (Week 104). Further exploration of this subgroup would be valuable as it may suggest that those individuals who lost response to tocilizumab 4 mg/kg and subsequently switched to the higher dose prior to Week 104 may have had increased clearance (for example, from the formation of neutralizing drug antibodies). However, participants who remained on tocilizumab 4 mg/kg at the study conclusion appeared to maintain the same drug clearance throughout the trial. The mean steady state trough concentrations of tocilizumab for those receiving 8 mg/kg was higher than the 4 mg/kg, and was maintained at a constant level throughout the 2-year study.

Efficacy

As noted above, the data for the extended RA indication is based on a single Phase III study (WA17823) that provided 2-year radiographic and physical functioning outcome data which is pivotal to the assessment of the sponsor's claim. Study WA17823 was conducted in adult patients with active RA who had an inadequate response to MTX. The study had a one year double-blind controlled period followed by a second year of open-label treatment with tocilizumab. The sponsor's claim is supported by the efficacy reports from open-label extension periods in Study WA17823, as well as two additional studies (WA18695 and WA18696) which recruited subjects involved in the pivotal studies that resulted in tocilizumab obtaining its original indication for RA treatment in Australia.

Study WA17823 (2 Year Status)

Study WA17823 was a prospective, multicentre, randomized, double-blind, placebo-controlled, parallel-group study with three treatment groups: placebo infusions + MTX, and two different doses of tocilizumab (4 mg/kg [low dose group] or 8 mg/kg [high dose group]) + MTX. Approximately 390 subjects were to be randomly assigned in a ratio of 1:1:1 to each of the three treatment groups. Randomization was administered by a central randomization centre (using an Interactive Voice Response System [IVRS]) and stratified by site using a randomization list provided by the sponsor.

Study WA17823 was designed with a one year double-blind controlled period followed by a second year of open-label treatment with tocilizumab 8 mg/kg + MTX. During the first year of the trial, patients received an infusion of either tocilizumab or placebo every 4 weeks for a total of 13 infusions. The study design also allowed for treatment modifications depending on a patient's disease status as assessed by tender and swollen joint counts. From Week 16 (and through to Week 48), patients could receive escape therapy with tocilizumab if they had

obtained less than a 20% improvement from baseline in both their tender and swollen joint counts at two prior scheduled consecutive assessment time points. These patients could also receive intra-articular steroids and/or an increase in oral corticosteroid dosage to a maximum of prednisolone 10 mg/day or equivalent. Tocilizumab escape therapy dosing occurred in a step-wise manner and remained double-blind throughout the first year of follow-up. The tocilizumab escape dose was determined by IVRS and based on the patient's initial treatment allocation. For patients randomized to either tocilizumab treatment group, the first and second step escape regimen was tocilizumab 8 mg/kg. For patients initially allocated to placebo infusions + MTX, the first step of escape therapy was tocilizumab 4 mg/kg (+ continued MTX). If after a minimum of three first step escape doses, patients continued to demonstrate an improvement from baseline in both tender and swollen joint counts of less than 20%, they could receive the second step of tocilizumab escape therapy (8 mg/kg). If any patient after three doses of second step escape therapy continued to show less than a 20% improvement in both tender and swollen joint counts, then treatment with tocilizumab was to be discontinued.

Year 2 of the core study started after completion of 52 weeks of follow-up. Patients who either completed 52 weeks of double-blind treatment or received tocilizumab escape therapy, received open-label treatment with tocilizumab 8 mg/kg (+ continued MTX) every 4 weeks for 12 months. However, if a patient was responding well to their blinded therapy at Week 52, as indicated by a 70% improvement from baseline in both the tender and swollen joint counts at two consecutive visits (that is, Weeks 48 and 52), he or she had the option to continue with their current treatment in a blinded manner (at either the investigators' or patients' decision) rather than switching to open-label treatment with tocilizumab. Patients who chose to continue with their double-blind treatment at Week 52 could still switch to open-label treatment between Weeks 52 and 104 if they were no longer achieving the same level of efficacy. Although adding complexity to the data analysis and communication of the results, the study design is akin to the treatment pathways undertaken for patients with moderate to severe RA in the clinical setting. During the 2-year study period, most safety and efficacy parameters were assessed every 4 weeks with the exception of radiographs of the hands, wrists and feet which were obtained every 6 months. Patients who withdrew from the study were asked to return for follow-up assessments 4, 8 and 12 weeks after their last dose of study medication. All patients who completed Year 2 of the study were eligible to enter an optional open-label, long-term, extension period for up to another 3 years.

The doses of tocilizumab (4 mg/kg or 8 mg/kg every 4 weeks) used in this study were based on the results from a dose-ranging Phase II trial (LRO301) which investigated doses ranging from 2-8 mg/kg every 2- 4 weeks and showed that these two dose regimens were associated with optimal efficacy while demonstrating an acceptable safety profile. Usual therapeutic doses of MTX were utilized with all patients receiving once weekly MTX (oral or parenteral) at a dose of 10-25 mg. In the event that a patient developed MTX related side-effects (for example, stomatitis) or certain toxicity criteria (for example, abnormal liver function tests or neutropenia) a dose reduction or change in route of administration was considered before withdrawal from the study. Otherwise the dose of MTX was to remain stable over the entire study period. All subjects received concomitant oral folic acid at a dose of at least 5 mg/week. All DMARDs other than MTX were withdrawn prior to baseline. The use of intra-articular corticosteroids were discouraged within 6 weeks prior to baseline but were permitted in a limited manner (that is, no more than 1 joint per 24 week period could be injected) throughout the 2 year trial period for severe RA flares.

Radiographs of the hands, wrists (posterior/anterior) and feet (anterior/posterior) for the assessment of the primary endpoint were read at a central reading facility by independent expert radiologists who were blinded to treatment allocation, chronological order of the

radiographs and the patients' clinical response. All radiographs were scored by two radiologists according to the Sharp method, modified by Genant, and the average of the two scores was used for the analysis.³ Checks for consistency were made between the readers and resolution of discrepancies was made through an independent third reader who derived an adjudicated score. Radiographs were read in two reading campaigns. Campaign 1 included the radiographs obtained at baseline, Week 24, Week 52, and early withdrawal or escape therapy readings taken up to the Week 52 visit. Campaign 2 included evaluations collected at baseline, Week 24, Week 52, Week 80, Week 104, and early withdrawal or escape therapy readings taken up to the Week 104 visit. Campaign 1 assessments were used for the Year 1 analysis and those of Campaign 2 were used for the Year 2 analysis. The data from the different campaigns were not mixed for a given patient.

Study Population Characteristics

Study WA17823 was conducted in 137 study sites (15 countries) in North, Central and South America, as well as Europe, South Africa, China and Australia between January 2005 and February 2009. Most centres recruited between 1 and 11 patients while 20 centres enrolled at least 20 patients. The four highest recruiting countries were USA, Poland, Mexico and Brazil who enrolled a combined total of 69% of patients (821/1196). Subjects were required to be >18 years of age with RA of at least 6 months duration, who had been previously treated with MTX for at least 12 weeks immediately prior to baseline, of which the last 8 weeks must have been at a stable dose of between 10 and 25 mg/week (oral or parenteral). At study entry, patients were required to have active disease as defined by the 1987-revised ACR criteria which included >6 swollen joints out of 66 joints assessed, >8 tender joints out of 68 joints assessed, raised serum inflammatory markers (CRP>10 mg/L or ESR>28 mm/hr), and at least one joint erosion on plain x-ray attributable to RA as determined by the central reading facility. Corticosteroids (oral prednisone <10mg/day or equivalent doses) and non-steroidal anti-inflammatory drugs (NSAIDs) were permitted if stable for at least 6 weeks prior to baseline. Significant exclusion criterion included major surgery (including joint surgery) within 8 weeks prior to screening or planned major surgery within 6 months following randomization, severe functional impairment (as defined as functional class IV by the ACR classification), unsuccessful treatment (lack of response or significant safety issue) with an anti-TNF agent and immunisation with a live/attenuated vaccine within 4 weeks prior to baseline. Additional patient exclusion characteristics limiting the external validity of the study population were: - history of recurrent infection, positive hepatitis B virus surface antigen or hepatitis C antibody, history of non-cutaneous malignancy within the last 10 years (20 years if prior breast cancer), significant underlying cardiac or pulmonary disease, history of alcohol or substance abuse, peripheral neuropathies that could interfere with pain evaluation, renal impairment (serum creatinine >124 µmol/L in female patients and >141 µmol/L in male subjects), baseline serum aminotransferases >1.5 times upper limit of normal and haematological abnormalities (for example, platelet count < 100 x 10⁹/L).

The studied population was clearly delineated and the three treatment groups were well matched with respect to demographic characteristics. Subjects had a median age of 52 (range: 18-84) years and were predominantly female (82-84% across the treatment groups). Caucasians (70-71% across the treatment arms) accounted for the major racial background followed by subjects of Hispanic ethnicity (34-36%). Nearly half of all patients were recruited from sites in the USA.

The patients involved in Study WA17823 were heterogeneous with respect to duration of RA (mean 8.2 years, median 7.2 years, range: 0.5-48.8 years). Over 80% of patients in each group were seropositive for rheumatoid factor (RF>20 IU/mL) which is a significantly higher

ratio compared to most RA patient cohorts where approximately 70% of patients are RF positive. In general, subjects had a moderate quantity of pre-existing joint damage (mean mTSS of 25.4 [range: 8-210]) with a mean annualized rate of progression (ARP) exceeding 4 indicating a population at relatively high risk of further joint destruction. The ARP is calculated as the baseline mTSS divided by the duration of RA.

The baseline disease parameters reflect severely active disease and were comparable among the three treatment groups. The baseline median tender joint count was 25-26 (of a possible maximum of 68), and the median swollen joint count was 15 (of a possible maximum of 66). The overall activity score, as measured by the DAS28-ESR score, was 6.48-6.52, indicating high disease activity.⁵ As a validated marker of disease progression, CRP values were high across the three treatment groups (mean 2.08-2.33 mg/dL). In addition, the mean HAQ-DI scores were high at 1.5 which is consistent with a significant functional impairment due to a severely active disease state.

The treatment groups were well-balanced with respect to previous and concomitant treatments for RA. All patients recruited into the study had received MTX immediately prior to enrolment. The median (and mean) dose of MTX was identical between the treatment arms at 15.0 mg/week. In addition to MTX, most patients (75-82% in each treatment group) had received previous treatment with either other conventional DMARDs or anti-TNF agents with no relevant differences in the incidence and types of previous treatments between the 3 initial randomization groups. Approximately a third of all subjects had received one DMARD other than MTX, 23.5% had received two other DMARDs, 10.7% had taken three DMARDs and less than 5% in total had received four or more prior DMARD treatments. The most common prior DMARDs were anti-malarial agents (46-49%) followed by sulfasalazine (29-35%), leflunomide (17-19%), cyclosporine (10-15%) and gold (17-18%). Between 11 and 12% of patients in each treatment group had previously received anti-TNF therapy with the majority of these subjects (78%) recording a history of use with a single agent only.

Oral corticosteroid therapy (median dose of 7 mg/day) was recorded in 65-69% of patients at study entry and was similar between the treatment groups. In addition, more than two thirds of all patients were taking anti-inflammatory medication at study entry.

Approximately three-quarters of the study population had at least one medical problem other than RA with the most common concurrent conditions being hypertension (32%), osteoporosis (14%), depression (10%) and gastro-oesophageal reflux disease (7%). At baseline, similar proportions of patients in each treatment group had significant risk factors for atherosclerosis, that is, current smokers (16-19%), family history of coronary artery disease (13%) and diabetes mellitus (8%). In addition, 51 patients had a history of tuberculosis and/or a positive tuberculin test at baseline.

⁵ The 28 joint Disease Activity Score (DAS 28) is a widely used and validated method used in research trials and clinical practice for measuring outcome in patients with RA. It is a composite disease activity index of 4 clinical variables involving the tender joint count (up to 28 joints), swollen joint count (up to 28 joints), ESR or CRP, and the patient's assessment of general health using a 10cm visual analogue scale. The final score is derived by a complex mathematical calculation of the individual elements. DAS 28 has a scale from 0 to 10, and most scores range from 2 to a maximum of 10. According to the European League Against Rheumatism (EULAR) guidelines, a DAS 28 >5.1 indicates high disease activity, >3.2 and up to 5.1 indicates moderate disease activity, 3.2 or less indicates low disease activity, and "clinical remission" is indicated by a DAS 28 score of <2.6.

Primary Efficacy endpoint

The primary radiographic endpoint in Study WA17823 was the mean change in the Genant-modified Total Sharp Score (mTSS) from screening to Week 104 between the three treatment groups.

The primary functional endpoint was the AUC for the change from baseline in the HAQ-DI.

Secondary Efficacy endpoints

Major secondary efficacy endpoints (all assessed at Week 104, unless otherwise specified) included:

- § Radiographic. The mean change from baseline in the erosion score and Joint Space Narrowing (JSN) score at Weeks 80 and 104, the mean change from baseline in the mTSS at week 80, the proportion of subjects with no x-ray progression in the individual components of the mTSS (defined as a change in either the erosion score or JSN of zero or lower, respectively);
- § Functional. The proportion of patients achieving an improvement of at least 0.30 units in the HAQ-DI;
- § Clinical signs and symptoms. The proportion of subjects achieving an ACR20, ACR50 and ACR70 response, the proportion of subjects achieving major clinical response (as defined by an ACR70 response maintained for at least 6 consecutive months), the mean change from baseline in the individual ACR core set parameters, the AUC of the ACRn, the change from baseline in mean DAS28 score, AUC of the mean DAS28, the proportion of subjects achieving EULAR clinical response (that is, a categorical DAS28 response) and the proportion of subjects achieving either DAS28 or ACR remission criteria;
- § Quality of Life. The mean change in FACIT-Fatigue score from baseline, and the mean change in the Physical and Mental Health Components of the SF-36; and^{6,7}
- § Other. The proportion of subjects who achieved a complete clinical response (defined as a continuous 6 month period of remission by ACR criteria and no radiographic progression).

Exploratory Endpoints

Several exploratory parameters relating to the assessment of radiographic outcomes were also included in the study report. In particular, the annualized rate of progression in the mTSS and

⁶ Functional Assessment of Chronic Illness Therapy (FACIT): The FACIT fatigue score has a range of 0 to 52, and in

this case a higher total score is better. The questionnaire includes 13 questions regarding how fatigue affected the

subject's activities over the previous 7 days. Each question is answered on a scale of 0 to 4, where 0 = not at all and

4 = very much.

⁷ SF-36 = Medical Outcomes Short-Form 36. The SF-36 is a validated, patient-based, measure of health-related quality of life. It is a 36-item questionnaire measuring 8 domains (physical functioning, role-physical, role-emotional, social functioning, bodily pain, mental health, vitality, and general health). Responses to questions within each dimension are summed and linearly transformed to scale scores that range from 0 (worst health) to 100 (optimal health) (Ware, 1993). In addition, 2 component scale scores, Standardized Physical Component Summary Scale and the Standardized Mental Component Scale, are computed based on weighted combinations of the 8 domain scores.

its components was compared between Year 1 and 2 of the trial for each of the study treatment groups. The annualized rate of progression in the mTSS, erosion score and JSN score was also compared for patient groups that underwent switches in their study treatment during the 2 year observation period.

Explanation and validity of the major efficacy variables

In general, the selected endpoints in Study WA17823 use well-accepted, validated metrics that have served as the basis of previous published studies, prior regulatory approvals, and are consistent with published guidelines. Further details of some of the key measures are provided.

The mTSS is an important supporting analysis for the evaluation of the drugs ability to inhibit structural progression in RA.

In addition to the mTSS being the appropriate radiological scoring method, the minimum time point in which it is assessed is crucial to deciding the validity of a drug's claim to inhibition of the rate of structural progression of RA. The TGA-adopted EU guideline states that for agents claiming to prevent structural joint damage, it is recommended to demonstrate radiological differences of the hands and forefeet on the basis of before and after treatment comparisons taken not less than 1 year apart, but ideally 2 years, using full randomization and pre-agreed criteria.⁸ Hence, the design of Study WA17823 meets the minimum requirement for this indication in that the maintenance of treatment effect should be demonstrable to 2 years of follow-up, and that double-blind data collection should be maintained for a minimum of 1 year. Furthermore, the FDA has two levels of efficacy claim for structural damage in RA – either “slowing” or “inhibiting” the progression of structural damage. The criteria for the higher therapeutic claim of “inhibiting” requires at least 75% inhibition in the progression of structural damage compared to a placebo treated group over a 104 week period of follow-up.

Assessments of disease activity were based on the criteria from the American College of Rheumatology (ACR) and the European League against Rheumatism (EULAR). Both of these measures are based on a combination of a core set of clinical outcome measures, some assessed by the physician and some by the patients themselves. Definitions of the ACR and EULAR score changes that represent clinically relevant improvements on disease activity have been developed and validated.

The ACR response criteria are a standard instrument used in RA trials. The ACR criteria of 20%, 50%, or 70% improvement in clinical manifestations are an attempt to quantify response to therapy.

The 28-joint Disease Activity Score (DAS 28) is a widely used and validated method used in research trials and clinical practice for measuring outcome in patients with RA.

There are three categories of EULAR response (good, moderate and non-responders) which include not only the individual's amount of change in the DAS but also the attainment of a particular DAS value (low, moderate or high) at the endpoint. A change from baseline of at least minus 1.2 (that is, 2 times the potential measurement error) in a patient's DAS is considered indicative of a significant change in disease activity (compared with > -0.6 to -1.2 as moderate change in disease activity, and -0.6 or less as no change in disease activity). Hence, to be classified as a good EULAR response, the patient must demonstrate a significant change from baseline (> -1.2) as well as reach low disease activity (DAS 28 <3.2). Moderate

⁸ EMEA, Committee for Proprietary Medicinal Products (CPMP), 17 December 2003. Points to Consider on Clinical Investigation of Medicinal Products other than NSAIDs for Treatment of Rheumatoid Arthritis (CPMP/EWP/556/95 Rev 1).

EULAR response is a minimum change from baseline in the DAS 28 of > -0.6 to -1.2 , as well as the endpoint achievement of a DAS 28 equal to or less than 5.1.

The measures that are most valuable in assessing major clinical response are the proportion of subjects who achieved DAS 28 responses to a score of <2.6 , and/or the proportion of subjects achieving an ACR 70 response for a continuous period of 6 months. Study WA17823 pre-specified both of these variables as secondary endpoints.

Statistical methods

Sample Size: A total of 1170 subjects were calculated (390 in each treatment arm) in order to detect a difference at a 2-sided significance level of 2.5% for a 1:1:1 randomization with 90% power for determining a treatment difference in preventing joint destruction at 12 months. For the mean change from baseline in the mTSS at Week 52, it was predicted that the difference between the control group (MTX + placebo infusions) and tocilizumab treatment groups would approximate 30% of the standard deviation (that is, a mean difference of 3 units with a standard deviation of 11 units). The sample size calculations based on ACR20 response rates and change from baseline in HAQ-DI yielded a similar estimate.

Methods: Radiographic endpoints were primarily analysed on the modified intention-to-treat (mITT) population principle which included all randomised patients with a screening and at least one post-baseline set of x-rays in the first year of follow-up (either at 26 or 52 weeks). As changes in radiographic outcomes are known to be skewed, a non-parametric analysis using the Van Elteren method (that is, confirmatory pairwise tests against control) were employed for the primary radiographic analysis stratifying by region. X-rays were taken at baseline and Weeks 26, 52, 80 and 104. Subjects who terminated early from the study were requested to obtain an x-ray evaluation at the time of withdrawal. Missing values for the mTSS were handled by importing data from a pre-defined, linear progression model based on the slope between 2 non-missing assessments. Several sensitivity analyses were also performed, repeating these analyses in different populations (such as the per protocol population) and accounting for missing data using alternative imputation assumptions. The secondary radiographic endpoint of the proportion of patients without progression was evaluated. Treatment comparisons were made between each dose of tocilizumab and the control group (placebo infusions + MTX). Unfortunately the submission did not contain pairwise statistical comparisons for any of the efficacy outcome measures between the high (8 mg/kg) and low dose (4 mg/kg) tocilizumab treatment groups to determine if a dose response effect exists.

The primary efficacy analysis of the AUC of the change from baseline in HAQ-DI at Week 104 was performed using an analysis of variance (ANOVA) model adjusted for region and original treatment group, according to the ITT population, defined as all randomized patients who received at least a part of any study infusion. For patients who prematurely withdrew from the study, the HAQ-DI was set to missing after that visit. For patients who received escape therapy, the HAQ-DI was set to missing from the time they entered escape treatment. For missing Week 104 HAQ-DI scores, the AUC of change from baseline was standardized to 104 weeks using the latest time point available for the calculation (for example, if the last HAQ-DI score was taken at 52 weeks, then the AUC was calculated using all the data up until Week 52 and then multiplied by 2 in order to standardize it to 104 weeks). Again, several sensitivity analyses were also performed, repeating these analyses in different populations (such as the per protocol population) and accounting for missing data using alternative imputation assumptions. Because both primary endpoints (radiographic and functional) were tested at 52 and 104 weeks, the nominal overall significance levels for each of these endpoints at each time point was set to 0.025.

A fixed sequence hierarchical approach was taken in testing the secondary endpoints. For the categorical efficacy endpoints such as the various levels of ACR response and EULAR response, a Cochran-Mantel-Haenszel (CMH) analysis was used, stratified by region. Continuous efficacy variables such as the change from baseline in DAS28 and ACRn were assessed using an ANOVA model. The Non-Responder Imputation (NRI) method was used to handle missing data for these endpoints.

Following the mITT analysis, a total of 22% of patients (87 for the placebo infusion + MTX group [22.1% of 393], 92 for tocilizumab 4 mg/kg [23.0% of 399] and 84 for tocilizumab 8 mg/kg [21.1% of 398]) were excluded from the per protocol analysis because of protocol violations such as receiving a dose of MTX beyond study protocol (59 patients), absence of radiographic data at baseline or post-baseline (50 subjects), other DMARDs not correctly ceased or withdrawn (29 patients), incorrect management of corticosteroids or NSAIDs (13 subjects), and receiving incorrect study medication or blinding compromised (31 patients).

Completion status

Of the 1196 patients enrolled into Study WA17823, 394 were randomized to placebo infusions + MTX, 401 to tocilizumab 4 mg/kg + MTX and 401 to tocilizumab 8 mg/kg + MTX. All but six subjects (1 in the control group, 2 in the tocilizumab 4 mg/kg arm and 3 tocilizumab in the 8 mg/kg group) received at least one dose of infusion study treatment. In addition to the enrolled subjects, a further 542 patients underwent screening but failed to meet eligibility criteria. The most common disease-related reasons for screening failure were insufficient elevation in baseline ESR or CRP (16.8%) followed by insufficient number of swollen or tender joints (8.4%), failure to show joint erosion on x-ray (4.6%) and elevated serum transaminases (2.3%).

Because of the complex study design in terms of access to escape therapy at any time after 16 weeks, Table 1 provides a summary of the disposition and treatment status for the patients in the three study treatment groups. Notably, at 104 weeks of follow-up, 73.2% (287/392) of patients originally randomized to placebo + MTX and 77.6% (619/797) of subjects randomized to either dose of tocilizumab (77.4% [309/399] for tocilizumab 4 mg/kg and 77.9% [310/398] for tocilizumab 8 mg/kg) completed treatment to this time point.

Table 1: Study WA17823 – Summary of patients who completed Week 52 and Week 104 of treatment

Patients, n (%)	Initial Randomized Treatment		
	Placebo +MTX N=392 ^a	TCZ 4 mg/kg + MTX N=399 ^b	TCZ 8 mg/kg + MTX N=398 ^c
Entered escape 1 therapy	196 (50%)	97 (24%)	60 (15%)
Entered escape 2 therapy	30 (8%)	8 (2%)	12 (3%)
Completed Week 52	326 (83%)	342 (86%)	338 (85%)
Initiated OL at Week 52 ^d	266 (68%)	253 (63%)	248 (62%)
Entered Yr 2 on DB treatment from initial randomized treatment ^e	34 (9%)	77 (19%)	86 (22%)
Entered Yr 2 on DB treatment from Escape 1 treatment	22 (6%)	9 (2%)	3 (1%)
Completed Week 104	287 (73%)	309 (77%)	310 (78%)
Completed Week 104 on OL	248 (63%)	269 (67%)	260 (65%)
Completed Week 104 on initial randomized DB treatment	21 (6%)	37 (10%)	48 (12%)
Completed Week 104 on DB Escape 1 or 2 treatment or other	18 (4%)	3 (1%)	2 (1%)

OL = open-label; DB = double-blind.

From Week 16 onwards, if subjects had a <20% improvement in both their tender and swollen joint counts, they were offered the option of initiating escape therapy. During the first 52 weeks of the study, 29.7% (353/1190) patients entered into the first stage of tocilizumab escape therapy with a higher proportion of subjects randomized to the control group receiving such therapy (50% [196/392] for placebo infusion + MTX compared with 24.3% [97/399] for low dose tocilizumab and 15.1% [60/398] for high dose tocilizumab). As early as 12 weeks after initiating the first stage of escape therapy, patients were allowed to partake in a second stage of escape therapy if they failed to achieve a satisfactory response. A total of 30 patients (7.7% of 392) in the placebo + MTX group, 8 subjects (2.0% of 399) in the tocilizumab 4 mg/kg + MTX arm and 12 patients (3.0% of 398) in the tocilizumab 8 mg/kg + MTX group entered the second stage of escape treatment before Week 52. The majority (83-86%) of patients across all three treatment groups completed the initial 52 week double-blind (or escape therapy) phase of the study.

After Week 52, the majority (62-68%) of patients in all three treatment groups were switched to open-label tocilizumab 8 mg/kg + MTX. However, a small proportion of subjects who maintained at least a 70% improvement from baseline in their tender and swollen joint counts elected to continue with double-blind treatment: 21 patients (5.4% of 392) in the placebo + MTX group, 37 subjects (9.3% of 399) in the tocilizumab 4 mg/kg + MTX arm and 48 patients (12.1% of 398) in the tocilizumab 8 mg/kg + MTX group.

In total, 6.9% (27/392) of patients originally assigned to placebo infusions + MTX withdrew for non-safety reasons prior to Week 104 which was a similar rate compared to tocilizumab treatment groups (5.7% [34/597] of patients in the low dose tocilizumab group and 6.4% [63/983] in the high dose tocilizumab arm). The most common reason for premature withdrawal for non-safety reasons was “refused treatment or failed to return”: 12 placebo + MTX patients, 23 low dose tocilizumab subjects and 41 high dose tocilizumab patients. “Insufficient therapeutic response” led to the discontinuation of 12 patients (3.1% of 392) in the placebo + MTX group, 8 patients (1.3% of 597) in the low dose tocilizumab group and 14

patients (1.4% of 983) in the high dose tocilizumab group. Because of unequal drug exposure, the rate of premature withdrawal due to lack of therapeutic response was higher in the placebo + MTX group (4.2 per 100 patient-years) than the tocilizumab treatment arms (1.5 per 100 patient-years for tocilizumab 4 mg/kg and 1.1 per 100 patient-years for tocilizumab 8 mg/kg).

Result for primary efficacy variables

Radiographic

Treatment with tocilizumab + MTX resulted in a reduction in the rate of progressive joint damage compared with MTX monotherapy as evaluated by the mean change from baseline in the mTSS at Week 104 (mean change in mTSS of 0.58 for tocilizumab 4 mg/kg and 0.37 for tocilizumab 8 mg/kg vs 1.96 for placebo infusions + MTX; $p < 0.0025$ for both pairwise comparisons). The primary radiographic analysis data excluded post-withdrawal and escape data, and used linear extrapolation as the imputation method for missing data. However, similar results for the primary radiological efficacy outcome were obtained for the sensitivity analyses performed on differently defined patient populations such as the per protocol population (mean change in mTSS of 0.53 for tocilizumab 4 mg/kg and 0.33 for tocilizumab 8 mg/kg vs 2.03 for placebo + MTX; $p < 0.0025$ for both pairwise comparisons) and the ITT population (mean change in mTSS of 0.47 for tocilizumab 4 mg/kg and 0.34 for tocilizumab 8 mg/kg vs 1.07 for placebo + MTX; $p < 0.0025$ for both pairwise comparisons).

The primary analysis of radiographic data included x-ray assessments for 74.8% (294/393) of patients in the control group, 86.0% (343/399) in the low dose tocilizumab arm and 88.7% (353/398) in the high dose tocilizumab group. Of those subjects, 140 in the control arm, 231 in the tocilizumab 4 mg/kg group and 252 of the tocilizumab 8 mg/kg patients had both a baseline and Week 104 x-ray, and thus, represented the observed change. Hence, the number of patients for which data for the primary x-ray analysis was imputed using a linear extrapolation method was 154 (52.4% of 294) for placebo + MTX, 112 (32.7% of 343) for low dose tocilizumab and 101 (28.6% of 353) for high dose tocilizumab. The two reasons for data imputation (rather than observed values) were either truly missing values or the Week 104 data was set to missing because post-escape or post-withdrawal data was censored from the primary radiographic analysis. Both of these reasons were equally represented reasons among the three treatment groups.

The favourable radiological result for tocilizumab + MTX treatment versus MTX alone was seen across all explored subgroups including baseline ESR or CRP, HAQ-DI score, ethnicity, treatment centre region, disease duration (< 6 months, 6 months-2 years, or > 2 years), and corticosteroid use.

Functional

The primary functional endpoint of the AUC of the change from baseline at Week 104 in the HAQ-DI showed a significantly greater decrease for patients (ITT population) in both tocilizumab groups compared with placebo + MTX (adjusted mean minus 287.5 for tocilizumab 4 mg/kg and minus 320.8 for tocilizumab 8 mg/kg versus minus 139.4 for placebo infusions + MTX; $p < 0.0001$ for both pairwise comparisons of the difference in adjusted means). For the primary analysis of functional outcome no imputation was used for missing HAQ scores, post-escape data was set to missing prior to the calculation of the AUC and where the last observed HAQ score was taken prior to Week 104, the AUC was standardized. However, the results of the sensitivity analysis (for example, using the last observation carried forward [LOCF] method for handling of missing data and including post-escape data) for the primary functional endpoint confirmed that treatment with either dose of

tocilizumab + MTX resulted in significantly greater decrease in the AUC of the mean change in HAQ-DI score compared with placebo + MTX.

Results for secondary efficacy variables

For the mITT population using a linear extrapolation methodology for missing data, the change from baseline at Week 80 in the mTSS was significantly lower for patients who were randomized to tocilizumab 4 mg/kg (mean change in mTSS of 0.46 [SD 1.845]; n=343; p=0.0007 vs control group) or tocilizumab 8 mg/kg (mean change in mTSS of 0.31 [SD 1.273]; n=353; p<0.0001 vs control arm) than for patients in the placebo + MTX group (mean change in mTSS of 1.60 [SD 4.658]; n=294). This result in favour of tocilizumab therapy was consistently derived with statistical significance when sensitivity analyses that included observed, post-withdrawal and escape data were performed.

Analysis of the radiographic data at Weeks 80 and 104 using the components of the mTSS consistently demonstrated a treatment effect in favour of tocilizumab (either dose) + MTX compared with MTX alone. In the mITT population, patients treated with tocilizumab had a statistically significant reduction in erosion score at both Week 80 and 104 (mean change 0.27 at Week 80 [p=0.0011] and 0.34 at Week 104 [p=0.0053] for tocilizumab 4 mg/kg; and 0.18 at Week 80 [p<0.0001] and 0.22 at Week 104 [p<0.0001] for tocilizumab 8 mg/kg) compared with subjects randomized to placebo + MTX (mean change 1.01 at Week 80 and 1.24 at Week 104). The result for the primary analysis of erosion scores at Weeks 80 and 104 was consistent when the observed data, including post-withdrawal and escape data, was applied. No progression of bone erosion was defined as a change from baseline in the erosion score of equal to or less than 0. At 104 weeks, a significantly higher proportion of patients randomized to tocilizumab 4 mg/kg (78.4%, 269/343; p=0.0006) or tocilizumab 8 mg/kg (85.6%, 302/353; p<0.0001) demonstrated no erosive progression versus 71.1% (209/294) of subjects in the control group.

In the mITT population, patients treated with tocilizumab had statistically significant lower JSN scores at both Week 80 and 104 (mean change 0.19 at Week 80 [p=0.0098] and 0.24 at Week 104 [p=0.0072] for tocilizumab 4 mg/kg; and 0.13 at Week 80 [p=0.0002] and 0.15 at Week 104 [p<0.0001] for tocilizumab 8 mg/kg) compared with subjects randomized to placebo + MTX (mean change 0.59 at Week 80 and 0.72 at Week 104). The result in favour of tocilizumab therapy for the primary analysis of mean change in JSN scores at Weeks 80 and 104 was consistent when the observed data, including post-withdrawal and escape data, was applied. No progression of JSN was defined as a change from baseline in the JSN score of equal to or less than 0. At 104 weeks, a significantly higher proportion of patients randomized to tocilizumab 4 mg/kg (86.0%, 295/343; p=0.0476) or tocilizumab 8 mg/kg (91.2%, 322/353; p=0.0001) demonstrated no progression in JSN compared with 80.3% (236/294) of subjects in the control group.

Significantly more patients in the tocilizumab treatment groups (4 mg/kg - 63.5% [256/343]; p=0.0239; and 8 mg/kg - 82.7% [292/353]; p<0.0001) showed no radiographic progression (that is, the change in mTSS of equal to or less than 0) at 104 weeks compared to subjects randomized to the placebo + MTX treatment arm (66.3%, 195/293). This was mainly accounted for by the higher proportion of patients in the tocilizumab groups with no progression in erosion score.

An exploratory analysis was done to compare the annualized progression rates (ARP) between Year 1 and 2 within each initially randomized treatment group for all three of the radiographic outcome measures. This analysis was limited to those subjects in whom the ARP could be calculated in both years. For patients who received treatment with tocilizumab

8 mg/kg for > 1 year, the comparison of Year 2 versus Year 1 showed a decrease in the rate of progression for the mTSS (0.07 in Year 2 vs 0.24; $p < 0.0001$), erosion ARP (0.04 in Year 2 vs 0.13; $p = 0.0007$) and JSN ARP (0.04 in Year 2 vs 0.11; $p = 0.0002$). Patients initially randomized to the placebo and tocilizumab 4 mg/kg groups exhibited lower rates of progression in Year 2 but the explanation of this observation is confounded by the majority of those patients switching to open-label tocilizumab 8 mg/kg in Year 2. For patients randomized to placebo + MTX, the ARP for the mTSS was 0.101 in Year 2 vs 0.86 in Year 1, erosion ARP was 0.04 in Year 2 vs 0.56 in Year 1 and the ARP for the JSN was 0.07 in Year 2 compared with 0.31 in Year 1 ($p < 0.0001$ for all comparisons of Year 2 vs Year 1). For patients randomized to tocilizumab 4 mg/kg + MTX, the ARP for the mTSS was 0.16 in Year 2 vs 0.25 in Year 1 ($p = 0.0346$), the erosion ARP was 0.09 in Year 2 vs 0.16 in Year 1 ($p = 0.1425$, not statistically significant) and the ARP for the JSN was 0.06 in Year 2 compared with 0.09 in Year 1 ($p = 0.0138$).

Another exploratory analysis undertaken was comparing the ARP for radiographic scores before and after a change in study medication. The analysis was performed without imputation of any missing data. A time window of 30 days before and after a switch of medication was allowed for an x-ray to be used in this analysis. Three groups of treatment switches were compared:

- § The patient group ($n = 198$) randomized to placebo + MTX who switched to tocilizumab 4 mg/kg + MTX as part of escape therapy because of insufficient response to placebo + MTX.
- § The group of patients ($n = 451$) who switched from low to high dose tocilizumab either as escape therapy or as open-label 8 mg/kg treatment in the second year of the trial (this also included subjects randomized to placebo who graduated from tocilizumab 4 mg/kg to 8 mg/kg as a 2 step escape treatment approach).
- § The subject cohort ($n = 133$) that changed from placebo + MTX to tocilizumab 8 mg/kg + MTX at Week 52 or during Year 2 of the study.

Selection bias due to response to initial treatment makes a direct comparison of ARP of limited value. The ARP in the mTSS decreased from 1.11 to 0.47 (relative decrease of 58%) for the first patient cohort (placebo to tocilizumab 4 mg/kg) and from 0.93 to 0.05 (relative decrease of 95%) for the patients in the third group (placebo to tocilizumab 8 mg/kg). For the subjects who switched from tocilizumab 4 mg/kg to 8 mg/kg, the ARP reduced from 0.31 to 0.10 (relative decrease of 68%). The absolute improvement in radiographic progression for this group was considerably smaller than that observed for patients who switched from placebo to either dose of tocilizumab. Similar trends for intra-group changes in the ARP were observed for erosion scores and the JSN score.

Another secondary endpoint was the proportion of patients in each of the original randomized treatment groups who achieved an improvement of at least 0.30 units from baseline in the HAQ-DI at Week 104. A similar percentage of subjects in each of the three treatment groups achieved this outcome – 62.3% (144/231) for tocilizumab 8 mg/kg + MTX, 63.3% (138/218) for tocilizumab 4 mg/kg + MTX and 58.3% (74/127) for placebo infusions + MTX. The lack of difference between the three treatment groups for this outcome is explained by the observation that most patients had switched to open-label tocilizumab 8 mg/kg at Week 52. Supporting this explanation is the data for the percentage of categorical HAQ responders (improvement of at least 0.30 units) with time. For the placebo + MTX group the rates of response were 48% at Week 24, 53% at Week 52 and 58% at Week 104. For the tocilizumab

treatment groups the corresponding rates of HAQ response at Weeks 24, 52 and 104 were 57%, 60% and 63% for 4 mg/kg dosing and 59%, 63% and 62% for 8 mg/kg dosing.

A summary of the ACR 20, 50 and 70 response rates at Week 52 and 104 is presented in Table 2. In the primary analysis of ACR response endpoints patients who either received escape therapy, withdrew prematurely or where an ACR could not be calculated were determined as non-responders. A higher proportion of patients randomized to tocilizumab achieved ACR responses at Week 104. The ACR 20 response rate at Week 104 was 49.1% (196/399) of subjects who received tocilizumab 4 mg/kg + MTX and 54.5% (217/398) of patients who received tocilizumab 8 mg/kg + MTX therapy compared to 29.3% (115/393) of subjects who received placebo + MTX. The proportion ACR 50 responses at Week 104 was 37.6% (150/399) of subjects who received tocilizumab 4 mg/kg + MTX and 38.9% (155/398) of patients who received tocilizumab 8 mg/kg + MTX therapy compared to 19.8% (78/393) of subjects who received placebo + MTX. The ACR 70 response rate at Week 104 was 24.3% (97/399) of subjects who received tocilizumab 4 mg/kg + MTX and 22.8% (89/398) of patients who received tocilizumab 8 mg/kg + MTX therapy compared to 12.2% (48/393) of subjects who received placebo + MTX. Consistent with the ACR responses, the mean ACRn at Week 104 was higher for patients treated with tocilizumab + MTX (56.17 for low dose tocilizumab [n=228] and 55.47 for high dose tocilizumab [n=249]) compared to 48.79 for patients who received placebo + MTX (n=138). In addition, the mean AUC of the ACRn at Week 104 (when escape data was set to missing) was higher for patients randomized to either tocilizumab 4 mg/kg (27,141.08) or 8 mg/kg (30,876.59) compared to patients in the placebo + MTX group (21,094.97).

Table 2: Study WA17823 – Summary of ACR20, ACR50, ACR70 and ACRn at Weeks 52 and 104

	Placebo + MTX (N=393)	TCZ 4mg/kg + MTX (N=399)	TCZ 8mg/kg + MTX (N=398)
WEEK 52			
n	393	399	398
ACR20 Responders	97 (24.7%)	191 (47.9%)	222 (55.8%)
First ACR20 Response	0 (0.0%)	1 (0.3%)	1 (0.3%)
ACR50 Responders	40 (10.2%)	121 (30.3%)	145 (36.4%)
First ACR50 Response	2 (0.5%)	2 (0.5%)	2 (0.5%)
ACR70 Responders	15 (3.8%)	66 (16.5%)	80 (20.1%)
First ACR70 Response	2 (0.5%)	6 (1.5%)	6 (1.5%)
n*	158	254	279
Mean ACRn	21.16	40.94	47.01
WEEK 104			
n	393	399	398
ACR20 Responders	115 (29.3%)	196 (49.1%)	217 (54.5%)
First ACR20 Response	1 (0.3%)	0 (0.0%)	0 (0.0%)
ACR50 Responders	78 (19.8%)	150 (37.6%)	155 (38.9%)
First ACR50 Response	2 (0.5%)	1 (0.3%)	0 (0.0%)
ACR70 Responders	48 (12.2%)	97 (24.3%)	89 (22.4%)
First ACR70 Response	2 (0.5%)	5 (1.3%)	1 (0.3%)
n*	138	228	249
Mean ACRn	48.79	56.17	55.47

* Number of patients with non-missing ACRn.

A positive ACRn score indicates an improvement.

LOCF used for tender and swollen joint counts, no imputation used for missing HAQ Score, CRP, ESR and VAS assessments. CRP is used primarily for the calculation of the ACR response, if missing, ESR is substituted. Patients who receive escape therapy, withdraw prematurely or where an ACR can not be calculated, are set to 'Non Responder'.

Major clinical response (as defined by an ACR70 response maintained for at least 6 consecutive months) was seen in a higher proportion of patients in both tocilizumab treatment groups (11.5% [46/399] for tocilizumab 4 mg/kg and 14.3% [57/398] for tocilizumab 8 mg/kg) compared to placebo + MTX (5.6%, 22/393).

ACR remission requires that at least five of the following indicators are achieved for at least two consecutive months (morning stiffness < 15 minutes; no fatigue, joint pain, tenderness or swelling and ESR < 30 mm/hr for a female or < 20 mm/hr for a male). The duration of morning stiffness was not included in the original study protocol but was later added as an amendment. However, by this time approximately half of all the trial patients had been enrolled and the ACR remission calculation was performed on the ITT population. No patients in the placebo + MTX arm (n=393) achieved ACR remission criteria and only a small number of evaluable subjects did so in the tocilizumab treatment groups (2.0% [8/399] for tocilizumab 4 mg/kg and 2.5% [10/398] for tocilizumab 8 mg/kg).

The changes from baseline in the individual ACR core set parameters followed the same results trend as the overall ACR response criteria with greater mean decreases consistently observed for all the variables (except the Patient's Global VAS) for subjects in either tocilizumab + MTX group compared with the placebo + MTX group.

A reduction in DAS28 is indicative of disease improvement. During the 52 week double-blind treatment period, there was a statistical and clinically significant greater reduction in mean DAS28 in the two tocilizumab + MTX groups (low dose minus 2.97 and high dose minus 3.80) than the placebo + MTX group (-1.88; p<0.0001 for both tocilizumab comparisons to placebo; escape data set to missing). During the tocilizumab 8 mg/kg open-

label treatment phase (between Weeks 52 and 104) patients who were initially randomized to tocilizumab showed a continued improvement in mean DAS28 score (low dose minus 3.82 and high dose minus 4.14) whereas those patients initially allocated to placebo infusions + MTX demonstrated a similar mean improvement in DAS28 (-3.70) to those observed at Week 52 for subjects randomized to either dose of tocilizumab.

The AUC of DAS28 at Week 104 was higher (indicating less response to therapy) for patients randomized to the control group (mean 2793.01; SD 675.84; n=134) than in subjects randomized to tocilizumab (4 mg/kg – mean 2426.11; SD 743.88; n=223 and 8 mg/kg – mean 2094.71; SD 749.71; n=238).

The EULAR response categorizes the change in DAS28 for individuals as good, moderate or no response, according to the DAS28 attained and the change in DAS28 from baseline. At Week 52, a significantly higher proportion of patients in either tocilizumab + MTX groups achieved a good or moderate EULAR response (57.9% [231/399] for tocilizumab 4 mg/kg and 68.1% [271/398] for tocilizumab 8 mg/kg) compared to treatment with placebo + MTX group (29.3% [115/393]). During open-label treatment with tocilizumab 8 mg/kg between Weeks 52 and 104, the percentage of patients who achieved a good EULAR response increased significantly for the groups initially randomized to placebo (from 7.1% [28/393] to 23.4% [92/393]) and tocilizumab 4 mg/kg (from 27.6% [110/399] to 39.6% [158/399]) and showed a maintenance of improvement for the subjects initially allocated to tocilizumab 8 mg/kg + MTX (44.0% [175/398] at Week 52 and 45.7% [182/398] at Week 104).

Treatment with both doses of tocilizumab was associated with a higher proportion of patients achieving low disease activity (DAS28 score equal to less than 3.2) and clinical remission (DAS28 score < 2.6) compared to placebo infusions + MTX. However, at Week 52, the best rates of response were seen in the tocilizumab 8 mg/kg group in which 64.0% [176/275] reached low disease activity and 48.0% [132/275] achieved DAS remission. In comparisons, the respective rates of low disease activity and clinical remission at Week 52 were 17.9% (28/156) and 7.7% (12/156) for placebo + MTX; and 45.4% (113/249) and 30.5% (76/249) for tocilizumab 4 mg/kg + MTX. During open-label treatment with tocilizumab 8 mg/kg between Weeks 52 and 104, the percentage of patients who achieved low disease activity or clinical remission increased significantly for the placebo + MTX treatment group (69.1% [94/136] and 52.9% [72/136] respectively). Response rates in both tocilizumab treatment groups also significantly improved over the second year of the trial (4 mg/kg – 71.0% [159/224] obtained low disease activity and 55.4% [124/224] achieved clinical remission; 8 mg/kg – 76.3% [184/241] showed low disease activity and 64.7% [156/241] demonstrated DAS defined remission).

Patients in the tocilizumab + MTX groups reported a statistically significant reduction in fatigue over the 52 weeks of observation (double-blind phase) compared to patients who received placebo + MTX. The FACIT-Fatigue score ranges from 0 to 52 with an increase in score reflecting improvement (less fatigue). In addition, a change from baseline of at least 5 points has been defined as a clinically meaningful improvement in RA patients. At baseline, the mean FACIT-F (fatigue) scores for all three treatment groups were similar at a mean of 27.8. At Week 52, the mean change in FACIT-F score for patients in the tocilizumab + MTX group was 8.14 for low dose tocilizumab (SD 10.88; n=250) and 8.27 for high dose tocilizumab (SD 9.39; n=276) compared to a mean change from baseline of 5.57 (SD 10.9; n=157) for the placebo + MTX group. At the end of Year 2 when the majority of patients were switched to open-label tocilizumab treatment, the mean change from baseline in FACIT-F remained higher for patients randomized to tocilizumab (7.85 [SD 10.58] for 4 mg/kg [n=224] and 8.63 [SD 9.74] for 8 mg/kg [n=244]) compared to subjects randomized to

the control group (6.62 [SD 9.54]; n=138). At Week 104, a higher proportion of patients in the tocilizumab treatment groups (59.8%, 134/224 for low dose tocilizumab and 63.5%, 155/244 for high dose tocilizumab) achieved the minimal clinically important difference in fatigue score compared with subjects in the placebo + MTX group (55.8%, 77/138).

Regarding the SF-36 results, the mean baseline scores for the Physical Component Score (PCS) and Mental Component Score (MCS) were similar between the three treatment groups (mean PCS of 31.5-31.9 and mean MCS of 41.2 - 41.6). The mean PCS improved across all treatment arms during the initial 52-week blinded phase but were higher in those who received tocilizumab (mean change of 9.2 [SD 8.29] for 4 mg/kg and 10.0 [SD 9.13] for 8 mg/kg) compared with placebo + MTX patients (mean change from baseline to Week 52 of 5.6 [SD 8.42]). At 104 weeks, the mean change from baseline in PCS was maintained for patients who initially were allocated to either tocilizumab treatment group (mean change of 10.1 [SD 9.50] for 4 mg/kg and 9.8 [SD 9.66] for 8 mg/kg) and improved for patients in the control group (mean change from baseline to Week 104 of 8.7 [SD 9.53]).

During the double-blind treatment period, the proportion of subjects who achieved a clinically significant improvement (defined as a change >5) in the PCS at Week 52 was greater in those treated with tocilizumab + MTX (64.8% [154/238] in the 4 mg/kg group and 67.8% [184/272] in the 8 mg/kg arm) compared with 47.9% (72/150) subjects treated with placebo infusions + MTX. At the end of 2 years, the percentage of patients with a clinically significant improvement in the PCS was maintained for patients initially randomized to either tocilizumab treatment group but increased to similar levels (62.3%) for the control group of subjects.

During double-blind treatment, the mean change from baseline to Week 52 in the SF-36 MCS was higher for patients randomized to tocilizumab 4 mg/kg (mean change of 5.6 [SD 11.94]) and tocilizumab 8 mg/kg (mean change of 5.5 [SD 11.49]) than for subjects randomized to placebo + MTX (mean change from baseline to week 52 of 3.7 [SD 10.67]). At the end of the second study year when the majority of patients had switched to open-label treatment with tocilizumab 8 mg/kg, the mean change from baseline to week 104 in the MCS remained slightly higher for patients randomized to either dose of tocilizumab (mean change of 5.7 [SD 11.22] for 4 mg/kg and 6.2 [SD 11.55] for 8 mg/kg) than for subjects allocated to placebo initially (mean change of 5.2 [SD 10.27]).

A clinically meaningful improvement in the SF-36 MCS was defined as a change from baseline of >5 in this study. During double-blind treatment in Year 1, a slightly higher proportion of subjects treated with tocilizumab + MTX (47.0% [119/253] in the 4 mg/kg group and 49.0% [137/280] in the 8 mg/kg arm) achieved a clinically significant improvement in the MCS compared with 43.1% (68/157) subjects treated with placebo infusions + MTX. At the end of 2 years, the percentage of patients with a clinically significant improvement in the PCS was maintained for patients initially randomized to tocilizumab (47.4% [107/226] in the 4 mg/kg group and 50.0% [124/248] in the 8 mg/kg arm) but increased to similar levels (50.0%, 68/136) for the control group of subjects.

A complete clinical response is defined as a continuous 6-month period of remission by ACR criteria and no radiographic progression. Five patients randomized to tocilizumab (1 in the 4 mg/kg group and 4 in the 8 mg/kg treatment arm) obtained a complete clinical response. No patients randomized to placebo + MTX achieved this outcome.

Efficacy conclusions

The efficacy data from Study WA17823 indicates that tocilizumab (either 4 or 8 mg/kg) + MTX is statistically superior in a clinically meaningful manner to continued MTX

monotherapy in reducing the rate of radiographic progression over 104 weeks in a heterogeneous group of patients with RA who had high disease activity at baseline and were at substantial risk of progression. Clinically and statistically significant improvements in physical function, as evaluated by the HAQ-DI, were observed for both doses of tocilizumab + MTX compared with placebo infusions + MTX.

Furthermore, both doses of tocilizumab + MTX were superior to MTX alone in reducing the signs and symptoms of RA, as assessed by ACR and EULAR criteria, including the proportion of patients achieving a major clinical response.

Supporting Open-Label Extension Studies (WA18695, WA18696 and WA17823)

Long-term efficacy data was obtained from three open-label extension (OLE) studies. Patients who completed the 24-week observation periods of the core Phase III controlled trials were allowed to continue on tocilizumab into one of two open-label extension studies (WA18695 and WA18696). In addition, subjects who completed the 2 year core study period for Study WA17823 were eligible to continue with tocilizumab therapy in an open-label extension phase. The primary objective of the OLE studies was to assess long-term safety and tolerability; however, efficacy measures (of the same outcome type in the controlled periods) were also collected to determine the durability of clinical benefit. Efficacy parameters were assessed every 12 weeks in Studies WA18695 and WA18696, and every 8 weeks in Years 3-5 of Study WA17823. The data cut-off date for the dataset was 6 February 2009.

Study WA18695 recruited 537 patients (including escape patients) who completed 24 weeks of follow-up in the forerunner Study WA17822. A total of 623 subjects were involved in Study WA17822 which enrolled patients with moderate-severe active RA who were responding inadequately to MTX at study entry.

Study WA18696 recruited 2066 patients who completed 24 weeks of follow-up in three prior Phase III studies and one clinical pharmacology trial: -

- § WA17824 (n=673) – subjects with moderate-severe active RA who were either MTX naïve or had MTX discontinued (but not because of toxicity or lack of response to MTX at study entry),
- § WA18062 (n=499) – patients with moderate-severe active RA with a history of inadequate response to anti-TNF medication,
- § WA18063 (n=1220) – subjects with moderate-severe active RA with inadequate response to DMARD therapy, and
- § WP18663 (n=23) – patients with active RA who participated in a PK study of simvastatin in combination with tocilizumab and MTX.

In the three OLE studies, patients were expected to receive tocilizumab treatment at a dose of 8 mg/kg every 4 weeks. The first dose of tocilizumab in the extension phase was to be given within 12 weeks of the patient receiving their last dose of infusion study medication in the preceding trial. Modifications to treatment were permissible including temporary treatment interruption or a dose reduction to tocilizumab 4 mg/kg. If the dose was reduced to 4 mg/kg, then treatment could continue at that dose as long as no further safety concerns developed and efficacy was being maintained (that is, the number of swollen and/or tender joints was the same or fewer than before the dose reduction). The majority of OLE patients continued with adjunctive conventional DMARD therapy (mainly, MTX). Other permitted DMARDs included chloroquine or hydroxychloroquine, parenteral gold, sulfasalazine, azathioprine and leflunomide. Conventional DMARDs could be used either alone (with tocilizumab) or in any combination, except for the combination of MTX and leflunomide which was not permitted.

It was recommended that the doses of conventional DMARDs remained stable for the first 48 weeks in Studies WA18695 and WA18696. All patients who enrolled in Study WA18696 from Study WA17824 received tocilizumab as monotherapy if they had achieved at least a 50% reduction from baseline in their tender and swollen joint counts during the initial controlled phase.

In all three OLE studies, stable background doses of oral corticosteroids (equal or less than 10 mg/day of prednisolone or equivalent) were allowed at initial entry to the controlled studies and could be continued if the patient did not achieve at least a 50% improvement from baseline in both the swollen and tender joint count. However, dose reductions of up to 1 mg/day of prednisolone (or equivalent) every 2 weeks were allowed in the OLE phase if the patient had improved by more than 50% from baseline in both the swollen and tender joint count. Parenteral corticosteroids were not permitted in any of the trials. Stable doses of NSAIDs were requested for at least 48 weeks during the OLE studies (unless safety concerns emerged). Intra-articular corticosteroids were not permitted within 6 weeks prior to baseline in Studies WA18695 and WA18696, or within 8 weeks of any of the scheduled study assessments. A maximum of three intra-articular steroid injections per year were allowed in the OLE trials with no single injection to exceed 40 mg (or equivalent) of triamcinolone, and the maximal total annual dose of injectable steroid being not greater than 80 mg of triamcinolone (or equivalent).

Study Population

The characteristics of the patients recruited into the OLE phase from Study WA17823 are well described in the assessment of the controlled study. The original recruited patient population for subjects obtained from the other Phase III controlled studies had moderately-severely active RA at baseline (at least 6 swollen joints [of a possible maximum of 66] and at least 8 tender joints [of a possible maximum of 68] as well as raised serum inflammatory markers [ESR >28 mm/hr or CRP >10 mg/dL]). Patients entered into Study WA18695 came from 72 centres in 17 countries and patients involved in Study WA18696 came from 291 centres in 30 countries. In general, most patients had previously failed MTX (Study WA17822), DMARDs (Study WA18063), or one or more anti-TNF medications within a year prior to the study (Study WA18062). The exception was the patient population from Study WA17824 with patients who were either MTX naïve or had discontinued MTX for reasons other than toxicity or lack of efficacy within the prior 6 months. The minimum duration of RA was 3 months in WA17824 and 6 months in all the other core studies. Hence, Study WA17824 was designed to recruit patients with shorter disease duration and predominately DMARD-naïve, compared to the other Phase III trials whereby patients had longer RA disease duration which had also been refractory to other treatment options.

Efficacy Parameters

The efficacy endpoints for the OLE studies were clinical in nature and included:

1. Proportion of patients with ACR 20, 50 and 70 responses up to Week 156 of therapy,
2. Proportion of patients achieving clinically significant improvements in components of the ACR core set variables between Weeks 48 and 96,
3. Mean change in HAQ-DI score up to Week 156,
4. Proportion of patients achieving DAS28 clinical remission up to Week 180,
5. Proportion of patients achieving “good” EULAR responses,

6. The ACR50 response rates achieved when patients switched from tocilizumab 4 mg/kg to 8 mg/kg, and
7. The relationship between loss of efficacy and the development of anti-tocilizumab antibodies.

Statistical Analysis and Data Handling Methods

Three study cohorts were defined within the “All exposure” population (defined as any patient who received at least 1 dose of tocilizumab either in the controlled or OLE phase), according to patient type identified in the core studies:

- 1) The “pooled” group which consisted of all patients randomized into Studies WA17822, WA17823 and WA18063 who had an inadequate response to MTX or other conventional DMARDs at baseline,
- 2) The WA17824 group who received tocilizumab monotherapy and were largely naïve to MTX, and
- 3) The WA18062 group who were inadequate anti-TNF responders at baseline.

The rationale for splitting the two latter groups away from the pooled analysis is appropriate given that these are likely to be sufficiently different types of patients with RA from the main pooled group. Furthermore, to coordinate the pooling of data from the three separate OLE studies, assessments for patients involved in Years 3-5 of Study WA17823 were performed every 8 weeks but time-windowed in 12-week intervals by selecting the assessment performed nearest to the pre-determined 12-week time points, so as to match the data acquisition scheduling of the other OLE trial results (assessments in Studies WA18695 and WA18696 were done every 12 weeks). The baseline used for patients included in the “All Exposure” population analysis was defined as the time when the patients received their first dose of tocilizumab, which could occur in the core study (either at entry or during escape therapy) or at any time in the OLE phase.

Because of the non-comparative, open-label design of the studies, no hypotheses were tested. However, there were pre-defined rules for handling of missing data depending on the efficacy outcome. For ACR responses (20/50/70) and DAS28 calculation, patients who withdrew were classified as missing and subsequently excluded from the summary statistics. Tender and swollen joint count assessments utilized a LOCF methodology but no imputation was used for missing HAQ scores. For serum inflammatory markers (ESR or CRP), the alternative marker was used for missing readings. EULAR responses were not determined unless the DAS28 was calculable.

Patient Disposition and Drug Exposure

The “All Exposure” population dataset contained a total of 4009 patients. Of these, 2644 received tocilizumab 4 mg/kg (n=774) or 8 mg/kg (n=1870) as part of their initial randomized therapy. In the total patient population involved in the OLE studies, the proportion of subjects from each of the preceding studies was 14.9% (n=597) from Study WA17822, 28.7% (n=1149) from Study WA17823, 15.4% (n=618) from Study WA17824, 11.6% (n=464) from Study WA18062, 28.9% (n=1158) from Study WA18063 and <0.01% (n=23) from Study WP18663. In the last study, all 23 participants received tocilizumab 10 mg/kg (every 4 weeks) + MTX in the controlled phase. All patients in the OLE phase received tocilizumab in combination with DMARDs (mostly, MTX) with the exception of 234 subjects (out of a possible 288) who continued to receive open-label tocilizumab 8 mg/kg monotherapy after commencing this same treatment regimen upon entry into controlled Study WA17824.

The total exposure to tocilizumab as of the data cut-off date (6 February 2009) was 8579.7 patient-years (817.2 for tocilizumab 4 mg/kg and 7760.7 for tocilizumab 8 mg/kg). The average duration of treatment follow-up (time from first dose of tocilizumab to final safety assessment) in the OLE phase was 2.35 (median 2.57 years; range: 0-4.1) years. Most patients (92.3%, 3701/4009) completed at least 6 months of treatment, 84.8% (3399/4009) completed at least 48 weeks of follow-up, 74.0% (2968/4009) completed at least 96 weeks of therapy and 62.3% (2499/4009) were still available at 144 weeks for assessment. A small proportion of patients (3.8%, 152/4009) discontinued due to insufficient response during the OLE phase. Other common non-safety reasons for withdrawal from the OLE population were withdrawal of consent (5.6%, 223/4009) and failure to return for follow-up (1.5%, 58/4009). In total, 26.5% (1064/4009) of subjects withdrew from the OLE phase – 547 (13.6%) for safety reasons and 517 (12.9%) for non-safety reasons.

Efficacy results

ACR response rates for each of the three defined groups in the “All Exposure” population demonstrated either maintenance or improved rates of response from tocilizumab therapy up to 156 weeks (Table 3). Patients recruited from Study WA17824 (who generally started on tocilizumab monotherapy and continued this approach in OLE) consistently showed the highest rates of response which reflects their earlier stage of disease at recruitment and history of fewer failed previous DMARDs. Those subjects enrolled from Study WA18062 (an anti-TNF inadequate responder population) consistently showed lower overall rates of response, reflecting their advanced stage and treatment refractory nature of disease.

Table 3: Summary of ACR20, ACR50 and ACR70 response rates by visit – All Exposure population

ACR Parameter	Week 48	Week 72	Week 96	Week 108	Week 132	Week 156
WA17824 (N=618)						
ACR response rates	n=521	n=487	n=450	n=386	n=229	n=77
ACR20 (%)	361 (69.3%)	351 (72.1%)	336 (74.7%)	302 (78.2%)	187 (81.7%)	64 (83.8%)
ACR50 (%)	256 (49.1%)	256 (52.6%)	246 (54.7%)	240 (62.2%)	148 (64.6%)	51 (66.2%)
ACR70 (%)	164 (31.5%)	152 (31.2%)	163 (36.2%)	145 (37.6%)	102 (44.5%)	33 (42.9%)
ACR70 response maintained	n=542	n=511	n=478	n=442	n=311	n=122
24 consecutive weeks (%)	70 (12.9%)	90 (17.6%)	98 (20.5%)	93 (21.0%)	68 (21.9%)	28 (23.0%)
48 consecutive weeks (%)	NA	52 (10.2%)	71 (14.9%)	70 (15.8%)	54 (17.4%)	22 (18.0%)
96 consecutive weeks (%)	NA	NA	NA	22 (5.0%)	33 (10.6%)	5 (4.1%)
WA18062 (N=464)						
ACR response rates	n=354	n=320	N=293	n=280	n=201	n=91
ACR20 (%)	225 (63.6%)	219 (68.4%)	207 (70.6%)	203 (72.5%)	151 (75.1%)	65 (71.4%)
ACR50 (%)	131 (37.0%)	143 (44.7%)	131 (44.7%)	129 (46.1%)	93 (46.3%)	50 (54.9%)
ACR70 (%)	66 (18.6%)	76 (23.8%)	69 (23.5%)	77 (27.5%)	57 (28.4%)	37 (40.7%)
ACR70 response maintained	n=368	n=335	n=310	n=296	n=247	n=124
24 consecutive weeks (%)	14 (3.8%)	30 (9.0%)	37 (11.9%)	40 (13.5%)	30 (12.1%)	16 (12.9%)
48 consecutive weeks (%)	NA	12 (3.6%)	19 (6.1%)	23 (7.8%)	19 (7.7%)	13 (10.5%)
96 consecutive weeks (%)	NA	NA	NA	6 (2.0%)	8 (3.2%)	6 (4.8%)
Pooled (N=2904)						
ACR response rates	n=2429	n=2284	n=2173	n=2030	n=1603	n=943
ACR20 (%)	1678 (69.1%)	1699 (74.4%)	1661 (76.4%)	1580 (77.8%)	1284 (80.1%)	771 (81.3%)
ACR50 (%)	1085 (44.7%)	1156 (50.6%)	1157 (53.2%)	1124 (55.4%)	949 (59.2%)	573 (60.8%)
ACR70 (%)	580 (23.9%)	687 (30.1%)	683 (31.4%)	705 (34.7%)	577 (36.0%)	379 (40.2%)
ACR70 response maintained	n=2530	n=2358	n=2220	n=2143	n=1758	n=1124
24 consecutive weeks (%)	192 (7.6%)	326 (13.8%)	360 (16.2%)	372 (17.4%)	355 (20.2%)	244 (21.7%)
48 consecutive weeks (%)	NA	137 (5.8%)	234 (10.5%)	239 (11.2%)	253 (14.4%)	182 (16.2%)
96 consecutive weeks (%)	NA	NA	NA	53 (2.5%)	112 (6.4%)	97 (8.6%)

The proportion of subjects achieving major clinical response (an ACR70 response for at least 24 consecutive weeks) was significant (for example, 21.7% [244/1124] at Week 156 for the pooled group) and generally increased with time on therapy.

The proportion of patients achieving clinically significant changes between Weeks 48 and 96 of therapy in the ACR core set components improved significantly for some variables (namely, tender or swollen joint count of 0) or were slightly better with time for other variables (in particular, patients achieving a HAQ score of 0, indicating no functional disability). The proportion of subjects demonstrating a zero swollen joint count at Week 48 was 35.6% (193/542) for Study WA17824, 16.8% (62/368) for Study WA18062 and 25.4% (642/2530) for the pooled group, and the corresponding respective rates were higher in all three groups at Week 96 (40.4% [193/478] for Study WA17824, 22.9% [71/310] for Study WA18062 and 35.7% [792/2220] for the pooled group). At Week 96, a higher or similar percentage of patients in all three defined populations in the “All Exposure” dataset showed a zero HAQ score (22.5% [102/453] for Study WA17824, 7.9% [23/292] for Study WA18062 and 14.6% [309/2117] for the pooled group) compared with the same result at Week 48 (20.5% [108/528] for Study WA17824, 3.9% [14/355] for Study WA18062 and 12.9% [307/2377] for the pooled group).

Mean scores for HAQ-DI in the “All Exposure” population decreased with tocilizumab therapy over time. While improvement in physical function, as indicated by a decrease in HAQ-DI score, was greatest for patients from Study WA17824, mean scores for all groups showed persistence of effect or continued improvement with extended duration of tocilizumab treatment. At Week 48, mean HAQ-DI scores had decreased from baseline by 44.0% (1.34 to 0.75) for patients from Study WA17824, 33.8% (1.48 to 0.98) for “pooled group” subjects and 25.1% (1.71 to 1.28) for patients from Study WA18062. At Week 96, mean HAQ-DI scores had decreased from baseline by 47.0% (1.34 to 0.71) for patients from Study WA17824, 37.8% (1.48 to 0.92) for “pooled group” subjects and 29.2% (1.71 to 1.21) for patients from Study WA18062. HAQ-DI score changes were also analysed by the proportion of patients achieving certain thresholds of improvement from baseline (defined as decreases of at least 0.25, 0.50 and 0.75). The minimal clinically relevant improvement from baseline in HAQ-DI is considered to be an improvement of at least 0.22. The percentage of subjects achieving significant threshold improvements in HAQ-DI increased for all three treatment groups over time, with the greatest response rates observed in patients enrolled from Study WA17824 and the least improvement demonstrated in subjects recruited from Study WA18062. At Week 96, the proportion of patients achieving a HAQ-DI improvement of at least 0.25, 0.5 and 0.75 ranged from 63.4 to 70.6%, 44.9 to 56.2% and 30.8 to 44.0%, respectively, across the three defined populations.

With extended treatment duration the proportion of patients who achieved and maintained DAS remission ($DAS28 < 2.6$) for at least 24 weeks appeared to increase. For example, at Week 144 the proportion of patients achieving and maintaining DAS clinical remission was 30.4% (436/1436) for the pooled group, 24.2% (51/211) for patients from Study WA17824 and 15.8% (29/183) for subjects from Study WA18062. These rates of remission were maintained in all three population groups up to Week 156, which is the last time point whereby meaningful numbers of continuing patients were available for assessment. A similar observation was apparent for the rates of EULAR good response up until Week 156.

For the subgroup analyses, the impact of patient body weight on clinical response was explored from the OLE data in the “All Exposure” population. In this analysis, ACR50 response rates by baseline body weight were evaluated in four patient sub-groups (60 kg, 60-79.9 kg, 80-100 kg and > 100 kg). Patients weighing less than 60 kg had the highest efficacy in long-term follow-up, indicating that a minimum tocilizumab dose of 480 mg per infusion is not required. As patient weight increased, response to tocilizumab reduced somewhat. After 48 weeks of therapy, ACR50 response rates in the < 60 kg patient subgroup were 49.6% (59/119) for patients recruited from Study WA17824, 42.4% (28/66) for subjects from

WA18062 and 47.1% (284/603) for patients from the pooled group. In contrast, ACR50 responses at Week 48 for patients > 100 kg were 34.9% (15/43), 32.6% (14/43) and 38.7% (72/186), respectively for the corresponding studies. After 96 weeks of tocilizumab treatment, patients weighing < 60 kg continued to show greater rates of improvement in ACR50 response rates (58.5% [62/106], 54.8% [34/62] and 56.9% [314/552] for the 3 population groups, respectively) compared with rates of ACR50 response in the > 100 kg sub-group of 39.4% (13/33), 40.6% (13/32) and 43.7% (66/151).

To further explore the relationship between tocilizumab drug exposure and efficacy in patients with a body weight exceeding 100 kg, the sponsor performed modeling simulations. The simulations compared 2 dosing regimens - tocilizumab 8 mg/kg every 4 weeks versus a capped dose of 800 mg every 4 weeks. Two response criteria were evaluated (EULAR good response and DAS28 remission) over 6 months of treatment. The modeling predicted that the proportion of patients > 100 kg achieving DAS28 remission at Week 24 following tocilizumab 8 mg/kg was 39.8% (SD 5.5, range: 28.9-53.0) was comparable to that achieved with dose capping at 800 mg (38.5%, SD 5.3, range: 26.5-51.8). Similarly, the proportion of subjects predicted to achieve a good EULAR response at 24 weeks was 50.5% (SD 5.1, range: 37.3-63.8) for 8 mg/kg which is comparable to the dose capping strategy (48.8%, SD 4.9, range: 36.1-60.2). Hence, the difference in response to tocilizumab 8 mg/kg compared with a fixed capped dose of 800 mg in patients > 100 kg is of no clinical significance. These results support the sponsor's proposal to cap the dose of tocilizumab to 800 mg per infusion for patients weighing > 100 kg.

With respect to the subgroup analysis of patients who switched from tocilizumab 4 to 8 mg/kg (subjects who originally received tocilizumab 4 mg/kg in the core studies WA17822, WA17823 or WA18062; and then received tocilizumab 8 mg/kg either as escape therapy or upon entering OLE), the results for all three efficacy parameters assessed (ACR50, HAQ-DI and DAS28 score) showed that both initial responders and non-responders (for ACR20 level) continued to demonstrate improved rates of response over time after the switch to tocilizumab 8 mg/kg. For example, for tocilizumab switch patients enrolled from Study WA17823, the rate of subsequent ACR50 response achieved increased from approximately 60% (for responders, n=242) and 20% (non-responders, n=255) at Week 48 to approximately 70% (for responders, n=221) and 35% (non-responders, n=213) at Week 96. Similar rates of improvement over time in the proportions of tocilizumab treatment switch patients achieving ACR50 response were observed for subjects recruited from studies WA17822 and WA18062.

The presence of anti-drug antibodies has been associated with a loss of efficacy with all biological drugs used in the treatment of RA. The development of anti-tocilizumab antibodies and its relationship with efficacy was also explored. A total of 152 patients in the "All Exposure" population withdrew because of insufficient therapeutic response and 66 of these patients (43.4%) were positive for neutralizing drug antibodies at any time. In addition, 41.2% (14/34) subjects who obtained either an ACR50 or good EULAR response prior to withdrawal from lack of efficacy in the OLE studies tested positive to neutralizing drug antibodies. Although it is difficult to interpret these data because of small patient numbers, the incidence of withdrawal from loss of efficacy in association with formation of anti-drug antibodies appears to be higher than the overall population. A total of 127 patients (3.2% of the total tested population of 3937 subjects) tested positive for neutralizing antibodies; of these, 66 withdrew because of lack of efficacy and 14 achieved good efficacy but subsequently lost it.

Efficacy conclusions

The efficacy data from the open-label extension experience indicates that treatment with tocilizumab (often in combination with MTX) results in significant proportions of patients either maintaining or continuing to improve in a clinically meaningful manner (ACR 50 and 70 responses, and clinical remission) for up to 156 weeks of follow-up. Patients initially received tocilizumab 4 mg/kg and then switched to open-label tocilizumab 8 mg/kg generally showed improvement in disease activity.

Safety

The safety analysis included all patients who received at least part of one dose of the study medication during the clinical trial program. Up to the cut-off date for this submission (11 April 2009), 4009 patients comprised the “All Exposure” population (that is, received at least one dose of tocilizumab, either in a controlled or open-label setting) for the assessment of safety. Just over 1000 of these patients received treatment for at least 156 weeks (3 years). The “All Exposure” population experience provides a total of 8579.7 patient-years of exposure and 9414.3 patient-years of observation following treatment with tocilizumab. In the “All Control” population (that is, those who received treatment under controlled clinical trial settings), a total of 2644 subjects have received at least part of one infusion of tocilizumab (774 patients on 4 mg/kg [total exposure of 500.1 patient-years] and 1870 subjects on 8 mg/kg [total exposure of 1013.2 patient-years]) and 1555 patients had received control treatment (exposure of 717.4 patient-years) as of the data cut-off date of 6 February 2009. In all but one of the earlier studies (WA17824), all patients continued to receive concurrent DMARDs (mostly MTX) with tocilizumab.

Study WA17823

The safety population consisted of all randomized patients who received at least one dose of the study medication, and who had at least one post-randomization safety assessment. Patients for this analysis were grouped according to the treatment they received at baseline, and this resulted in reporting safety outcomes according to five treatment groups (three groups of non-switch patients and two groups who had switching regimens):

- § Placebo (n=392) – this includes subjects randomized to placebo + MTX until they received escape therapy in Year 1 or switched to open-label tocilizumab treatment in Year 2,
- § Tocilizumab 4 mg/kg (n=146) – this includes patients randomized to tocilizumab 4 mg/kg + MTX until they withdrew or completed Year 2; and patients from placebo + MTX group who switched to escape therapy with tocilizumab 4 mg/kg and either withdrew or completed the trial on this regimen,
- § Tocilizumab 8 mg/kg (n=532) – this includes subjects initially allocated treatment with tocilizumab 8 mg/kg until they withdrew or completed Year 2; and patients randomized to placebo + MTX who switched directly to tocilizumab 8 mg/kg after 52 weeks,
- § Tocilizumab 4 to 8 mg/kg but only while receiving 4 mg/kg (n=451) – this includes patients initially randomized to either placebo + MTX who then switched to tocilizumab 4 mg/kg; and patients originally randomized to tocilizumab 4 mg/kg + MTX who then switched to tocilizumab 8 mg/kg as part of escape treatment or open-label therapy in Year 2, and
- § Tocilizumab 4 to 8 mg/kg but only while receiving 8 mg/kg (n=451) – this includes patients initially randomized to either placebo + MTX who then ultimately switched

to tocilizumab 8 mg/kg as part of a 2-step escape treatment; and subjects originally randomized to tocilizumab 4 mg/kg + MTX who then switched to tocilizumab 8 mg/kg as part of escape treatment or open-label therapy in Year 2.

Safety information was recorded on Days 1, 15 and 28, and then every 4 weeks thereafter until Week 112 (up to 8 weeks post-study). For patients who switched to open-label treatment with tocilizumab 8 mg/kg at Week 52 but were previously naïve to this therapy, fortnightly visits (rather than 4 weekly assessments) occurred between Weeks 52 and 60 as part of the safety monitoring schedule. Adverse events (AEs) were classified using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE, version 3) which grades events as mild, moderate, severe, or life-threatening. The dates of onset and resolution of the AE were recorded, and the relationship of the AE to treatment was also assessed.

Drug Treatment Exposure

The safety analysis in this submission was the cumulative dataset obtained from the blinded study period (previously presented in the original tocilizumab marketing application), escape data during Year 1 and the second year of treatment with tocilizumab 8 mg/kg + MTX in the majority of subjects. As such, the total treatment duration in the tocilizumab 8 mg/kg group increased from 349.15 patient-years at Week 52 (n=399) to 1320.4 patient-years at Week 104 (n=983; comprising 532 whose only dose was 8 mg/kg and 451 patients switching from tocilizumab 4 mg/kg).

For the tocilizumab 4 mg/kg group, exposure to therapy increased from 328.71 patient-years at Week 52 (n=399) to 521.9 patient-years at Week 104 (n=597; 451 of whom switched to tocilizumab 8 mg/kg). The absolute number of patients receiving tocilizumab 4 mg/kg + MTX at each of the critical evaluation time points in the study was 399 at baseline, 194 at Week 52, 21 at Week 54 and less than 10 after Week 84.

Expectedly, for the placebo infusion + MTX arm, there was only a minimum change in treatment exposure between Weeks 52 and 104 (from 256.13 to 284.8 patient-years). The absolute number of continuing patients in the placebo + MTX group declined from 392 at baseline to 155 (39.5% of the original cohort) at Week 52, 30 (7.7%) at Week 54 and only 20 (7.9%) at Week 104.

Because few patients remained on placebo or tocilizumab 4 mg/kg during Year 2 of the study, median treatment durations up to Week 104 were dissimilar between the three original treatment groups, it was 1.99 years for those subjects whose only therapy was tocilizumab 8 mg/kg, 0.92 years for patients in the tocilizumab 4 mg/kg arm and 0.54 years for subjects randomized to placebo infusions + MTX.

For the two treatment switch groups, the total duration of exposure was 338.6 and 475.9 patient-years, respectively for tocilizumab (4→8) 4 mg/kg group (n=451; median duration 0.70 years) and tocilizumab (4→8) 8 mg/kg group (n=451; median duration 1.00 years).

Protocol Rules for Dose Modification

The following rules applied to dose modifications or changes in dose administration during both the double-blind and open-label phases of the study.

If subjects experienced an increase in serum transaminases (alanine transaminase [ALT] or aspartate transaminase [AST]) of at least 3 x the upper limit of normal (ULN) then the study medication was to be interrupted and follow-up blood samples were to be taken fortnightly. Once the serum transaminases were below 3 x ULN then study treatment could be recommenced at the next scheduled 4 weekly visit. Discontinuation of treatment was required

if any one of the following were recorded: (1) the subject had serum transaminases > 5 x ULN more than 4 weeks after their last infusion of tocilizumab, (2) serum transaminases > 10 x ULN at any time, or (3) if the AST and/or ALT were > 3 x ULN in association with any one of the additional features (total serum bilirubin > 2 x ULN, international normalised ratio [INR] > 1.5 ULN, serum alkaline phosphatase > 2 x ULN, or symptoms consisting of worsening fatigue, nausea, vomiting, fever, rash or eosinophilia).

The presence of any signs suggestive of infection required withholding of treatment and the study medication was to recommence at the next scheduled 4 weekly visit after resolution of the infection. Patients with an absolute neutrophil count of $< 1000/\text{mm}^3$ were to interrupt study treatment or discontinue therapy if the neutrophil count was $< 500/\text{mm}^3$.

For possible infusion-related reactions (IRR) - fever, chills, pruritis, urticaria or cardiovascular manifestations - the infusion rate was reduced by at least half as an initial management strategy. If the patient continued to show any symptoms or signs of an IRR, an intravenous dose of antihistamine, corticosteroids and/or adrenaline was recommended. If cardiovascular collapse accompanied the IRR, the subject was withdrawn from the study.

Overview of Adverse Events

During the first 52 weeks of treatment, almost half of the patients randomized to placebo infusions + MTX initiated escape therapy with tocilizumab after Week 16, whereas the majority of patients allocated to either dose of tocilizumab maintained their initial treatment. Patient data for those who initiated escape therapy were analysed separately and, although the Week 52 analysis provides valuable insight into the comparative incidence of AEs, there is some bias in its interpretation. In particular, the median exposure to study treatment for subjects randomized to placebo + MTX is approximately half that for patients randomized to either dose of tocilizumab. The overall percentages of patients who experienced AEs, serious adverse events (SAEs) and AEs leading to withdrawal or dose interruption were higher for patients who received tocilizumab 4 or 8 mg/kg compared to placebo + MTX subjects (Table 4). When differences in drug exposure are taken into account the event rate for all of these different types of AEs remained higher in the two tocilizumab treatment groups compared to placebo + MTX. Infections (overall and serious), gastrointestinal perforations and abnormal investigations (mainly, those related to liver function tests) were reported at higher event rates for patients who received either dose of tocilizumab. Furthermore, patients treated with tocilizumab recorded greater mean increases in serum transaminases, total and LDL-cholesterol values and greater mean decreases in absolute neutrophil counts compared with patients on placebo + MTX. These changes in mean laboratory parameters often remained in the normal reference range but a tocilizumab dose response relationship was additionally observed.

Table 4: Study WA17823 – Overview and extent of exposure and adverse events during initial randomization treatment up to Week 52: escape data excluded (Safety Population)

	Placebo + MTX N = 392	TCZ 4 mg/kg + MTX N = 399	TCZ 8 mg/kg + MTX N = 399
Extent of Exposure to Trial Treatment			
Total patient years of duration on trial treatment	256.13	328.71	349.15
Adverse Events, n (%)			
All AEs [#]	252 (64%)	310 (78%)	310 (78%)
No of AEs [P100-PY] [@]	663[258.85]	988[300.57]	1054[301.88]
Severe AEs [#]	33 (8%)	56 (14%)	51 (13%)
No of Severe AEs [P100-PY] [@]	40[15.62]	73[22.21]	71[20.34]
SAEs [#]	22 (6%)	35 (9%)	34 (9%)
No of SAEs [P100-PY] [@]	26[10.15]	42[12.78]	40[11.46]
AEs that led to withdrawal #	9 (2%)	28 (7%)	32 (8%)
No AE leading to withdrawal [P100-PY]	9[3.51]	28[8.52]	32[9.17]
AEs that led to dose interruption [#]	42 (11%)	75 (19%)	88 (22%)
No AE leading to dose interruption [P100-PY] [@]	47[18.35]	99[30.12]	117[33.51]
Deaths^a	1(<1%)	–	3(<1%)

^a Two additional deaths were reported for patients on escape therapy, one patient was receiving 4 mg/kg and one was receiving 8 mg/kg.

[#] Total patients with at least one AE

[@] Multiple occurrences of the same adverse event in one individual are counted once.

The cumulative dataset up to Week 104 was presented in terms of the actual treatment pathway that the patient received and included information from those subjects who received escape treatment. Given the study design in which all patients were eligible to receive open-label tocilizumab 8 mg/kg + MTX in Year 2 (and many subjects followed that treatment pathway), the placebo treatment dataset at Week 104 remained unchanged from Year 1, and most of the additional data accrued primarily for the tocilizumab 8 mg/kg group in Year 2. The nature and frequency of AEs (including deaths, SAEs and AEs leading to treatment withdrawal or dose modification) and laboratory parameters at Week 104 remained consistent with the profile observed in Year 1 for tocilizumab 8 mg/kg + MTX (Table 5).

Table 5: Study WA17823 – Overview of adverse events for patients on TCZ 8 mg/kg at Week 52 and Week 104 (Safety Population)

	Week 52	Week 104	
	TCZ 8 mg/kg + MTX Initial Randomized ^a N = 399	TCZ 8 mg/kg + MTX Non-switchers ^b N=532	TCZ 8 mg/kg + MTX Pool ^c N = 983
Median duration in study, years	ND	1.99	1.08
Total patient years of duration on trial treatment (PY)	349.15	844.56	1320.41
All AEs			
No. of AEs [P100-PY]	1054 (301.88)	2140 [253.4]	3481 [263.6]
Severe AEs			
No. of AEs [P100-PY]	71 [20.34]	148 [17.5]	260 [19.7]
SAEs			
No. of AEs [P100-PY]	40 [11.46]	96 [11.4]	150 [11.4]
AEs that led to withdrawal			
No. of AEs [P100-PY]	32 [9.17]	62 [7.3]	97 [7.3]
AEs that led to dose interruption			
No. of AEs [P100-PY]	117 [33.51]	257 [30.4]	429 [32.5]

^a Excludes patients who initiated escape therapy.

^b Excludes patients who previously received TCZ 4 mg/kg.

^c Includes all patients who received TCZ 8 mg/kg, regardless of previous treatment.

Multiple occurrences of the same adverse event in one individual are counted once

The safety analysis of data at Week 104 performed by pooling subjects according to the treatment they received showed that the rates of AEs, SAEs and in particular AEs leading to withdrawal and dose interruption were higher for patients who received either dose of tocilizumab than for subjects who received placebo infusions + MTX (Table 6).

Table 6: Study WA17823 – Overview of adverse events pooled by treatment received up to Week 104 (Safety Population)

	Placebo + MTX N = 392	TCZ 4 mg/kg + MTX N = 597	TCZ 8 mg/kg + MTX N = 983
Median duration on study, years	0.54	0.92	1.08
Total patient years of duration on trial treatment (PY),	284.81	521.90	1320.41
All AEs			
No. of AEs [P100-PY]	716 [251.4]	1439 [275.7]	3481 [263.6]
SAEs			
No. of AEs [P100-PY]	31 [10.9]	63 [12.1]	150 [11.4]
AEs that led to withdrawal			
No. of AEs [P100-PY]	12 [4.2]	44 [8.4]	97 [7.3]
AEs that led to dose interruption			
No. of AEs [P100-PY]	58 [20.4]	160 [30.7]	429 [32.5]
Deaths, n	1[0.35]	1 [0.19]	8 [0.61]

Interestingly, patients treated with tocilizumab 4 mg/kg + MTX from study commencement had the highest incidence of SAEs, and AEs resulting in withdrawal and dose modification (Table 7).

Table 7: Study WA17823 – Overview of adverse events by treatment switch groups up to Week 104 (Safety Population)

	Non-Switch Patients			TCZ 4 mg/kg to 8 mg/kg Switch regimens	
	Placebo + MTX N = 392	TCZ 4 mg/kg + MTX N = 146	TCZ 8 mg/kg + MTX N = 532	4 mg/kg + MTX N = 451	8 mg/kg + MTX N = 451
Median duration of exposure, years	0.54	1.29	1.99	0.70	1.00
Total duration on trial treatment	284.81 PY	183.28 PY	844.56 PY	338.62 PY	475.85 PY
All AEs					
No. of AEs [P100-PY]	716 [251.4]	444 [242.3]	2140 [253.4]	995 [293.8]	1341[281.8]
Severe AEs					
No. of AEs [P100-PY]	45 [15.8]	46 [25.1]	148 [17.5]	56 [16.5]	112 [23.5]
SAEs					
No. of AEs [P100-PY]	31 [10.9]	43 [23.5]	96 [11.4]	20 [5.9]	54 [11.3]
AEs that led to withdrawal					
No. of AEs [P100-PY]	12 [4.2]	43 [23.5]	62 [7.3]	1 [0.3]	35 [7.4]
AEs that led to dose interruption					
No. of AEs [P100-PY]	58 [20.4]	53 [28.9]	257 [30.4]	107 [31.6]	172 [36.1]
Deaths					
No. of deaths [P100-PY]	1 [0.35]	1 [0.55]	6 [0.71]	–	2 [0.42]

P100-PY = per 100 patient years of exposure to trial treatment.

Multiple occurrences of the same adverse event in one individual are counted once.

However, among patients who switched from tocilizumab 4 mg/kg to 8 mg/kg, the event rate of all types of AEs were similar to those observed for patients treated with tocilizumab 8 mg/kg from the trial outset. However, these switch patients did demonstrate increased event rate frequencies for some selected AEs (for example, neutropenia, increased serum transaminases and hypercholesterolaemia) to suggest that these AEs may be dose-dependent. Moreover, patients who switched to tocilizumab 4 mg/kg had an incidence of AEs that approximated the placebo + MTX treatment group or high dose tocilizumab + MTX. This result is in contrast to the observations recorded for the group of subjects that received tocilizumab 4 mg/kg + MTX from study commencement.

Adverse events leading to withdrawal or dose interruptions

Subjects who received tocilizumab (either dose) recorded a higher incidence of withdrawal from the study due to AEs. A total of 69 patients withdrew from the study at Week 52 due to AEs – 9 patients (2.3% of 392; 3.51 per 100 patient-years) treated with placebo + MTX, 28 patients (7.0% of 399; 8.52 per 100 patient-years) treated with tocilizumab 4 mg/kg and 32 patients (8.0% of 399; 9.17 per 100 patient-years) treated with tocilizumab 8 mg/kg. During the second year of treatment where most patients received open-label tocilizumab 8 mg/kg + MTX, the incidence of withdrawals due to AEs in this group did not increase (7.3 per 100 PY in year 2 versus 9.17 per 100 PY in year 1).

The pattern of AEs resulting in withdrawal showed some important differences between the three treatment groups with respect to the comparative incidence and type of AEs. Abnormal investigation results (mainly, elevated serum transaminases) were observed at a higher rate in patients treated with tocilizumab (1 AE [0.4 per 100 PY] for placebo + MTX, 12 AEs [6.5 per 100 PY] for tocilizumab 4 mg/kg + MTX and 29 AEs [3.4 per 100 PY] for tocilizumab 8 mg/kg + MTX). Six patients treated with tocilizumab 4 mg/kg + MTX withdrew due to IRRs (anaphylactic reactions and drug hypersensitivity). This type of AE was not recorded in either of the other two treatment groups. Withdrawals due to malignancy occurred in 10 patients: 1

treated with placebo + MTX, 6 who were receiving tocilizumab 4 mg/kg and 3 being treated with tocilizumab 8 mg/kg. In total, 15 patients withdrew due to infections, 2 patients (0.4 per 100 PY) in the placebo + MTX group, 6 subjects (3.3 per 100 PY) in the low dose tocilizumab arm and 7 patients (0.8 per 100 PY) in the high dose tocilizumab + MTX group. The other AEs leading to withdrawal occurred equally amongst the treatment groups and affected less than 4 individuals in total: pulmonary embolus, gastrointestinal disorders and skin rash. The pattern of AEs did not alter during the second year of treatment. In addition, subjects who switched from tocilizumab 4→8 mg/kg did not demonstrate a higher incidence or different type of AE.

In addition to AEs resulting in patient withdrawal, a significant number of subjects had their study medication interrupted for safety reasons. This occurred more commonly in patients who received tocilizumab but there was no observed tocilizumab dose-toxicity relationship at 22.1% (88/399; 33.51 per 100 PY) for tocilizumab 8 mg/kg + MTX and 18.8% (75/399; 30.12 per 100 PY) for tocilizumab 4 mg/kg compared to 10.7% (42/392; 18.35 per 100 PY) for placebo + MTX. The most common reasons for medication interruptions were infections of minor severity (mainly, upper respiratory tract infections [URTIs]), abnormal investigations (primarily, hepatic enzyme elevations) and gastrointestinal disorders. These AEs occurred at similar rates across the treatment groups.

The rate of AEs leading to dose interruptions was slightly higher in patients who switched from tocilizumab 4 mg/kg→8 mg/kg (30.12 per 100 PY for tocilizumab 4 mg/kg versus 36.1 per 100 PY for the switch subjects) although the type of AEs was similar to that seen for the both tocilizumab dose groups in which subjects received stable treatment doses.

Most Frequent Adverse Events (Event rate frequency >2 per 100 patient-years)

The most common AE was URTI which occurred at a similar frequency in patients treated with placebo + MTX group (29/392; 10.2 per 100 PY) and both doses of tocilizumab (51/597; 9.8 per 100 PY for 4 mg/kg and 127/983; 9.6 per 100 PY for 8 mg/kg). Other common AEs (event frequency >2 per 100 PY) had a similar incidence across the three pooled treatment groups with the exception of hypertension, headache and increased serum transaminases which had a higher incidence in the tocilizumab treatment groups. For hypertension, the incidence was 6.7 per 100 PY (35/597) for tocilizumab 4 mg/kg and 5.3 per 100 PY (70/983) for tocilizumab 8 mg/kg compared to 4.2 per 100 PY (12/392) for placebo + MTX. Regarding the incidence of increased serum transaminases, this occurred at a rate of 5.4 per 100 PY (28/597) for tocilizumab 4 mg/kg and 5.1 per 100 PY (68/983) for tocilizumab 8 mg/kg compared to 2.1 per 100 PY (6/392) for placebo + MTX. Headaches were recorded with an incidence of 4.8 per 100 PY (24/597) for tocilizumab 4 mg/kg and 3.3 per 100 PY (43/983) for tocilizumab 8 mg/kg compared to 2.8 per 100 PY (12/392) for placebo + MTX.

Other common events occurring at either a similar event frequency in all groups or with the highest incidence in the placebo + MTX arm included urinary tract infection (5.0-7.4 per 100 PY), bronchitis (5.2-7.0 per 100 PY), nasopharyngitis (4.7-6.3 per 100 PY), sinusitis (3.5-5.6 per 100 PY), cough (2.0-3.9 per 100 PY) and gastroenteritis (2.3-3.9 per 100 PY).

Infusion Related Reactions

Adverse events occurring during or within 24 hours of each infusion were recorded and may be linked to cytokine release and/or acute infusion-related reactions (IRRs). Symptoms or signs suggesting an acute IRR include pruritus, fever, urticaria/rash, pyrexia, chills, rigors, angioedema, throat irritation, cough and bronchospasm with or without associated hypotension or hypertension.

Patients receiving tocilizumab 4 mg/kg (28.74 per 100 PY [95% CI 24.33, 33.73]) and placebo infusions (24.23 per 100 PY [95% CI 18.85, 30.66]) experienced AEs during or within 24 hours of their infusion at a higher event rate compared to subjects who received tocilizumab 8 mg/kg infusions (18.17 per 100 PY [95% CI 15.95, 20.63]). The majority of IRRs (>80%) had an onset after the infusion was completed but within 24 hours of drug administration. The pattern of IRRs was similar between the placebo and tocilizumab groups with the most common AEs being gastrointestinal (for example, nausea and diarrhoea, affecting 2.0-4.0% of patients in any treatment group), minor infections (usually urinary or respiratory tract, affecting 2.8-4.1%), abnormal investigations (1.1-3.4%) and fatigue (3.0-3.4%). However, some AEs occurred at a higher incidence in both of the tocilizumab + MTX groups compared to placebo + MTX and these include elevated hepatic enzymes (3.0-3.4% vs 0) and headache (2.0-2.1% vs 0.3%).

Nearly all of the IRRs were either Grade 1 or 2 severity, but 4 patients who received tocilizumab 4 mg/kg + MTX and 2 patients while receiving tocilizumab 8 mg/kg + MTX experienced severe (Grade 3 or more) AEs. All of these severe IRRs occurred during the initial three infusions of tocilizumab and were consistent with either an anaphylactic reaction or drug hypersensitivity (angioedema, laryngeal oedema, throat irritation, and hypotension). In general, the management of these severe AEs involved ceasing the drug infusion and giving IV corticosteroids and/or adrenaline.

In total, 17 patients (10 on tocilizumab 4 mg/kg, 6 receiving tocilizumab 8 mg/kg and 1 placebo + MTX patient) withdrew as a result of an IRR. Most of the withdrawing patients experienced either abnormal investigations (increased serum transaminases or thrombocytopenia) or displayed features consistent with anaphylactic or anaphylactoid reactions (such as airway oedema/irritation and/or bronchospasm, and cardiovascular changes – tachycardia with either hyper- or hypotension).

In addition, a total of 38 patients had their infusion medication interrupted because of a suspected IRR, typically characterized by either hypotension and/or flushing, or gastrointestinal complaints (such as nausea, abdominal pain and mouth ulcers). Infusion reactions that led to dose interruptions occurred at rates per 100 PY of 2.1 for placebo, 3.3 for tocilizumab 4 mg/kg, 1.5 for tocilizumab 8 mg/kg, 1.7 for tocilizumab (4→8) 4 mg/kg and 2.1 for tocilizumab (4→8) 8 mg/kg.

The study report did not elucidate whether patients who experienced clinically significant IRRs were tested for the presence of antibodies directed against tocilizumab.

Serious Adverse Events (SAEs)

The rate of SAEs up until 104 weeks was comparable between all treatment groups except for the tocilizumab 4 mg/kg + MTX group which had a higher rate of occurrence: 31 of 392 (10.9 per 100 PY) for patients in the placebo + MTX group, 43 of 146 (23.5 per 100 PY) for subjects in the tocilizumab 4 mg/kg + MTX arm and 96 of 532 (11.4 per 100 PY) for patients in the tocilizumab 8 mg/kg + MTX group. Both of the treatment switch groups had an event rate similar to or less than the tocilizumab 8 mg/kg arm, 20/451 (5.9 per 100 PY) for tocilizumab (4→8) 4 mg/kg group and 54/451 (11.3 per 100 PY) for the tocilizumab (4→8) 8 mg/kg arm. Furthermore, for patients whose only dose of tocilizumab was 8 mg/kg, the rate of SAEs at Week 104 (11.40 per 100 PY) showed no significant change from that observed at Week 52 (11.46 per 100 PY).

The most common types of SAE were infections, injuries, neoplasms and gastrointestinal disorders. Overall, gastrointestinal disorders occurred at a similar rate (0.7-1.1 per 100 PY in each group) in patients treated with tocilizumab compared with placebo + MTX treated

patients. However, infectious SAEs were more commonly seen in patients treated with tocilizumab. The event rate (and number of SAE/population) for tocilizumab 4 mg/kg and 8 mg/kg was 7.1 per 100 PY (13/146) and 3.3 per 100 PY (28/532) respectively, compared with 2.1 per 100 PY (6/392) for the placebo + MTX group. Fractures resulting from injurious events occurred at a higher rate (4/146 – 2.2 per 100 PY) in the tocilizumab 4 mg/kg group compared to the high dose tocilizumab arm (10/532 – 1.2 per 100 PY) and placebo + MTX group (2/392 – 0.7 per 100 PY). In pre-clinical data, IL-6 has been shown to indirectly stimulate osteoclastic activity and bone resorption, so altering the balance between osteoclastic and osteoblastic activity and has the potential to increase the risk of osteoporotic fractures.

In addition, neoplasms were identified at a higher incidence (7/146 – 3.8 per 100 PY) in the tocilizumab 4 mg/kg group compared to the other two main treatment arms (1/392 [0.4 per 100 PY] for placebo + MTX and 5/532 [0.6 per 100 PY] for tocilizumab 8 mg/kg).

All other types of SAEs (for example, skin disorders and abnormal investigations) occurred in such small patient numbers that no conclusions can be drawn about comparative incidence between the treatment groups. However, of note, there was a single case of bilateral optic neuritis (onset Day 607) which affected a 73 year old female treated with tocilizumab 4 mg/kg + MTX. The diagnosis was confirmed by visual-evoked potential testing but brain magnetic resonance imaging (MRI) showed no evidence of demyelination. The SAE was considered unrelated to the study medication and the patient continued in the trial. Another patient treated with tocilizumab 8 mg/kg + MTX experienced worsening of pre-existing autoimmune hepatitis during the second year of treatment and subsequently withdrew from the study.

Also noteworthy was the small number of serious laboratory test abnormalities, which included 9 haematological SAEs (in particular, 2 cases of neutropenia, 1 patient from the tocilizumab 4 mg/kg arm and 1 in the tocilizumab (4→8) 8 mg/kg group), and 7 significantly abnormal events of abnormal liver function tests (1 in a patient who received placebo + MTX, 1 in a subject on tocilizumab 8 mg/kg + MTX and 5 events in 4 subjects in the tocilizumab (4→8) 8 mg/kg group. These events will be discussed further in the laboratory test abnormality section.

Infectious Adverse Events

(a) Overall

In the cumulative dataset up to Week 104, the overall infection rate was similar in subjects treated with tocilizumab + MTX (522 infections/597 patients [100.02 per 100 PY; 95% CI 91.62, 108.98] for tocilizumab 4 mg/kg and 1207/983 [91.41 per 100 PY; 95% CI 86.33, 96.72] for tocilizumab 8 mg/kg) to those who received placebo + MTX (266/392, 93.40 per 100 PY [95% CI 82.51, 105.32]). The rates of infection across all treatment groups were highest during the first 6 months of therapy and did not increase over time up to Week 104. For patients whose only dose of tocilizumab was 8 mg/kg, the rate of infections per 100 PY was 104.2 for the first 6 months, 90.08 for months 7-12, 82.33 for months 13-18 and 80.3 for months 18-24. For patients switching from tocilizumab 4 mg/kg to 8 mg/kg, the overall rates of infection reduced slightly after the dose increase (107.79 per 100 PY while on tocilizumab 4 mg/kg and then 94.15 per 100 PY for tocilizumab 8 mg/kg).

The most frequently (>2.5%) recorded types of infection, occurring in a slightly higher proportion of patients treated with either dose of tocilizumab, involved the upper respiratory tract (7.4-14.3%), urinary tract (5.4-8.2%), gastrointestinal system (2.8-4.3%) and nasopharynx (2.5-3.2%). The majority of infections were of mild or moderate severity. Broad

spectrum antibiotics such as penicillins, macrolides, quinolones and cephalosporins were commonly used (80-83%) for suspected infections in similar proportions of subjects in each of the treatment arms. However, antifungal drugs (8% versus 5%) and antiviral medicines (7% versus 5%) were more commonly used in tocilizumab-treated patients in comparison to subjects from the placebo + MTX arm.

Among subjects who experienced infections, a higher proportion of those treated with tocilizumab had received treatment with corticosteroids in the month prior to developing the infection: 68.5% (100/146) for tocilizumab 4 mg/kg and 68.4% (364/532) for tocilizumab 8 mg/kg compared with 38.8% (152/392) for placebo + MTX.

There was no clear association between the occurrence of infections, including serious infections, and absolute neutrophil counts (ANC). Based on the worst ANC in the month prior to infection, the majority of patients who experienced any type of infection had an ANC above the lower limit of normal. One patient who was receiving placebo + MTX developed a tooth abscess with an ANC of $< 500 \times 10^6/L$. Three patients while receiving tocilizumab 8 mg/kg had an ANC between 500 and $1000 \times 10^6/L$ and recorded infections (1 case each of bronchitis, oral herpes and peri-orbital abscess which lasted 3 days and did not relapse). In addition, 5 infections occurred in 2 patients on tocilizumab (4→8) 8 mg/kg who had an ANC between 500 and $1000 \times 10^6/L$ (1 case of sinusitis and another individual suffered oral candidiasis, necrotizing pneumonia, lung abscess and empyema). Of these, only the empyema was considered to be a serious infection.

The rate of infections that led to dose interruptions ranged from 15.3 (4 mg/kg) to 18.9 (8 mg/kg) per 100 PY for tocilizumab-treated subjects compared with 8.4 per 100 PY for placebo infusions + MTX. Similar to the overall pattern of infections most of these infections were of minor intensity and involved the upper respiratory tract or nasopharynx.

(b) Serious infectious AEs

Sixty-four serious infections (defined as those reported as SAEs and/or treated with IV antibiotics) were recorded up until 104 weeks of follow-up: 6 of 392 patients (2.11 per 100 PY; 95% CI 0.77, 4.59) in the placebo + MTX group, 13 of 146 subjects (7.09 per 100 PY; 95% CI 3.78, 12.13) in the tocilizumab 4mg/kg arm and 29 of 532 patients (3.43 per 100 PY; 95% CI 2.30, 4.93) in the tocilizumab 8mg/kg group. For the two treatment switch (4→8 mg/kg) groups, the event rates were lower: 0.89 per 100 PY (95% CI 0.18, 2.59; 3/451) for 4 mg/kg and 2.73 (95% CI 1.45, 4.67; 13/451) for 8 mg/kg. Consistent with the overall rate of infections, the rates of serious infection across all treatment groups were highest during the first 12 months of the trial and lessened in frequency during Year 2 of the study. For patients whose only dose of tocilizumab was 8 mg/kg, the rate per 100 PY of serious infection was 1.25 during the first 6 months, 7.51 in months 7-12, 2.33 for months 13-18 and 1.32 for months 18-24.

The most frequently reported types of serious infection were pneumonia (11 cases, 2 for placebo + MTX, 3 for tocilizumab 4 mg/kg and 6 for tocilizumab 8 mg/kg) and cellulitis/erysipelas (9 cases, 1 for tocilizumab 4 mg/kg and 8 for tocilizumab 8 mg/kg). Five opportunistic infections were observed during the 2 year trial. All of these patients had received tocilizumab 8 mg/kg + MTX. The cases include *Candida* osteomyelitis of the spine, gastrointestinal candidiasis, cryptococcal pneumonia, tuberculous pleurisy and septic olecranon bursitis due to *Pseudomonas* and *Serratia* infection.

Three deaths as a result of infection, all of which occurred in patients receiving tocilizumab 8 mg/kg + MTX, were observed up to 2 years of follow-up in Study WA17823. The infection-related deaths were bronchopneumonia in a 62 year old female who had *Candida*

osteomyelitis of the spine, gastroenteritis due to *E. coli* leading to septicaemia in a 74 year old female and staphylococcal septicaemia from an unknown source in a 54 year old woman. None of the patients had a history of recurrent infection or were diabetic.

Gastrointestinal Perforation

Gastrointestinal (GI) perforation was an AE of special interest. In pre-clinical data, IL-6 depletion has been associated with impaired mucosal integrity of the GI tract. Overall, 4 patients experienced GI perforation in Study WA17823, 3 of whom received tocilizumab 8 mg/kg + MTX and 1 received tocilizumab 4 mg/kg + MTX. The estimated rate of GI perforation was 0.19 per 100 PY [95% CI 0.0048, 1.06] for tocilizumab 4 mg/kg and 0.23 per 100 PY [95% CI 0.047, 0.67] for tocilizumab 8 mg/kg. Two of the events occurred during Year 1 of the study (Days 286 and 312) and the other two happened in Year 2 (Days 467 and 650). Two of the subjects had underlying diverticular disease, and both were taking concurrent low dose oral corticosteroids, which may have been significant contributing factors. In addition to the GI perforation, there were two further cases of diverticulitis reported during the study. Both of these patients were receiving tocilizumab 8 mg/kg + MTX. No patients in the placebo + MTX arm suffered a GI perforation or were reported to develop diverticulitis.

Cardiovascular (CVS) Events

Patients with long-standing active RA have an increased risk of CVS morbidity and mortality. The overall rate of cardiac disorders was low but higher in the treatment groups which received tocilizumab (8/146 [4.4 per 100 PY] for the 4 mg/kg arm; and 33/532 [3.9 per 100 PY] for 8 mg/kg) than in the placebo + MTX group (6/392; 2.1 per 100 PY). Serious cardiac AEs appeared to have occurred at a higher frequency (albeit in small total numbers) in the tocilizumab treatment groups (3 patients in the 4 mg/kg group [1.1 per 100 PY] and 11 subjects who received 8 mg/kg [1.1 per 100 PY] versus 1 event in the placebo group [0.4 per 100 PY]). Five patients were reported to have coronary artery disease or stenosis (4 in the tocilizumab 8 mg/kg arm and 1 in the tocilizumab 4 mg/kg group), 3 patients experienced myocardial infarction (2 on tocilizumab 4 mg/kg and 1 receiving 8 mg/kg) and another 2 patients treated with tocilizumab 8mg/kg group had new onset of cardiac failure. In addition, 4 cases of stroke (3 subjects received tocilizumab 8 mg/kg and 1 had tocilizumab 4 mg/kg) were recorded during the 104 week follow-up period.

The rates of hypertension were higher in patients treated with tocilizumab, 10.37 per 100 PY (95% CI 6.24, 16.19) for 4 mg/kg and 6.99 per 100 PY (95% CI 5.32, 9.01) for 8 mg/kg compared to subjects who received placebo infusions + MTX (4.56 per 100 PY [95% CI 2.34, 7.81]). The rates of hypertension did not appear to increase with time on tocilizumab treatment as they were at their highest in the first 6 months of the study but thereafter declined. For example, patients treated with tocilizumab 8 mg/kg had an incident rate of hypertension of 10.42 per 100 PY in the first 6 months, 6.62 per 100 PY in months 7-12, 7.00 per 100 PY in months 13-18 and 2.63 per 100 PY in months 19-24. For the group of subjects who switched from tocilizumab 4→8 mg/kg, the rate of hypertension did not increase after the treatment switch and assumed the temporal occurrence profile of that seen in patients whose only dose of tocilizumab was 8 mg/kg.

Malignancy

A total of 25 patients (2 in placebo + MTX group, 10 receiving tocilizumab 4 mg/kg and 13 in the tocilizumab 8 mg/kg group) developed malignancies to Week 104 of Study WA17823. The adjusted rate of malignancy (for drug exposure) was low across all treatment groups with the exception of the cohort who received treatment with tocilizumab 4 mg/kg + MTX (4.36

per 100 PY [95% CI 1.88, 8.60] compared to tocilizumab 8 mg/kg 0.83 per 100 PY [95% CI 0.33, 1.71] and placebo + MTX 0.70 per 100 PY [95% CI 0.09, 2.54]). Furthermore, 17 of the 23 cancers to which occurred in tocilizumab-treated subjects were reported within the first 52 weeks of the trial. This observation was explained by the higher rate of cancer detected in patients treated with tocilizumab 4 mg/kg during Year 1. The adjusted rate of malignancy did not significantly alter between Years 1 and 2 for subjects treated with tocilizumab 8 mg/kg + MTX. Moreover, 2 subjects treated with tocilizumab 8 mg/kg + MTX, had their malignancy (endometrial cancer and gastro-oesophageal cancer) diagnosed soon after a single dose of therapy suggesting a pre-existing condition.

In the patients who received placebo + MTX there was a case of basal cell carcinoma (BCC) of the skin and breast cancer. For the subjects receiving tocilizumab, the most common types of cancer were basal cell carcinoma (4 cases; 2 from each of the tocilizumab dose groups), lung cancer of various histology (3 cases; 1 each from tocilizumab 4 mg/kg, 8 mg/kg and 4→8 mg/kg groups; all with a significant smoking history), prostate cancer (2 cases; both receiving tocilizumab 4 mg/kg), endometrial cancer (2 cases; both receiving tocilizumab 8 mg/kg) and cervical carcinoma (2 cases; both in the tocilizumab 4 mg/kg group). The type and incidence of skin malignancies with immunosuppression are of particular interest in Australia. In addition to the cases of skin BCC already mentioned, there were singular cases of metastatic malignant melanoma, squamous cell carcinoma and “skin cancer” (the first 2 cases occurred in subjects receiving high dose tocilizumab). The other malignancies that were identified in subjects treated with tocilizumab were individual examples of anal, renal cell, tongue, gastroesophageal and thyroid cancer.

Deaths

Ten patients (8 in the tocilizumab 8 mg/kg group, and 1 each from the low dose tocilizumab and placebo + MTX groups) died during the 104 week study follow-up period. Six deaths occurred in the initial 52 week study period, 1 patient who received placebo + MTX (due to Wegener’s granulomatosis, Day 103), 1 in the tocilizumab 4 mg/kg arm (due to pulmonary embolism, Day 182) and 4 in the tocilizumab 8 mg/kg group (due to cerebral haemorrhage [Day 280], gastrointestinal infection [Day 324], bronchopneumonia while rehabilitating from spinal fusion surgery [Day 275] and sepsis [Day 284]). Three deaths in the second year of the study were due to malignancy – metastatic lung adenocarcinoma, metastatic malignant melanoma and gastro-oesophageal cancer. All of these patients received tocilizumab 8 mg/kg in Year 2 (the first 2 cases had received tocilizumab 4 mg/kg in Year 1 of the trial, and the other had received placebo + MTX in Year 1). Another subject, a 42 year old male, who received tocilizumab 8 mg/kg + MTX from study commencement, died on Day 757 of cardiomyopathy. Autopsy confirmed this as the cause of death and attributed hypertension as the causative mechanism.

Use in Pregnancy

The effect of the study medication on pregnancy and lactation was not specifically examined in Study WA17823. Female subjects were to have a negative pregnancy test at screening, and patients of either gender were requested to use a reliable method of contraception (barrier and/or hormonal) during the study. Five patients (2 in the placebo infusion + MTX group and 3 in the tocilizumab 8mg/kg + MTX group) became pregnant up to Week 104 of the study. Among the 3 patients who became pregnant while receiving tocilizumab 8 mg/kg + MTX, 2 patients withdrew from the study and continued with their pregnancy, while the other patient elected to terminate the pregnancy and continue with the trial. Both patients who became pregnant while receiving placebo infusions + MTX had spontaneous abortions and subsequently continued on treatment in the trial.

Laboratory Test Evaluations

The results for all laboratory parameters were presented by treatment switch groups. Patients who switched treatment (either by escape or open-label therapy) were reset to baseline upon changing treatment and then grouped according to their subsequent treatment. Hence, except for patients originally randomized to tocilizumab 8 mg/kg (most of whom remained on that treatment up until Week 104), the median duration of treatment was 1 year or less for all other treatment groups.

(a) Haematology

In general, no concerning changes in red blood cell counts or haematocrit fractions were observed in any of the treatment groups up to Week 104. Many patients at baseline had a haemoglobin value at the lower end of normal (mean = 135 g/L) reflecting active inflammatory disease. Mean haemoglobin levels remained within the normal range in all treatment groups up until Week 104, but patients treated with either dose of tocilizumab had a mean increase in haemoglobin of 10-12 g/L whereas subjects receiving placebo + MTX had no significant mean change from baseline.

An increase in haemoglobin value from low or normal at baseline to a high result (>180 g/L) was seen in a total of 53 patients: 5 of 390 (1.3%) for placebo + MTX, 1 of 146 (0.7%) for tocilizumab 4 mg/kg, 28 of 531 (5.27%) for tocilizumab 8 mg/kg, 5 of 449 (1.11%) for tocilizumab (4→8) 4 mg/kg and 15 of 450 (3.33%) for tocilizumab (4→8) 8 mg/kg. The sponsor did not analyse whether these results of elevated haemoglobin value correlated with cardiovascular AEs such as hypertension.

The cumulative dataset up to Week 104 did not identify an increased rate of elevated haemoglobin with time in patients who received treatment with tocilizumab 8 mg/kg, 3.90 per 100 PY in Year 1 (using original dose group) and 3.62 per 100 PY in Year 2 (using pooled patients for this dose).

Baseline mean absolute neutrophil counts (ANC) were in the high normal range at $8.5 \times 10^9/L$ which may reflect the presence of active inflammatory disease or high rates of concurrent corticosteroid therapy. Mean ANC remained in the normal range throughout the study in all treatment groups but patients who received tocilizumab had greater mean decreases in ANC (mean decline of $1.8 \times 10^9/L$ for 4 mg/kg and $2.2 \times 10^9/L$ for 8 mg/kg dosing) compared with subjects who received placebo + MTX (mean decline of $0.1 \times 10^9/L$). This dose dependent decline in mean ANC was also seen in patients who switched from tocilizumab 4 to 8 mg/kg. The initial decline in ANC was frequently observed during the first 2-4 weeks of follow-up after infusion of the high dose of tocilizumab.

Among patients who had ANC abnormalities, most experienced only minor Grades (CTC Grade 1 or 2) of severity. A higher proportion of subjects (4.2%, 22/532) treated with tocilizumab 8 mg/kg + MTX developed Grade 3 ANC compared with any other tocilizumab treatment cohort including those in the switch treatment groups (1.1-2.1%) and placebo + MTX (0.03%, 1/392). However, Grade 4 ANC abnormalities occurred in a higher percentage of patients (1.4%, 2/146) treated with tocilizumab 4 mg/kg + MTX than any other treatment group (0.06% [3/532] for tocilizumab 8 mg/kg + MTX and 0.05% [2/392] for placebo + MTX). The event rate frequency of Grade 3 or 4 ANC abnormalities is 2.96 per 100 PY (25/532; 844.56 PY exposure) for tocilizumab 8 mg/kg, 2.73 per 100 PY (5/146; 183.28 PY exposure) for tocilizumab 4 mg/kg and 0.11 per 100 PY (3/392; 284.81 PY exposure) for placebo + MTX.

In total, 7 patients (5 receiving tocilizumab 8 mg/kg and 2 on tocilizumab 4 mg/kg) developed Grade 4 neutropenia (ANC $<0.5 \times 10^9/L$), all of which were single occurrences.

According to the study protocol, patients were to withdraw from the trial if they developed Grade 4 neutropenia, however 2 of the 7 subjects continued in the study as their low ANC was a transient observation detected 8 and 14 days post-dose which normalized within 2 weeks. Five of the 7 cases of severe neutropenia occurred in Year 2 of the study (between Weeks 60 and 92) and all of the AEs were detected within 31 days of tocilizumab infusion (mean 23.4 days, median 28 days, range: 8-31 days). No significant changes in lymphocyte, monocyte or eosinophil counts were observed in any of the treatment groups.

Mean baseline platelet counts were also in the high normal range ($330 \times 10^9/L$) in all treatment groups due to the presence of inflammatory disease. Mean platelet counts remained in the normal range throughout the study in all treatment groups but patients who received tocilizumab had greater mean decreases in platelet count (mean decline of $88 \times 10^9/L$ for 4 mg/kg and $103 \times 10^9/L$ for 8 mg/kg dosing) compared with subjects who received placebo + MTX (mean decline of $32 \times 10^9/L$). This dose dependent decline in mean platelet count was also seen in patients who switched from tocilizumab 4 to 8 mg/kg. The initial decline in platelet count was observed during the first 2-4 weeks of follow-up after tocilizumab infusion and generally remained constant thereafter.

Among patients who had significant changes from baseline in platelet counts, most experienced only CTC Grade 1 abnormalities. A higher proportion of subjects (14.8%, 79/532) treated with tocilizumab 8 mg/kg + MTX developed Grade 1 platelet count abnormalities compared with tocilizumab 4 mg/kg treatment (6.8%; 10/146) and placebo + MTX (1.5%, 6/392). The same pattern of an increased percentage of subjects developing Grade 1 platelet changes was seen in the 2 tocilizumab switch groups (4 mg/kg – 7.3% [33/451] versus 8 mg/kg – 13.6% [61/350]). More severe Grades (3 and 4) of platelet abnormalities were rare. Clinical sequelae occurred in three patients who developed Grade 4 thrombocytopenia (platelet count $<100 \times 10^9/L$). One patient treated with tocilizumab 8 mg/kg + MTX developed increased post-menopausal bleeding on Day 29 with a platelet count of $85 \times 10^9/L$ on Day 26. Endometrial cancer was subsequently diagnosed soon thereafter. Moderate epistaxis occurred on Day 670 in another patient with a platelet count of $96 \times 10^9/L$ on Day 559 who received tocilizumab 8 mg/kg (as a switch treatment from tocilizumab 4 mg/kg). A third patient who had received treatment with placebo + MTX experienced signs of symptomatic severe thrombocytopenia with a persistent platelet counts of $<100 \times 10^9/L$ from Week 58 onwards. On further investigation the patient was found to have a hypoplastic bone marrow.

(b) Liver Enzyme and Serum Bilirubin Abnormalities

Patients treated with tocilizumab + MTX had a higher incidence of elevations in hepatic transaminases (ALT and/or AST) or bilirubin than subjects who received placebo infusions + MTX. The changes in liver function tests were also more common with the higher dose of tocilizumab suggesting a dose-related toxicity effect.

During the 2 year study, mean ALT values (baseline of 33 U/L) increased in tocilizumab-treated subjects from Week 2 onwards, remaining stable within the normal range (ULN: 55 U/L). The increase was most evident and sustained in patients who received tocilizumab 8 mg/kg + MTX (mean increase of 15 U/L to a total level of 48 U/L), while patients treated with tocilizumab 4 mg/kg + MTX exhibited a sawtooth pattern during the first 52 weeks, with the maximum increase being seen in the first 2 weeks following dosing and a return to baseline levels immediately prior to the next infusion, before a stable pattern of values was observed in Year 2. Patients treated with tocilizumab 4 mg/kg + MTX had a mean increase of ALT over 104 weeks of 5 U/L (absolute mean ALT of 38 U/L). Mean ALT results for subjects on placebo + MTX remained unaltered over the course of the trial. For patients who

switched from tocilizumab 4 mg/kg to 8 mg/kg, mean ALT values increased to levels of those seen with subjects who received the 8 mg/kg dose.

Several arbitrary cut-off points above the value for the ULN (in particular, $> \times 1.5$ and $> \times 3$) were defined to determine the effect of treatment upon liver function tests. At 104 weeks, a higher percentage of patients treated with tocilizumab had ALT results $> \times 1.5$ ULN (from normal at baseline) at any time point – 23.9% (127/532) for tocilizumab 8 mg/kg and 20.5% (30/146) for tocilizumab 4 mg/kg compared with 16.3% (64/392) for placebo + MTX. A similar observation was recorded in the two tocilizumab treatment switch groups – 28.4% (128/451) for 8 mg/kg and 26.2% (118/451) for 4 mg/kg. Supporting this dose-related phenomenon was the proportion of subjects who recorded $> \times 3$ ULN results for ALT from previously normal values at baseline. At week 104, a higher percentage of patients treated with tocilizumab had ALT results $> \times 3$ ULN: 10.2% (54/532) for tocilizumab 8 mg/kg and 8.9% (13/146) for tocilizumab 4 mg/kg compared with 1.0% (4/392) for placebo + MTX. Similarly, in the two tocilizumab treatment switch groups (4.4% [20/451] for 8 mg/kg and 5.1% [23/451] for 4 mg/kg) a higher proportion of ALT elevations $> \times 3$ ULN were seen compared to placebo + MTX, but these results were not as marked as for the group who initiated tocilizumab (either dose) at study commencement. For all treatment groups, the majority of ALT increases above the ULN were either single events (20-25%) or non-consecutive observations ($>50\%$). However, a small proportion of individuals with ALT increases had consecutive elevations ($\sim 15\%$) or a sustained increase ($\sim 5\%$) which was defined as > 2 consecutive abnormal blood test results. For patients whose only dose of tocilizumab was 8 mg/kg from study commencement, prolonged exposure to therapy did not appear to be associated with an increased likelihood of developing increases in ALT as the numbers of patients developing increased ALT values was highest in the first 6 months of treatment (46.1% [41/89] for 0-6 months, 27.0% [24/89] for 6-12 months, 15.7% [14/89] for 13-18 months and 11.2% [10/89] for Months 19-24).

In all treatment groups, AST values followed the same trend as observed for ALT with regard to mean values over time and the proportion of subjects who experienced shifts from baseline to values greater than the ULN, although the magnitude of the changes in mean AST were smaller than those recorded for mean ALT.

Serum bilirubin results in all treatment groups followed a similar trend to that seen for ALT and AST with respect to mean values over time and percentage of patients who experienced shifts above the ULN from baseline. The proportion of subjects up to Week 104 who recorded a change from normal in total serum bilirubin up to $\times 3$ ULN (defined as $17 \mu\text{mol/L}$) was higher in the tocilizumab treatment groups (11.0% [16/146] for tocilizumab 4 mg/kg, 13.7% [73/532] for tocilizumab 8 mg/kg) compared to the placebo + MTX arm (1.5%, 6/390). A similar figure (11.3%, 51/451) was seen in the tocilizumab (4 \rightarrow 8) 8 mg/kg treatment switch group but this percentage was lower in the other treatment switch group of (4 \rightarrow 8) 4 mg/kg (4.4%, 20/451).

A total of 13 patients (1 patient treated with tocilizumab 4 mg/kg, 8 treated with tocilizumab 8 mg/kg and 4 subjects in the high dose tocilizumab treatment switch group, 8 mg/kg) had a total serum bilirubin reading $> \times 2$ ULN, most of which were non-consecutive or single elevations. In all cases, indirect bilirubin was the predominant component and no patients had increases in direct serum bilirubin $> \times 2$ ULN. One of the 13 patients (treated with tocilizumab 8 mg/kg + MTX) developed an increased serum total bilirubin level that was between $\times 3$ -5 ULN, but with normal serum transaminases. This occurred on study Day 57 and the patient was immediately withdrawn from the trial. By study Day 128, her total serum bilirubin had decreased to the ULN. In another 9 of these 13 patients, a change in their study

medication ensued because of the increased serum bilirubin (3 patients were dose interrupted and 6 had their study treatment withdrawn). In 7 of the 9 cases, the serum bilirubin was documented to return to normal with follow-up.

Two patients with increased serum transaminases were considered to have experienced an SAE. One patient while receiving tocilizumab 8 mg/kg + MTX developed an ALT $> x 5$ ULN (309 U/L) and an AST $> x 3$ ULN (159 U/L) and her study medication withdrawn. Serum transaminases returned to normal within 18 days of ceasing treatment. The other patient received tocilizumab 8 mg/kg (as part of switch therapy) and experienced an elevation of ALT $> x 8$ ULN (484 U/L) and AST $> x 3$ ULN (127 U/L) at the Week 104 assessment. Again, serum transaminases quickly returned to normal (within 28 days of treatment discontinuation).

The trial protocol required that patients have their study treatment interrupted or ceased if they developed clinically important elevations of ALT, AST and/or serum bilirubin. The rates of dose interruptions because of elevated serum transaminases (mainly for $> x 3$ ULN) were higher for patients who received tocilizumab + MTX (2.18-4.20 per 100 PY) than for patients on placebo + MTX (1.4 per 100 PY). In addition, using pooled data from the original and treatment switch groups, the higher dose of tocilizumab had a higher rate of dose interruption for increased ALT/AST than the low dose (3.8 per 100 PY for 8 mg/kg versus 2.7 per 100 PY for 4 mg/kg). Amongst the tocilizumab-treated patients who interrupted treatment because of increased serum transaminases, the majority (36/47) experienced normalization of readings and returned to study treatment. In 24 of these 36 subjects, no recurrence of the event occurred. However, 7 of these subjects (6 on tocilizumab 8 mg/kg and 1 receiving 4 mg/kg) subsequently had to withdraw because of persistently increased serum transaminases.

The rates of withdrawal due to increased hepatic enzymes or bilirubin were higher for patients who received tocilizumab (2.31-5.46 per 100 PY) than for the placebo + MTX arm (0.35 per 100 PY). Of the 50 tocilizumab-treated subjects who withdrew because of liver laboratory abnormalities, 25 (50%) had serum transaminases $> x 5$ ULN (2 patients also had a total serum bilirubin $> 43 \mu\text{mol/L}$), 18 had increased serum transaminases between $x 3$ - 5 ULN and 7 had an isolated increase in total serum bilirubin of between $x 1.5$ - 2 ULN. For most of these patients (38/50, 31 with increased serum transaminases and 7 with raised serum bilirubin), results normalized with withdrawal of tocilizumab and this typically occurred within 60 days of drug cessation.

Although not required by the study protocol, 4 patients who developed varying levels of increased serum transaminases (1 with serum bilirubin also increased to $< x 1.5$ ULN) during the 2 year trial underwent liver biopsies. All subjects were receiving tocilizumab + MTX. The biopsies revealed 3 patients to have mild-moderate steatohepatitis and the other biopsy was non-diagnostic.

In addition, 5 patients (4 treated with tocilizumab 8 mg/kg and 1 receiving placebo + MTX) developed cholelithiasis during the 2 year study. This resulted in dose interruptions for all of the subjects. Two of the events occurred in year 1 (including the placebo + MTX case) and the rest happened in the second year of the trial.

(c) Lipid Parameters

During the first 52 weeks of treatment, mean fasting total cholesterol (TC), low-density lipoprotein (LDL), high-density lipoprotein (HDL) and triglycerides (TG) increased in the tocilizumab-treated subjects up to Week 24 and then remained stable. The increases in lipid parameters were most marked for the tocilizumab 8 mg/kg dose group. However, mean values for the placebo arm showed no significant alteration from baseline ($< 0.20 \text{ mmol/L}$

change). At baseline, the mean fasting TC was 5.14 mmol/L and mean fasting LDL was 2.98 mmol/L. For the tocilizumab 4 mg/kg group the mean TC increased to 5.57 mmol/L and mean LDL increased to 3.27 mmol/L at Week 52. For the tocilizumab 8 mg/kg group the mean TC increased to 5.97 mmol/L and mean LDL increased to 3.58 mmol/L at Week 52. For patients who switched from tocilizumab 4 to 8 mg/kg, mean lipid parameters attained the same level observed in subjects who were continuing with the 8 mg/kg dose. In addition, increases in mean apolipoprotein A and apolipoprotein B were recorded for all tocilizumab treatment groups, with the magnitude of increase greatest in the 8 mg/kg dosing groups (original and treatment switch arm). The above results indicate that tocilizumab (particularly, at the 8 mg/kg dose) is associated with the genesis of an atherogenic lipid profile for which long-term patient follow-up will be required, especially for the development of atherosclerotic cardiovascular disease.

A higher proportion of patients treated with tocilizumab had significant elevations from baseline values of TC, LDL and TG up to Week 104 (using the LOCF methodology). The thresholds for determining significant elevations in lipid parameters were based on the ATP (Adult Treatment Panel) III guidelines of the National Cholesterol Education Program.⁹ For patients whose treatment was tocilizumab 8 mg/kg, the proportion of subjects who had an increase in TC from a baseline value of < 240 mg/dL to > 240 mg/dL (6.2 mmol/L) was 24.4% (130/532) compared to 10.3% (15/146) for tocilizumab 4 mg/kg and 7.1% (28/392) for placebo + MTX. For the 2 tocilizumab treatment switch groups, the percentages of affected individuals for this change in TC was 14.9% (67/451) for the 4 mg/kg group and 14.4% (65/451) for the 8 mg/kg arm.

The analysis at 104 weeks for a significant change in LDL was in accordance with the TC observation. Patients who received tocilizumab 8 mg/kg from the study outset had a higher rate of significant increases in LDL (from < 160 mg/dL to > 160 mg/dL, that is, 4.14 mmol/L) – 19.0% (101/532) compared to 7.5% (11/146) for tocilizumab 4 mg/kg and 4.1% (16/392) for placebo + MTX. For the two tocilizumab treatment switch groups, the percentages of affected individuals for this significant change in LDL was 12.0% (54/451) for the 4 mg/kg group and 10.4% (47/451) for the 8 mg/kg arm.

For TG, the significant value threshold was set at 150 mg/dL (that is, 3.88 mmol/L). The difference between the treatment groups (tocilizumab versus placebo + MTX) was also evident for this lipid parameter. At 104 weeks, 10.5% (41/392) patients in the placebo + MTX had a significant increase in their TG compared to 17.5% (93/532) for tocilizumab 8 mg/kg, 16.4% (24/146) for tocilizumab 4 mg/kg, 14.4% (65/451) for tocilizumab (4→8) 4 mg/kg and 14.6% (66/451) for tocilizumab (4→8) 8 mg/kg.

However, the results for significant change from baseline in HDL values (cardiovascular protective cholesterol) do not show a consistent result in favour of tocilizumab treatment if the threshold of 60 mg/dL (that is, 1.55 mmol/L) is taken as the arbitrary cut-off value. At 104 weeks, 9.2% (36/392) patients in the placebo + MTX had a significant increase in their HDL compared to 12.4% (66/532) for tocilizumab 8 mg/kg, 9.6% (14/146) for tocilizumab 4 mg/kg, 14.0% (63/451) for tocilizumab (4→8) 4 mg/kg and 6.9% (31/451) for tocilizumab (4→8) 8 mg/kg.

Up to Week 104, lipid lowering therapy was commenced in 61 patients treated with tocilizumab (55 receiving 8 mg/kg and 6 on 4 mg/kg) who developed a new significant change (elevation) in TC during the 2 year study. Of the 54 subjects who have had a follow-

⁹ Grundy SM, Cleeman JI, Merz CN, et al. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. *Circulation* 2004; 110: 227-239.

up blood sample collected, values were seen to either normalize or reduce to an acceptable level in 34 cases.

Vital Signs

With the exception of patients treated with tocilizumab 8 mg/kg + MTX from trial commencement, no treatment-based trend of change in vital signs (blood pressure, heart rate and temperature) was observed. For patients in the tocilizumab 8 mg/kg group, the percentage of patients with high systolic (SBP) and diastolic blood pressure (DBP) readings was higher compared to any other treatment group, including the two treatment switch groups. Significant elevations in SBP were defined at two levels (an absolute measurement of at least 150 mm Hg, with firstly an increase from baseline of between 10-20 mm Hg and secondly, an increase from baseline of >20 mm Hg) while significant elevations in DBP were similarly defined at two levels (an absolute measurement of at least 90 mm Hg as well as an increase from baseline of 10-20 and > 20 mm Hg). At 104 weeks of follow-up, the percentage of patients treated with tocilizumab 8 mg/kg + MTX who recorded increases in SBP were 26.0% (138/531) for Level 1 changes and 7.3% (39/531) for Level 2 increases; and for increases in DBP were 18.1% (96/531) for Level 1 changes and 16.8% (89/531) for Level 2 increases. For the other four treatment groups there was no significant difference in the percentage of patients with significant increases in blood pressure. The increases in SBP were 14.9-18.8% for Level 1 changes and 2.8-4.4% for Level 2 increases; and for increases in DBP were 9.0-12.9% for Level 1 changes and 9.0-14.7% for Level 2 increases.

Safety conclusions

In Study WA17823, tocilizumab (4 mg/kg and 8 mg/kg) in combination with MTX was generally well tolerated in patients with moderately severely active RA. The first 6-12 months of the 2 year study provided some insight into the comparative incidence and type of adverse events with tocilizumab therapy against placebo + MTX. However, because of the trial design whereby escape treatment (after Week 16) or open-label (Year 2) treatment with tocilizumab 8 mg/kg was available and often utilized, the increasing differences in drug exposure between the control arm and various tocilizumab groups limited direct comparisons of incidence of adverse events. The second year of the study with open-label tocilizumab 8 mg/kg + MTX did provide some insight into potential side effects over the medium term. Using the safety data up to 104 weeks, patients receiving tocilizumab (either dose) experienced a higher rate of adverse events overall, serious adverse events (particularly, serious infections and gastrointestinal perforation), adverse events resulting in withdrawal or dose interruption, and hypertension (of unclear explanation) than patients treated with placebo infusions + MTX. In addition, infections with any dose of tocilizumab therapy were most frequent during the first 6-12 months of therapy. Neoplasms and fractures resulting from an injurious event were more commonly observed in the tocilizumab 4 mg/kg + MTX group but a biologically plausible explanation for this observation was not apparent.

For the largest subset of patients whose only dose of tocilizumab was 8 mg/kg, no new safety signals were observed over time (up to 2 years) and the overall rates of adverse events (overall, serious and leading to dose interruption or premature withdrawal) remained stable. For patients who switched from tocilizumab 4 to 8 mg/kg (the second large subset of subjects), the rate of adverse events either remained stable or increased within expectations for those side effects (including laboratory data) that are dose-dependent such as elevated serum transaminases, risk of neutropenia and lipid values. However, the long-term consequences of some of the tocilizumab-related adverse effects require continued vigilance, in particular, event rates for adverse cardiovascular outcomes given the inducement of an atherogenic lipid profile and increased rates of hypertension.

Extended Safety Follow-Up Analysis

This application was further supported by the cumulative safety data obtained from the three open-label extension (OLE) studies. Subjects who completed the 2 year core study period for Study WA17823 were eligible to continue with tocilizumab 8 mg/kg therapy in an open-label extension phase. In addition, patients who completed the 24 week observation periods of the core Phase III controlled trials were allowed to continue on tocilizumab 8 mg/kg into one of two open-label extension studies (WA18695 and WA18696). Study WA18695 recruited 537 patients who completed 24 weeks of follow-up in the forerunner Study WA17822 (including escape patients). A total of 623 subjects were involved in Study WA17822 which enrolled patients with moderate-severe active RA who were responding inadequately to MTX at study entry. Study WA18696 recruited 2066 patients who completed 24 weeks of follow-up in 3 prior Phase III studies (WA17824 [n=673], WA18062 [n=499], and WA18063 [n=1220]) and the clinical pharmacology Study WP18663 (n=23).

The analysis of safety was presented separately by two population experiences. The “All Exposure” population was the primary cohort for assessment of the long-term safety and tolerability of tocilizumab and includes patients from Studies WA17822, WA17823, WA17824, WA18062, WA18063 and WP18663 who received at least one dose of tocilizumab at any time. The data cut-off date for the OLE dataset was 6 February 2009. The “All Exposure” population contained a total of 4009 patients resulting in a total drug exposure of 8579.7 patient-years and 9414.3 patient-years of observation. Of these, 2644 received tocilizumab at the two doses used in the new pivotal study for this submission (n=774 for 4 mg/kg [817.2 patient-years of exposure]; and n=1870 for 8 mg/kg [7760.7 patient-years of exposure]). The average duration of treatment follow-up (time from first dose of tocilizumab to final safety assessment) in the OLE phase was 2.35 (median 2.57; range: 0-4.1) years. Most patients (92.3%, 3701/4009) completed 6 months of treatment, 84.8% (3399/4009) completed 48 weeks of follow-up, 74.0% (2968/4009) completed 96 weeks of therapy and 62.3% (2499/4009) were still available at 144 weeks for assessment.

Safety data was also presented for the “All Control” population to display the effect of tocilizumab dose on specific AEs of interest. This dataset included all patients randomized into one of the five core Phase III studies (listed above). Only data from the double-blind treatment phases of each core study was included. Patients who participated in the clinical pharmacology Study WP18663 (n=23) had their safety data excluded from the “All Control” population analysis. Under controlled conditions, 1555 patients received control treatment with placebo infusions + MTX (717.4 PY of exposure and 824.6 PY of observation), 774 subjects received tocilizumab 4 mg/kg (500.1 PY of exposure and 564.6 PY of observation) and 1870 patients received tocilizumab 8 mg/kg (1013.2 PY of exposure and 1194.1 PY of observation).

Safety parameters were assessed every 12 weeks in Studies WA18695 and WA18696, and every 8 weeks in years 3-5 of Study WA17823. Adverse Events (AE) were classified using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE, version 3) which grades events as mild, moderate, severe, or life-threatening. The dates of onset and resolution of the AE were recorded, and the relationship of the AE to treatment was also assessed.

Overview of Adverse Events

In the “All Control” population, a dose-dependent increase in the overall rate of AEs was observed for the tocilizumab 8 mg/kg group (381.6 per 100 PY) compared with the tocilizumab 4 mg/kg group (358.0 per 100 patient-years). In the “All Control” population, infections were the most frequently reported type of AE and occurred at a higher event rate in

the 2 tocilizumab-treatment groups compared to the control therapy arm (Table 8). The most reported types of infections were URTIs (12.4 per 100 PY for control group, 12.0 per 100 PY for tocilizumab 4 mg/kg and 13.8 per 100 PY for tocilizumab 8 mg/kg) and nasopharyngitis (7.5 per 100 PY for control group, 7.1 per 100 PY for tocilizumab 4 mg/kg and 10.4 per 100 PY for tocilizumab 8 mg/kg).

Significant differences were also observed between the tocilizumab and control treatment groups in the rate of AEs for the following categories:

- § *Skin and Subcutaneous Disorders*, which was primarily driven by events of rash and pruritus (3.9 per 100 PY for control, 7.3 per 100 PY for tocilizumab 4 mg/kg and 7.7 per 100 PY tocilizumab 8mg/kg),
- § *Investigations*, primarily driven by events of increased transaminases (8.0 per 100 PY for control, 10.3 per 100 PY for tocilizumab 4 mg/kg and 15.3 per 100 PY for tocilizumab 8 mg/kg),
- § *Neoplasms* (1.7 per 100 PY for control, 5.1 per 100 PY for tocilizumab 4 mg/kg and 2.6 per 100 PY for tocilizumab 8 mg/kg),
- § *Vascular System Disorders*, primarily driven by hypertension (5.1 per 100 PY for control, 8.0 per 100 PY for tocilizumab 4 mg/kg and 8.2 per 100 PY for tocilizumab 8 mg/kg),
- § *Eye Disorders* (5.0 per 100 PY for control and 6.4 per 100 PY for tocilizumab 4 mg/kg and 8.2 per 100 PY for tocilizumab 8 mg/kg),
- § *Blood and Lymphatic System Disorders*, primarily driven by events of neutropenia (0.4 per 100 PY for control, 1.6 per 100 PY for tocilizumab 4 mg/kg and 4.1 per 100 PY for tocilizumab 8 mg/kg),
- § Hypercholesterolemia (1.0 per 100 PY for control, 0.9 per 100 PY for tocilizumab 4 mg/kg and 2.2 per 100 PY for tocilizumab 8 mg/kg), and
- § Hepatic steatosis (none in control, 0.2 per 100 PY for tocilizumab 4 mg/kg and 0.5 per 100 PY for tocilizumab 8 mg/kg).

Table 8: “All Control” Population – Adverse events by System Organ Class and treatment group

	Control N = 1555	TCZ 4 mg/kg + DMARD N = 774	TCZ 8 mg/kg + DMARD N = 1870
Exposure	824.56	564.59	1194.09 PY
System Organ Class	N [P100-PY]	N [P100-PY]	N [P100-PY]
Infections and Infestations	725 [87.9]	530 [93.9]	1115 [93.4]
Gastrointestinal Disorders	456 [55.3]	267 [47.3]	678 [56.8]
Skin and Subcutaneous Disorders	162 [19.6]	166 [29.4]	378 [31.7]
Musculoskeletal and Connective Tissue Disorders	320 [38.8]	171 [30.3]	347 [29.1]
Investigations	102 [12.4]	99 [17.5]	299 [25.0]
Nervous System Disorders	169 [20.5]	121 [21.4]	287 [24.0]
Respiratory, Thoracic, and Mediastinal Disorders	122 [14.8]	104 [18.4]	209 [17.5]
General Disorders and Administrative Site Conditions	150 [18.2]	99 [17.5]	215 [18.0]
Injury, Poisoning, and Procedural Complications	115 [13.9]	89 [15.8]	189 [15.8]
Vascular Disorders	85 [10.3]	80 [14.2]	148 [12.4]
Eye Disorders	41 [5.0]	36 [6.4]	98 [8.2]
Psychiatric Disorders	65 [7.9]	47 [8.3]	99 [8.3]
Blood and Lymphatic Disorders	44 [5.3]	32 [5.7]	87 [7.3]
Metabolism and Nutrition Disorders	52 [6.3]	42 [7.4]	85 [7.1]
Reproductive and Breast Disorders	36 [4.4]	24 [4.3]	63 [5.3]
Cardiac Disorders	29 [3.5]	15 [2.7]	48 [4.0]
Renal and Urinary Disorders	33 [4.0]	15 [2.7]	49 [4.1]
Ear and Labyrinth Disorders	27 [3.3]	22 [3.9]	35 [2.9]
Neoplasms Benign, Malignant, Unspecified (including cysts and polyps)	14 [1.7]	29 [5.1]	31 [2.6]
Hepatobiliary Disorders	14 [1.7]	6 [1.1]	33 [2.8]
Immune Disorders	16 [1.9]	10 [1.8]	29 [2.4]
Endocrine Disorders	4 [0.5]	7 [1.2]	17 [1.4]
Surgical and Medical Procedures	8 [1.0]	6 [1.1]	14 [1.2]
Pregnancy, Puerperium, and Perinatal Conditions	5 [0.6]	-	3 [0.3]
§ Congenital, Familial, and Genetic Disorders	1 [0.1]	4 [0.7]	1 [0.1]

In the “All Exposure” population, the overall rate of AEs was 332.2 per 100 PY, which is similar to the rate reported in similar patient cohorts. The rate of AEs was highest in the first 6 months of treatment with tocilizumab and decreased thereafter. Stable or decreasing rates of AEs per 100 PY were observed when the data was analysed by 6 monthly intervals of exposure (up to 48 months). There was no evidence of an increase in AE rates for any events that may be associated with tocilizumab (that is, infusion reactions, infections, GI events, skin and subcutaneous disorders, elevations of hepatic aminotransferases or total/indirect bilirubin, neutropenia, or hyperlipidaemia) with increasing duration of drug exposure. The most frequently reported types of AEs in tocilizumab-treated patients were infections (74.4 per 100 PY; most commonly URIs and nasopharyngitis) and GI disorders (36.4 per 100 PY; most commonly diarrhoea and nausea).

Adverse Events Leading to Withdrawal

In total, 26.5% (1064/4009) of subjects withdrew from the OLE studies – 547 (13.6%; 39 deaths and 508 AEs) for safety reasons and 517 (12.9%) for non-safety reasons. In the “All Control” population, the rate of AEs leading to withdrawal was 6.9 per 100 PY in the control DMARD group compared with 10.1 and 10.2 per 100 PY in the tocilizumab 4 mg/kg and 8 mg/kg groups, respectively. The type of events leading to withdrawal differed between the

control and tocilizumab treatment groups, with infections being the most common reason for subjects in the control group, and investigation AEs (mainly abnormal liver function tests) being the most common reason in the two tocilizumab treatment groups.

In the “All Exposure” population, the rate of AEs leading to withdrawal was 5.8 per 100 PY with the highest AE-related withdrawal rate (11.5 per 100 PY) occurring in the first 6 months of treatment and steadily decreasing thereafter (up to 48 months of follow-up). Consistent with previous observations, the most frequently reported type of AE leading to withdrawal were abnormal investigations (1.3 per 100 PY, primarily due to altered liver function tests), infections (1.1 per 100 PY), and neoplasm (0.7 per 100 PY).

Adverse Events Leading to Dose Modification or Interruption of Medication

The strategies for modification of treatment differed between the controlled studies and OLE trials. In the controlled double-blind studies, dose modifications were limited to skipping or interrupting the ongoing infusion of tocilizumab. In the extension studies, investigators at their own discretion were also allowed to skip the dose of tocilizumab, or decrease the dose from 8 mg/kg to 4 mg/kg. In all studies, investigators could also modify the dose of any concomitantly administered DMARDs or other medications.

In the “All Control” population, 11.8% (183/1555) patients in the control group, 17.4% (135/774) subjects in the tocilizumab 4 mg/kg group, and 16.9% (316/1870) patients in the tocilizumab 8 mg/kg group had at least one AE that led to dose modification. The rate of AEs that led to dose modifications was 27.8 per 100 PY for the control group, 32.9 per 100 PY for tocilizumab 4 mg/kg and 34.2 per 100 PY for tocilizumab 8 mg/kg group. The most common type of AE resulting in treatment modification were infections which were reported at a lower rate in the control (11.6 per 100 PY) and tocilizumab 4 mg/kg groups (11.58 per 100 PY) compared to 14.8 per 100 PY for the tocilizumab 8 mg/kg group. Investigation AEs were also common, reported at a rate of 4.6 per 100 PY in the control and tocilizumab 4 mg/kg groups, and 6.2 per 100 PY in the tocilizumab 8 mg/kg group. Again, abnormalities in liver function tests primarily accounted for this observation.

In the “All Exposure” dataset, the rate of AEs leading to dose modifications did not vary appreciably over time (approximately 36 per 100 PY up to 48 months of therapy). The types of AEs leading to dose modifications were consistent with that previously reported. Infections were the most frequently reported events leading to dose modifications (17.8 per 100 PY). The most common infections were URTI (2.3 per 100 PY), bronchitis (1.7 per 100 PY), nasopharyngitis (1.3 per 100 PY), and sinusitis (1.1 per 100 PY). Abnormal liver function tests (raised serum transaminases and bilirubin) were the second most common AE that led to a dose modification (3.3 per 100 PY). The overall rate of dose modifications due to decreases in neutrophil count was 1.4 per 100 PY.

An assessment of the effectiveness of the dose modification strategy was also undertaken. Overall, the results indicate that skipping or reducing the dose of tocilizumab to manage an AE was effective at maintaining patients on therapy. Of the 2050 AEs that led to either a skipped or reduced dose of tocilizumab, 1859 (91%) were successfully managed in a way that resulted in patients not withdrawing from treatment. Most AEs were managed by skipping a dose of tocilizumab (87%, 1793/2050) rather than only reducing the dose from 8 mg/kg to 4 mg/kg. The most common type of AE leading to a missed dose of tocilizumab was infection. The most common types of AEs leading to a reduction in the dose of tocilizumab from 8 mg/kg to 4 mg/kg were abnormal investigations, mainly abnormalities in liver function tests. Of the 257 events managed with a dose reduction, 247 (96%) were successful at keeping the patient on tocilizumab.

Clinically Significant Infusion Reactions

A total of 9 serious anaphylactic reactions related to tocilizumab infusion were recorded in the “All Exposure” population. Of the 9 events, 5 occurred with tocilizumab 4 mg/kg and 4 occurred with tocilizumab 8 mg/kg. Most events occurred early in the course of tocilizumab treatment: three occurred during the second infusion, three occurred during the third infusion, one occurred during the fourth infusion and two occurred following completion of the third and 15th infusions. The presence of anti-drug antibodies was not correlated with the occurrence of significant infusion reactions.

Serious Adverse Events (SAEs)

In the “All Control” population, the rate of SAEs was similar across the three treatment groups: - 14.4 per 100 PY for control therapy, 13.6 per 100 PY for tocilizumab 4 mg/kg and 14.5 per 100 PY for tocilizumab 8 mg/kg. The most frequently reported type of SAEs was infections which occurred at a higher rate in the tocilizumab 8 mg/kg group (4.8 per 100 PY) compared with the tocilizumab 4 mg/kg (3.5 per 100 PY) and control treatment groups (3.3 per 100 PY). The frequencies of SAEs in other system categories were comparable between patients treated with tocilizumab and control DMARD treatment. The rate of fractures was higher in the tocilizumab 8 mg/kg at 1.0 per 100 PY compared to other two treatment groups (0.4 per 100 PY for both control therapy and tocilizumab 4 mg/kg).

In the “All Exposure” population, the rate of SAEs was 14.9 per 100 PY, which is similar to rates reported previously. There was no evidence of an increased risk of SAEs with prolonged exposure to tocilizumab (up to 48 months), as demonstrated by similar rates of SAEs per 100 PY when SAEs are divided by 6 monthly intervals of exposure. The most frequently reported type of SAE was infection (4.4 per 100 PY), of which pneumonia (0.8 per 100 PY) and cellulitis (0.5 per 100 PY) were the most common types of infection. The second most frequently reported type of SAE was injury complications (1.3 per 100 PY), with fractures contributing to the majority of the events reported in this category.

Infectious Adverse Events

In the “All Control” population, the overall rate of infections was 95.9 per 100 PY for the control treatment group, 101.8 per 100 PY for the tocilizumab 4 mg/kg group, and 102.3 per 100 PY for the tocilizumab 8 mg/kg group. URIs and urinary tract infections were most commonly reported types of infections.

The overall rate of infections reported in the “All Exposure” population was 108.0 per 100 PY of exposure. The rate of all infections was highest in the first 6 months and decreased thereafter. The overall profile of infections was consistent with data reported previously with the upper respiratory tract and urinary tract being most commonly reported.

Serious Infections

In the “All Control” population, the overall rate of serious infections was 3.4 per 100 PY for the control group, 3.5 per 100 PY for the tocilizumab 4 mg/kg group, and 4.9 per 100 PY for the tocilizumab 8 mg/kg group. The events most commonly reported were pneumonia, cellulitis, urinary tract infection and gastroenteritis.

In the “All Exposure” population, the rate of serious infections was 4.66 per 100 PY, which is similar to the rate of serious infections reported previously and to that reported in the literature for other biological DMARDs used in patients with severe RA. Pneumonia was the most commonly reported serious infection in this population (98 events in total at an event rate of 1.0 per 100 PY of exposure). The incidence of pneumonia remained stable over time with extended treatment durations. In the “All Exposure” population, a total of 82 serious

skin and soft tissue infections in 79 patients (0.9 per 100 PY) were reported at a stable incidence rate with prolonged treatment exposure. Of the 79 patients who reported serious skin and soft tissue infections, 73 (92.4%) had a single occurrence and 6 (7.6%) subjects had two episodes. Of note, three patients developed infected fluid collections in the iliopsoas muscle region which is an unusual site of infection. There were 9 serious cutaneous herpes zoster events and one serious herpes zoster ophthalmic event reported in the “All Exposure” population.

Opportunistic Infections

A total of 24 opportunistic infections were reported in 20 patients in the “All Exposure” population (event rate for opportunistic infections of 0.2 per 100 PY). Fourteen of the 22 opportunistic infections were serious. Of the 22 opportunistic infections, two (9%) led to a fatal outcome, nine (41%) led to discontinuation from tocilizumab treatment, and five (23%) led to tocilizumab dose modification. One patient with systemic candidiasis also had concomitant staphylococcal sepsis which resulted in death. Other notable single case events included *Pneumocystis jiroveci* pneumonia, cryptococcal pneumonia and fatal invasive aspergillosis.

Cumulatively, nine events of tuberculosis (8 pulmonary and 1 extra-pulmonary) were reported in the “All Exposure” population. Three of the nine tuberculosis events were reported in a single patient (involving the lung and pleural space with bronchopleural fistula formation). In addition to the TB cases listed above, 6 patients in the “All Exposure” population recorded a positive tuberculin test without overt disease and 2 subjects experienced atypical mycobacterium infections (urinary tract and cellulitis). The case of cellulitis progressed to necrosis with abscess formation despite antibiotic treatment. *Mycobacterium chelonae* was identified and the patient withdrew from tocilizumab due to this AE.

Infection-Related Deaths

Twelve infections (all receiving tocilizumab 8 mg/kg) led to a fatal outcome in the “All Exposure” population. The overall rate of death due to infection was 0.13 per 100 PY of exposure.

Subgroup Analysis

Further exploration of safety in certain subgroups was performed for serious infectious AEs in the pooled control and long-term safety populations. In summary, serious infections occurred at a higher rate in the following subgroups: patients aged > 65 years, patients weighing > 100 kg (or body mass index [BMI] > 30), subjects with co-morbidities predisposing them to infection (such as diabetes mellitus or chronic obstructive pulmonary disease), and for those who had previously received anti-TNF medication or were taking background corticosteroids. The highest rates were observed for patients receiving tocilizumab 8 mg/kg. Using the “All Control” patient dataset, an increased rate of infection was observed for patients aged > 65 years regardless of the type of therapy (control or either dose of tocilizumab. In the “All Exposure” population, the rate of serious infection was 2.8 per 100 PY for patients aged < 50 years, 4.9 per 100 PY for patients 50-64 years of age and 7.7 per 100 PY for patients older than 65 years. For events of serious pneumonia, the rate increased from 0.5 per 100 PY for patients aged < 50 years to 0.9 per 100 PY for patients 50-64 years of age to 2.8 per 100 PY for patients older than 65 years. A similar trend for increasing age-related incidence was observed for skin and soft tissue infection.

In the “All Control” population, the rates of serious infection were significantly higher in patients weighing greater than 100 kg when they received treatment with tocilizumab 8

mg/kg (8 events in absolute terms at a rate of 9.97 per 100 PY). A similar trend was demonstrated in the “All Exposure” dataset with the rate of serious infection being 3.3 per 100 PY for patients weighing less than 60 kg, 4.2 per 100 PY for subjects 60 to < 80 kg, 5.0 per 100 PY for patients 80 to < 100 kg and 8.5 per 100 PY for subjects weighing > 100 kg. Consistent with this observation was the subgroup analysis by BMI in both the “All Control” and “All Exposure” cohorts, whereby patients with a BMI > 30 had the highest incidence of serious infection, particularly if they received treatment with tocilizumab 8 mg/kg (compared to control DMARD or tocilizumab 4 mg/kg). Very few patients had a BMI < 18.5 to make a meaningful conclusion about the rate of serious infection in undernourished subjects. The presence of diabetes mellitus and chronic pulmonary disease also was associated with an increased rate of serious infection but this occurred at similar rates regardless of the treatment given (control DMARD and both doses of tocilizumab). Likewise, patients with a history of prior anti-TNF therapy or oral corticosteroid use (previous and/or concurrent) had increased rates of serious infection but this did not appear to depend upon by whether they received tocilizumab (4 or 8 mg/kg) or conventional DMARD treatment as the 95% confidence intervals were wide and overlapping when effect by treatment was explored.

Gastrointestinal (GI) Perforation

In the “All Exposure” population, a total of 26 patients experienced GI perforation(s) at an overall event rate of 2.8 per 1000 PY. The development of anal fistula was not included as a GI perforation because this pathology is sequelae to anal gland infection resulting in abscess formation. In 16 of 18 patients (89%) with colon perforation (1.9 per 1000 PY), the pathology underlying the perforation was diverticulitis. The age of these 16 patients ranged from 51 to 82 years (mean of 63.3 years). In additional, diverticulitis was identified as the underlying pathology in one patient who experienced jejunal perforation.

Cardiovascular (CVS) Events

The rate of cardiac disorders among the three treatment populations in the “All Control” dataset was comparable, 3.5 per 100 PY for control, 2.7 per 100 PY for tocilizumab 4 mg/kg and 4.0 per 100 PY for tocilizumab 8 mg/kg. In the “All Exposure” population the rate of cardiac events was stable over 42 months of follow-up at 3.9 per 100 PY. The most frequent cardiac AEs were arrhythmias, ischaemic events and ventricular dysfunction. Given the changes in lipid parameters associated with tocilizumab, myocardial ischaemic events and strokes were of particular interest during analysis. The event rate for both AE types was low and within expectations (0.25 per 100 PY for MI and 0.19 per 100 PY for strokes in the “All Exposure” population). The event rate frequencies did not significantly change over time for up to 48 months of drug exposure.

In the “All Control” population, the overall rate of hypertension recorded as an AE was 5.8 per 100 PY for the control group, 9.4 per 100 PY for tocilizumab 4 mg/kg and 9.6 per 100 PY for tocilizumab 8 mg/kg. In the “All Exposure” population, the overall rate of newly reported hypertension was 6.1 per 100 PY with the highest incidence observed in the first 6 months of receiving tocilizumab. The proportion of subjects with Grade 1 (18.5%) or 2 (3.5%) hypertension recorded over 3 years of follow-up did not alter.

Malignancy

In the “All Exposure” population a total of 112 malignancies have been recorded at an overall event rate of 1.19 per 100 patient-years, which is an incidence similar to that observed for other biological DMARDs used in moderate-severe RA. Cases of malignancy were divided into solid cancers (68 cases), non-melanoma skin cancers (37 cases, 25 basal cell carcinomas of the skin and 12 squamous cell cancers), haematological malignancies (4 cases) and other

types of cancer (3 cases, 2 of which were metastatic skin cancers). Solid cancers reported by more than one patient included lung neoplasms (14), gastrointestinal cancer (9), breast cancer (8), prostate cancer (6), cervical and endometrial cancer (4 each), thyroid cancer (2) and tongue carcinoma (2). In the haematological cancer category, there were 2 cases of B-cell lymphoma, 1 case of acute myeloid leukaemia and 1 case of chronic lymphocytic leukaemia, which is an incidence and pattern of malignancy not beyond expectations (irrespective of type of treatment). When the rate of new cases of malignancy was assessed in 6 monthly periods up to 42 months, the incidence was stable.

In the “All Control” population, the rates of malignancy (1.6 per 100 PY – 9 cases [5 solid cancers, 3 non-melanoma skin cancers and 1 other]) were higher in the tocilizumab 4 mg/kg group compared with an event rate of 0.7 per 100 PY in both the control (6 cases, 3 each of solid cancers and non-melanoma skin cancers) and tocilizumab 8 mg/kg treatment groups (8 cases, 4 each of solid cancers and non-melanoma skin cancers).

Deaths

A total of 50 deaths have been recorded in the “All Exposure” population. The principle causes of death reported by the investigators include cardiac events (13 cases) serious infections (12 cases), and malignancies (8 cases). Serious infections were ongoing in 5 patients at the time of death. In tocilizumab-treated patients, the overall rate of death is 0.53 per 100 PY of exposure, which is consistent with the peer reported rate of mortality. In comparison, the overall rate of death for patients on control therapy is 0.73 per 100 patient-years (6 deaths in 824.56 patient-years exposure). Of the 50 deaths reported in patients treated with tocilizumab, 1 occurred in a patient receiving 4 mg/kg and 49 occurred in patients receiving 8 mg/kg (resulting in mortality rates of 0.97 and 0.53 deaths per 100 PY, respectively). The overall rate of death due to infection is 0.13 per 100 PY of exposure which is also consistent with the rate reported in several patient cohorts with severe RA requiring aggressive therapy.

Other Clinical Events of Special Interest

In the “All Exposure” population, 6 of 4009 reported a clinically overt autoimmune condition that may have been related to tocilizumab. In particular, one patient developed systemic lupus erythematosus (SLE) while another two were observed to develop “lupus-like” syndromes. Three patients developed Crohn’s Disease. In addition, one patient had a worsening of their pre-existing autoimmune hepatitis that required treatment with high dose corticosteroid. Furthermore, another 14 patients either developed skin psoriasis *de novo* or experienced an exacerbation, 13 reported significant sicca symptoms, 11 had cutaneous vasculitis and 6 experienced autoimmune thyroiditis. An etiological relationship between tocilizumab therapy and these autoimmune conditions is unclear.

A total of 9 patients were identified as having potential demyelinating conditions (such as multiple sclerosis, optic neuritis and transverse myelitis) in the “All Exposure” population but the relationship to tocilizumab is unclear. There are two reports of relapse of previously known multiple sclerosis, 1 case of bilateral optic neuritis and the remainder of the reports relate predominately to various types of peripheral neuropathy.

Laboratory Parameters

Certain laboratory parameters of interest were analysed in the “All Exposure” population dataset.

Neutropenia

In the “All Exposure” population, Grade 3 neutropenia (ANC of $0.5-1.0 \times 10^9/L$) was recorded in 165 patients (4.1% of 4009). The incidence of Grade 3 neutropenia was highest during the first year of tocilizumab treatment (2.3% [for 0 to 6 months of exposure], 1.4% [for 7 to 12 months of exposure]) and decreased to <1% thereafter. One patient (<1%) reported a serious infection (empyema) which had an onset temporally associated with the development of Grade 3 neutropenia. In the “All Exposure” population, twenty-nine patients (<1% of 4009) reported Grade 4 neutropenia (ANC < $0.5 \times 10^9/L$), all observed at a single time point. None of the patients with Grade 4 neutropenia experienced a temporally associated serious infection.

Thrombocytopenia

In the “All Exposure” population of 4002 subjects, 30 patients developed Grade 2 thrombocytopenia (platelet count between 50 and $75 \times 10^9/L$), 13 experienced Grade 3 thrombocytopenia (platelet count $25-50 \times 10^9/L$) and 19 developed Grade 4 thrombocytopenia (platelet count < $25 \times 10^9/L$) which cumulatively represents 1.5% of total exposed population. Two patients experienced serious bleeding as a consequence of thrombocytopenia; one upper GI haemorrhage and the other haemorrhagic stomatitis. Five patients in total developed pancytopenia in association with tocilizumab, one of which had major haemorrhage from epistaxis.

Liver Enzymes and Bilirubin

The percentage of tocilizumab-treated patients in each group with normal serum ALT and AST values at baseline who then experienced an increase to values more than x 3 ULN during the 6 month controlled studies was relatively low at approximately 3-4%.

For the “All Exposure” dataset, shifts in ALT and AST from normal baseline values to >ULN at some point during the studies were observed in 66.7% (2462/3689) and 54.6% (2081/3812) of patients, respectively (excluding patients with missing values). Shifts in either ALT or AST that worsen from normal at baseline to a maximum value of up to x 3 ULN, x 3-5 ULN and > x 5 ULN were observed in 57.3% (2112/3689), 7.2% (267/3689) and 2.2% (83/3689) of patients, respectively, in the “All Exposure” population. A total of 91 (2.2% of 4002) subjects prematurely withdrew due to elevated serum transaminases.

In the “All Exposure” population, 23 patients (0.6% of 4002) recorded an indirect serum bilirubin level more than 2-fold the ULN. Of these 23 patients, 10 (43.5%) were recorded to have experienced an AE which led to withdrawal from treatment. All but 2 of the AEs were asymptomatic laboratory abnormalities (of increased serum bilirubin) but 2 patients developed clinical symptoms that may have related to the increased serum bilirubin level (1 case each of hepatic steatosis and impaired healing following a wound infection).

Genetic Study on Patients with Indirect Hyperbilirubinaemia

The sponsor has also performed analyses of the UGT1A1 gene to further the understanding of indirect serum bilirubin elevations in association with treatment with tocilizumab. The results of these analyses demonstrate that many patients with elevated indirect serum bilirubin > $30 \mu\text{mol/L}$ in association with tocilizumab carry one or two copies of a specific UGT1A1 gene variant found commonly in individuals with Gilbert’s Syndrome. These data support the conclusion that elevations in indirect and total bilirubin are a pharmacodynamic effect of tocilizumab treatment.

Effect on Liver Function Tests of Co-administration of Statins

During the clinical study program, a subgroup of patients started taking lipid lowering agents while receiving treatment with tocilizumab. Using the “All Exposure” population dataset, the proportion of patients who commenced statins while receiving tocilizumab was 11.4% (456/4009). For this subgroup, transient elevations in ALT and/or AST from normal pre-treatment levels to $\times 3$ ULN was 47.3% (147/311) and to $> \times 3$ ULN occurred in 2.6% (8/311) of patients. For comparison using the entire “All Exposure” population (including patients who initiated statins while receiving tocilizumab and those who did not), transient elevations in ALT and/or AST from normal at baseline to $> \times 3$ ULN were observed in 57.3% (2112/3689) and to $> \times 3$ ULN was 9.5% (350/3689) of subjects. This data indicates that there was no evidence to suggest that concomitant use of statins with tocilizumab and MTX is associated with an increased risk of serum transaminase elevations.

Clinical Hepatic AEs

Three serious events suggestive of possible hepatotoxicity were identified in the “All Exposure” population; one case each of exacerbation of pre-existing autoimmune hepatitis, hepatic steatosis, and ischaemic hepatitis. The ischaemic hepatitis event required hospitalization, while the autoimmune hepatitis and hepatic steatosis events were diagnosed by liver biopsy and managed on an outpatient basis.

Lipid Parameters

As previously reported, mean and median fasting LDL-cholesterol values increased by the first assessment at 6 weeks in the controlled studies and remained relatively stable thereafter. However, categorical analysis of LDL-cholesterol changes using the ATP III guidelines showed that at baseline 29.2% (1061/3633) of patients had an LDL-cholesterol > 130 mg/dL, yet this proportion increased to 50.1% (1524/3041) at week 24 and remained at similar levels (50.8-55.3% of measured subjects) all the way through to 152 weeks of follow-up. Other lipid parameters (such as TC and TG) demonstrated a similar pattern of change upon exposure to tocilizumab.

Anti-Tocilizumab Antibodies

Of the 3937 patients in the “All Exposure” population screened for anti-drug antibodies, 39 (1.0%) were positive for assay specific anti-tocilizumab antibodies and 127 (3.2%) developed neutralizing antibodies (screening test) on at least one occasion. The frequency of developing both specific and neutralizing anti-tocilizumab antibodies was similar for patients receiving either tocilizumab monotherapy or combination DMARD treatment, although the absolute number of patients in the monotherapy group was very low. Most patients (62.9%) developed anti-drug antibodies before Week 24 and more than 90% did so before Year 1 of therapy. The proportion of patients who experienced AEs and SAEs (including infusion-related reactions) was similar in subjects with or without anti-tocilizumab antibodies. Furthermore, subgroup analysis of patients who missed at least two consecutive doses of tocilizumab does not show that this leads to an increased rate of anti-drug antibody formation.

Conclusions for Extended Exposure Populations

The extended duration safety data obtained from the open-label extension studies (WA18695, WA18696 and WA17823) suggest that the incidence and types of adverse events occurring in patients receiving tocilizumab for up to 156 weeks is similar to the experience known from the controlled trials. Some adverse events such as the increased incidence of serious infections, abnormal liver function tests and risk of neutropenia in tocilizumab-treated

patients compared to subjects treated with control DMARD therapy persist but do not increase in incidence with prolonged duration of follow-up.

Post-Marketing Data

A specific post-marketing report for tocilizumab use in RA was not submitted with this application because the drug was only recently approved for use in Europe (19 January 2009) and at the data cut-off date of 11 April 2009 only 78 European patients were estimated to be exposed to tocilizumab. However, the sponsor did submit three additional pieces of information which have relevance to post-marketing drug experience.

The first piece of information relates to the Japanese experience with tocilizumab. In Japan, tocilizumab is available for three indications under a registry system in a closed distribution program: Castleman's Disease (since June 2005), adult patients with RA and systemic juvenile arthritis (the latter two indications since June 2008). As of 15 April 2009, an estimated 5700 Japanese patients with inflammatory arthritis have been treated for a calculation assessed exposure duration of 2956 patient-years. The Marketing Authorization Holder (MAH) in Japan provided the EU drug regulatory body with an update (as of 25 March 2009) of 27 fatal cases of tocilizumab-treated patients from the Japanese RA database. The estimated death rate in the Japanese post-marketing surveillance (PMS) program is 10.12 per 1000 patient-years which is similar to that in the Japanese RA database for anti-TNF medications (10.9 and 11.0 per 1000 patient-years for etanercept and infliximab respectively). However, this event rate is significantly higher when compared to the mortality rate in the initial 6 month controlled periods of the Phase III trials of tocilizumab (4.1 per 1000 patient-years for tocilizumab [5 patients in 1234.3 patient-years of exposure] and 8.8 per 1000 patient-years for placebo + MTX [6 patients in 682.8 patient-years of exposure]). The higher death rate observed in tocilizumab-treated patients with RA in the Japanese PMS reflects patient selection in the "real-world" clinical experience as opposed to clinical trials. In general, the patients in the Japanese PMS were older (mean age 69 years), had a greater extent and acuity of co-morbid medical conditions and extensive prior treatment with immunosuppressants. A review identified that in 15 of the 27 fatal cases, infection was a significant contributor to the death. None of the deaths were attributed to tuberculosis. The MAH in Japan is attempting to obtain further information on the deaths that have already occurred and has a specific plan of action to obtain adequate information concerning any future deaths. It is also estimated that approximately 20% of the patients treated in the Japanese PMS experience would not have fulfilled the EU requirements for patient selection (as contained within the EU licensing approval).

Secondly, the sponsor provided a brief summary of the sole Periodic Safety Update Report (PSUR) that has been lodged with the EU drug regulatory body. This PSUR summarized safety data for tocilizumab collected globally by Roche and Chugai (the Japanese MAH) between 11 October 2008 and 10 April 2009. The estimated tocilizumab exposure during this PSUR period (via both commercially obtained drug and through clinical trials) is 10,022 patients including 195 paediatric patients with juvenile arthritis in the Japanese PMS program, 78 subjects with RA in the non-trial setting, as well as 284 patients treated for Castleman's disease. During the reporting period, a total of 491 patients reported 919 AEs (80 spontaneous reports), of which 532 were serious. The most frequently AEs were within the categories of infection (31.0%), abnormal investigations (14.1%) and GI disorders (8.2%). The same categories represented the majority of SAEs - infection (33.5%), abnormal investigations (9.2%) and GI disorders (7.9%). In total, 24 deaths were recorded in the PSUR reporting period. Little additional information concerning the nature of the AEs and SAEs was provided with this submission other than the stratification of AEs by treatment

indication. The majority of reports related to the treatment of adult patients with RA (73.2% of total AEs and 82.7% of SAEs) which reflects the greater drug exposure for this indication, followed by Castleman's disease (14.3% of AEs and 5.3% of SAEs) and juvenile arthritis (9.2% of AEs and 9.0% of SAEs). In addition, during the PSUR period it became apparent that some cases of GI perforation were occurring in the RA clinical trials (up to 31 December 2008). There was no evidence to suggest this AE was of increased incidence with time, but given the seriousness of the AE the core data sheet for tocilizumab was modified to include a warning about the risk of gastrointestinal perforation and complications of diverticulitis. The majority of GI perforations that had been recognized until then were located in the lower GI tract and were frequently associated with diverticular disease.

Thirdly, the sponsor submitted a Risk Management Plan (RMP, version 6.0, developed for the EU and dated September 2009). This is discussed under *Section V*.

Clinical Summary and Conclusions

The clinical efficacy data for the extension of indications in RA is supported by a single new pivotal Phase III trial (WA17823) of 2 years duration which involved a total 1190 adult patients with moderately to severely active RA. Study WA17823 was designed as a 1 year double-blind controlled study followed by a second year of open-label treatment with tocilizumab 8 mg/kg + MTX. This design allowed for an assessment of the efficacy of tocilizumab (versus an active comparator) regarding the progression of joint damage and improvement in physical function in RA patients at Year 1, and then an assessment of the maintenance of the efficacy with continued tocilizumab treatment at 2 years. Supportive data was supplied from 2 open-label extension studies (WA18695 and WA18696) as well as the extension phase (Years 3-5) of Study WA17823. Collectively, the open-label extension trials involved more than 2600 patients who had received the two mostly commonly recommended doses of tocilizumab (4 mg/kg and 8 mg/kg).

The rationale for this current submission is to extend the treatment indications in adult patients with RA to include additional disease aspects such as inhibiting the rate of radiographic progression and improving physical function. The efficacy of tocilizumab in the newly presented controlled study (WA17823), as well as the previous Phase III trials, was assessed by a number of means, which were appropriate, clinically meaningful, and relevant to the sponsor's application. The selected endpoints use well accepted, validated metrics that have served as the basis for previous published studies in RA management and are consistent with the published guidelines recommended by regulatory authorities. The statistical analysis plans for the controlled study were clearly delineated and appropriate. The degree of statistical significance for the primary endpoints and most of the secondary endpoints provides confidence that the effects seen in the study are unlikely to be due to random chance. In addition, the result of the sensitivity analyses for the primary endpoints and the secondary analyses of radiographic outcomes, functional indices, ACR response, EULAR response, and quality of life measures support the primary endpoints and demonstrate internal consistency for the studies. The study populations were adequately defined to assess efficacy in moderately to severely active disease in patients that were mostly treatment refractory to conventional DMARDs with variable durations of RA. The demographic characteristics of the subjects involved in the controlled studies were representative of patients who may be encountered in routine Australian clinical practice. The overall efficacy findings included in this submission demonstrate that: -

- § Treatment with tocilizumab 8 mg/kg + MTX resulted in less progression of joint damage compared with placebo + MTX, as indicated by the mean change in total Sharp-Genant score from baseline to Week 52. This rate of inhibition was maintained

in tocilizumab-treated subjects (from baseline to Week 104) and supported by corresponding consistently favourable changes in both the erosion and joint space narrowing scores;

- § The proportion of patients with no radiographic progression (defined as < 0 change in the total Sharp-Genant score) was significantly higher in the tocilizumab 8 mg/kg + MTX group compared with the placebo + MTX group, and increased in Year 2 compared with Year 1;
- § Patients treated with tocilizumab 8 mg/kg + MTX had a significant improvement in physical function at Week 52 compared with placebo + MTX, as indicated by the AUC of the change in HAQ-DI, and these improvements were maintained at Week 104. This finding is supported by the high proportion of patients achieving the clinically important improvement of 0.3 at Weeks 52 and 104;
- § The data concerning improvement in physical function is additionally supported by the results of other patient reported functional outcomes including improvements in FACIT-fatigue and SF-36 physical function scores;
- § The treatment effect of tocilizumab 8 mg/kg + MTX on improving the signs and symptoms of RA achieved at Year 1, was maintained (ACR50 and 70 responses) or showed further improvement (tender and swollen joint counts) at Year 2, with increasing proportions of patients achieving clinically relevant endpoints such as a major clinical response, Disease Activity Score (DAS28) remission, and EULAR response; and
- § Overall response rates to therapy with tocilizumab 8 mg/kg (usually with concomitant DMARD) were maintained or continued to improve with prolonged durations of treatment, as evidenced by increasing numbers of patients achieving high rates of response (ACR50, ACR70 and DAS28 remission) over extended follow-up periods (up to 156 weeks).

The safety of tocilizumab use in RA was assessed by reviewing the safety data collected from the 4009 patients who received at least part of one infusion of tocilizumab in the clinical development program (controlled or open-label setting). This represents a total drug exposure to tocilizumab for adult RA patients that approximates to 8580 patient-years (as of the data cut-off date of 11 April 2009). In general, tocilizumab was well tolerated in patients concurrently receiving MTX or other conventional DMARDs. Individual follow-up time ranges from 16 weeks to more than 3 years with the majority of safety data collected from patients involved in the three open-label extension studies. The majority of adverse events were mild or moderate in severity, often self-limiting, and did not necessitate permanent withdrawal from treatment.

The safety analyses from the RA clinical trial program reveals five particular safety risks requiring ongoing vigilance: risk of serious infection, complications of diverticular disease (including gastrointestinal perforation), development of neutropenia, liver enzyme and serum bilirubin elevations and minor sustained increases in serum lipid parameters. In the controlled studies, acute infusion reactions during or within 24 hours of infusion of tocilizumab was also a rare but significant safety concern. Dose modifications or interruptions to tocilizumab therapy, mainly due to laboratory abnormalities such as elevated serum transaminases and cytopenias, is also of concern. Rates of hypertension were also higher in tocilizumab-treated patients in the controlled population dataset.

Infectious risk is of particular interest because of the mode of action of tocilizumab, and patients with advanced RA are at a higher risk of infection than the general population. In the

“All Exposure” population, the rate of serious infection was 4.66 per 100 patient-years which was comparable to that observed in similar RA patient cohorts (for example, those with severe RA receiving anti-TNF medications [5.32 per 100 patient-years] and non-biologic DMARDs [4.11 events per 100 patient-years]). The rate and types of serious infection remained stable over time. The most common types of serious infection were pneumonia, and skin and soft tissue infections. A total of 24 patients developed opportunistic infections in the “All Exposure” population database with 9 of these events being tuberculosis.

The incidence of overall adverse events, deaths, malignancy and other adverse events of special interest (namely, cardiovascular disease) was consistent with the expected incidence in RA populations from epidemiological studies. The safety profile of tocilizumab was consistent across the limited doses studied apart from dose-related laboratory abnormalities, as well as the patient populations and subgroups with the exception of a higher rate of serious infection in patients with age > 65 years, and a weight > 100 kg or BMI > 30.

Conclusion/Recommendation

In conclusion, the data included with this submission shows a favourable benefit to risk ratio for the use of tocilizumab in patients with moderately to severely active RA of variable disease duration that is refractory to conventional DMARD therapy. The two aspects of the sponsor’s application for an extended indication in patients with RA are considered below.

1) The evaluator recommended acceptance of the sponsor’s application for the extension of indications in the treatment of RA to the inhibition of radiographic progression (that is, the higher level of efficacy claim with respect to structural damage in RA). The submitted dataset shows a consistent effect of tocilizumab when added to MTX in inhibiting the rate of radiographic progression in RA as evidenced by lower comparative mean changes in the mTSS and its components over 2 years of observation, as well as the proportion of patients without radiographic evidence of erosive progression.

2) The evaluator recommended acceptance of the sponsor’s application for the extension of indications in the treatment of RA to improving physical function. The trial data included with this submission shows a consistent effect for tocilizumab (when added to MTX) in improving physical function as demonstrated by statistically significant comparative improvements in HAQ-DI (versus continued MTX monotherapy) in Study WA17823, and several longer term, open-label extension trials.

V. Pharmacovigilance Findings

Risk Management Plan

The sponsor submitted a Risk Management Plan (RMP, version 6.0, developed for the EU and dated September 2009). The data cut-off dates for the EU-RMP was 6 February 2009 for any clinical trial information and 11 April 2009 for post-marketing surveillance data. The RMP proposed by the sponsor outlines the current and planned safety risk management activities for tocilizumab in patients with RA. The sponsor has identified three important risks:

- § serious infections (including reactivation of chronic Hepatitis B viral infection)
- § serious hypersensitivity reactions (that is, acute infusion reactions)
- § complications of diverticular disease (including GI perforation).

In addition, seven potential risks that require on-going surveillance or evaluation have been identified:

- § development of neutropenia (and the potential risk of infection)
- § thrombocytopenia (and the potential risk of bleeding)
- § liver enzyme and serum bilirubin elevations (and the risk of hepatotoxicity)
- § elevated lipid levels (and the impact on cardiovascular and cerebrovascular disease)
- § malignancy
- § demyelination disorders
- § the potential for interaction with cytochrome P450 substrates.

The clinical evaluator noted that the last potential risk (normalization of CYP450 enzyme activity) does not appear to be actively addressed by the sponsor in its Risk Management Plan (that is, there is no plan to perform any future drug interaction studies). Inflammatory cytokines such as IL-6 have the potential to down-regulate the activity of CYP450 enzymes involved in drug metabolism. Hence, normalization of this mechanism by inhibition of serum inflammation can result in decreased exposure of medicines metabolized by CYP450 enzymes. In the submission, a drug interaction study (WP18663) in 23 patients with RA found that levels of simvastatin (CYP3A4) were decreased by 57%, one week after a single dose of tocilizumab, to a concentration similar to those observed in healthy subjects. Conversely, when tocilizumab is ceased or withheld an increased drug effect for CYP450 drug substrates may occur. However, because tocilizumab has a relatively long elimination half-life, if therapy is temporarily interrupted it is likely to take several weeks before changes in CYP450 enzyme activity would ensue.

The pharmacovigilance plan outlines routine practice including regular review of reported adverse events (obtained either spontaneously or by various established means) as a means of signal detection, the provision of periodic safety updates to regulatory authorities, and the prompt notification of potential serious and/or unexpected adverse events to healthcare professionals.¹⁰ In addition, the product information and labeling should refer to all of these safety matters. Key additional elements of the PMS plan involve additional pharmacoepidemiology measures such as liaising with several international RA patient registries and databases (Britain, Sweden, Germany and USA), review of AEs of special interest (such as serious infections and neutropenia) with specific guided questionnaires, and additional long-term observational studies addressing concerns (such as serious infection) or populations (such as juvenile arthritis) relevant to the assessment of risk. In addition to the clinical trial program, the sponsor is planning to do studies evaluating the effects of tocilizumab on lipids, arterial stiffness and markers of atherogenic risk (Study WA19923); safety and efficacy of killed vaccines administered concurrently with tocilizumab (sub-study of the on-going, open-label extension of WA18696) and a study to elucidate the mechanism of neutrophil count reduction. For the last study, there is pre-clinical data to show that neutrophils express IL-6 receptor and therefore tocilizumab is expected to be able to bind to neutrophils.

¹⁰ Routine pharmacovigilance practices involve the following activities:

- § All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- § Reporting to regulatory authorities;
- § Continuous monitoring of the safety profiles of approved products including signal detection and updating of labeling;
- § Submission of PSURs;
- § Meeting other local regulatory agency requirements.

The RMP also acknowledges the limited sub-population data in certain groups, and outlines the rationale as to why specific populations were excluded from the clinical trials. In particular, very few patients aged > 75 years (n=50; ~2% overall) were involved in the clinical RA trials and patients aged > 65 years were also probably under-represented (n=435; ~17% of the overall population). Women of childbearing potential were advised to not attempt becoming pregnant. As of 6 February 2009, 31 pregnancies were reported in 30 patients receiving tocilizumab in the clinical trials. For 25 of the 31 pregnancies the outcome is known: - 13 had therapeutic termination, 7 resulted in spontaneous miscarriage, 4 delivered normal healthy babies (2 receiving tocilizumab monotherapy) and 1 died of respiratory distress. The majority of women (24/30) who became pregnant were receiving tocilizumab in combination with MTX. Patients with a history of significant cardiac, liver or renal disease were also excluded.

VI. Overall Conclusion and Risk/Benefit Assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

There was no requirement for a quality evaluation in a submission of this type.

Nonclinical

Two new pharmacodynamic studies were provided in this submission. The first was a cross-reactivity study which showed specific binding of MR16-1 (a rat monoclonal antibody) to mouse IL-6R, but not to human IL-6R. In another study which assessed a new *in vitro* assay with tocilizumab, the recombinant antibody was shown to competitively bind to IL-6R and to functionally inhibit the growth of IL-6 dependent cells.

The new study findings did not raise any concerns with regard to the safety profile of tocilizumab.

Clinical

This application for extension of indication in RA is supported by a single pivotal study (WA17823) which enrolled adult patients with active RA who had an inadequate response to MTX. The trial assessed the outcomes of radiographic analyses of the reduction in progression of joint damage and data on improvement in physical function. The current application is also supported by the cumulative long-term efficacy and safety data from the open-label extension phase of Study WA17823 as well as two ongoing open-label extension studies (WA18695 and WA18696) which recruited patients from the controlled trials in the original tocilizumab registration application.

The clinical evaluator has recommended acceptance of the sponsor's application for the extension of indications in the treatment of RA to include both the inhibition of radiographic progression and improvement in physical function.

Pharmacology

There was no new specific pharmacodynamic data to be evaluated as part of this submission. As noted by the evaluator, the submission did not contain any pharmacodynamic data in relation to biochemical markers of cartilage and bone matrix turnover such as urinary levels of collagen, telopeptides or pyridinolines. It was the view of the clinical evaluator that such information may have supported the biological plausibility of tocilizumab in its claim of inhibiting structural joint damage in RA. It was also noted by the clinical evaluator that pre-clinical data indicates that IL-6 can indirectly stimulate osteoclastic activity and bone

resorption and by altering the balance between osteoclastic and osteoblastic activity has the potential to change the dynamics of bone modelling. The sponsor was requested to make a comment on these observations by the clinical evaluator.

Pharmacokinetic sampling was a secondary endpoint in Study WA17823 and was explored in a consenting subset of the overall study population. The mean trough tocilizumab concentrations for those receiving 4 mg/kg appeared to decline after Week 24 before returning to baseline at study conclusion (Week 104). This is first observable at Week 52 when the numbers of subjects still on 4 mg/kg remains comparable with those who were on the same dose at Week 24. By contrast, the pre-dose concentrations for those on 8 mg/kg did not fall. There was a steady but slight rise. The median values of the pre-dose concentrations in the 4 mg/kg group were consistently zero, meaning that at least 50% of the subjects in this group did not have any measurable active at pre-dose testing at any of the time points tested. The sponsor was asked to provide a detailed comment on these findings.

Efficacy

Efficacy with regard to the inhibition of radiographic progression and to the improvement in physical function

For the proposed extensions of indication, Study WA17823 was the pivotal study. It was a prospective, multicentre, randomized, double-blind, placebo-controlled, parallel-group study with 3 treatment groups: placebo infusions + MTX, tocilizumab 4 mg/kg [low dose group] + MTX or tocilizumab 8 mg/kg [high dose group] + MTX.

There were two primary efficacy endpoints. The first, radiographic, was the mean change in the Genant-modified Total Sharp Score (mTSS) from screening to Week 104 between the three treatment groups and the second, functional, was the AUC for the change from baseline in the HAQ-DI. There were a number of secondary efficacy endpoints, a number of them radiographic and one functional as well as a number of others including clinical signs and symptoms (involving ACR20, ACR50, ACR70, DAS28 and EULAR responses) and quality of life measures (FACIT-Fatigue and SF-36).

Radiographic results

Treatment with tocilizumab + MTX, compared with MTX monotherapy, resulted in a reduction in the mean change from baseline in the mTSS at Week 104 (mean changes in mTSS of 0.58 for tocilizumab 4 mg/kg, $p = 0.0025$ and 0.37 for tocilizumab 8 mg/kg, $p < 0.0001$ versus 1.96 for placebo + MTX). Analysis of the patient primary radiographic data excluded post-withdrawal data and escape data and used linear extrapolation as the imputation method for missing data. Similar results for the primary radiological efficacy outcome were obtained for sensitivity analyses performed on the PP and ITT populations.

Results for improvement in physical function

The primary functional endpoint of the AUC of the change from baseline at Week 104 in the HAQ-DI showed a significantly greater decrease for patients in the ITT population in both tocilizumab groups compared with placebo + MTX (adjusted mean change of -287.5 for tocilizumab 4 mg/kg + MTX and -320.8 for tocilizumab 8 mg/kg + MTX versus -139.4 for placebo + MTX, $p < 0.0001$ for each pairwise comparison).

Results for radiographic secondary efficacy variables

The results for the radiographic secondary efficacy variables were all supportive. The changes from baseline at Week 80 in the mTSS were significantly lower in both active-treated groups than in the control group. Patients treated with tocilizumab had a statistically

significant reduction in erosion scores at both Weeks 80 and 104 (mean change 0.27 at Week 80 [$p = 0.0011$] and 0.34 at Week 104 [$p < 0.0001$] for tocilizumab 4 mg/kg + MTX and 0.18 at Week 80 [$p < 0.0001$] and 0.22 at Week 104 [$p < 0.0001$] for tocilizumab 8 mg/kg + MTX) compared with subjects randomised to placebo + MTX (mean change 1.01 at Week 80 and 1.24 at Week 104). At 104 weeks, a significantly higher proportion of subjects randomised to tocilizumab 4 mg/kg + MTX (78.4%, 269/343, $p = 0.0006$) or tocilizumab 8 mg/kg + MTX (85.6%, 302/353, $p < 0.0001$) demonstrated no erosive progression versus 71.1% (209/294) of subjects in the control group. Similar supportive changes were observed with the joint space narrowing score and with the parameter of no radiographic progression.

Results for other secondary efficacy variables

There was no significant difference in the proportions of patients in each of the original randomised groups who achieved an improvement of at least 0.30 units from baseline in the HAQ-DI at week 104 – 62.3% (144/231) for tocilizumab 8 mg/kg + MTX, 63.3% (138/218) for tocilizumab 4 mg/kg + MTX and 58.3% (74/127) for placebo + MTX. This lack of difference between the three treatment groups for this outcome is said to be explained by the fact that most patients had switched to open-label tocilizumab 8 mg/kg + MTX at Week 52.

The results for a wide range of secondary efficacy criteria were all consistent with the known efficacy profile of tocilizumab and the radiographic and functional outcomes summarised above. These criteria included ACR 20, 50 and 70 response rates, major clinical response rates, ACR remission, changes from baseline in the individual ACR core set parameters, change from baseline in DAS28 score, the AUC of DAS28 at Week 104 and the EULAR response.

Efficacy in general – the supporting open-label extension studies WA18695, WA18696 & WA17823

Long-term efficacy data was obtained from three open-label extension (OLE) studies. Patients who completed the 24 week observation periods of the core Phase III controlled trials were allowed to continue on tocilizumab into one of two open-label extension studies – WA18695 and WA18696. In addition, subjects who completed the 2 year core study period for Study WA17823 were eligible to continue with tocilizumab therapy in an open-label extension phase.

Study WA18695 recruited 537 patients (including escape patients) who completed 24 weeks of follow-up in the forerunner study WA17822 (in which 623 subjects were involved). Study WA18696 recruited 2066 patients who completed 24 weeks of follow-up in 3 prior Phase III studies and one clinical pharmacology trial (out of 2415 patients involved in these 4 trials). There were 1149 subjects from WA17823 (the pivotal study above). The “All Exposure” population contained a total of 4009 patients. All patients in the OLE phase received tocilizumab in combination with DMARDs (mostly MTX) with the exception of 234 subjects who continued to receive tocilizumab 8 mg/kg monotherapy. The efficacy data from this phase indicated that treatment with tocilizumab (mostly in combination with MTX) resulted in significant proportions of patients either maintaining or continuing to improve in a clinically meaningful manner (ACR 50 and 70 responses and clinical remission) for up to 156 weeks of follow-up. Patients who initially received treatment involving tocilizumab 4 mg/kg and then switched to open-label treatment involving tocilizumab 8 mg/kg generally showed an improvement in disease activity.

Safety

Study WA17823: Because of the trial design whereby escape treatment (after Week 16) or open-label (Year 2) treatment with tocilizumab 8 mg/kg was available and often utilized, the

increasing differences in drug exposure between the control arm and the various tocilizumab groups limited direct comparisons of the incidence of adverse events. Using the safety data up to 104 weeks, patients receiving either dose of tocilizumab experienced a higher rate of adverse events overall, serious adverse events (in particular, serious infections and gastrointestinal perforations), adverse events resulting in withdrawal or dose interruption and hypertension (of uncertain cause) than patients treated with placebo + MTX. For the largest subset of patients (those whose only dose of tocilizumab was 8 mg/kg), no new safety signals were observed over time (up to 2 years) and the rates of adverse events (overall, serious and leading to dose interruption or premature withdrawal) remained stable. For patients who switched from tocilizumab 4 to 8 mg/kg (the second largest subset of subjects), the rates of adverse events either remained stable or increased within expectations for those side effects (including laboratory data) that are dose-dependent such as elevated serum transaminases, neutropenia and lipid values. The clinical evaluator expressed concern for some tocilizumab-related adverse events which long-term monitoring is required, in particular event rates for adverse cardiovascular outcomes which may result from the more atherogenic lipid profile and the increased rates of hypertension, both of the latter having been observed on tocilizumab.

Extended Safety Follow-up Analysis: The application was further supported by the cumulative safety data obtained from three open-label extension studies – Studies 17823, 18695 and 18696. There were two different population data-sets. The “All Exposure” population was the primary cohort for assessment of the long-term safety and tolerability of tocilizumab. This population contained a total of 4009 patients with a total drug exposure of 8579.7 patient-years and 9414.3 patient-years of observation. Safety data was also presented for the “All Control” population to show the effect of tocilizumab dose on specific AEs of interest. This dataset included all patients randomised into any of the five core Phase III studies. Only data from the double-blind treatment phase of each core study was included. Under such conditions there were 1555 patients who received treatment with placebo + MTX (717.4 PY of exposure), 774 subjects who received treatment involving tocilizumab 4 mg/kg (500.1 PY of exposure) and 1870 patients who received treatment involving tocilizumab 8 mg/kg (1013.2 PY of exposure).

In the “All Control” population, a dose-dependent increase in the overall rate of AEs was observed for the tocilizumab 8 mg/kg group (381.6 per 100 PY) compared with the tocilizumab 4 mg/kg group (358.0 per 100 PY). Infections, mostly URIs and nasopharyngitis, were the most frequently reported type of AE and occurred at a higher rate in the two tocilizumab-treated groups compared to the control. Significant differences were also observed between the tocilizumab and control treatment arms as follows:

- § *Skin and Subcutaneous Disorders*, mainly rash and pruritus (3.9 per 100 PY for control, 7.3 per 100 PY for tocilizumab 4 mg/kg and 7.7 per 100 PY tocilizumab 8mg/kg);
- § *Investigations*, mainly increased transaminases (8.0 per 100 PY for control, 10.3 per 100 PY for tocilizumab 4 mg/kg and 15.3 per 100 PY for tocilizumab 8 mg/kg);
- § *Neoplasms* (1.7 per 100 PY for control, 5.1 per 100 PY for tocilizumab 4 mg/kg and 2.6 per 100 PY for tocilizumab 8 mg/kg). The Delegate requested that the sponsor confirm and comment on this result;
- § *Vascular System Disorders*, mainly hypertension (5.1 per 100 PY for control, 8.0 per 100 PY for tocilizumab 4 mg/kg and 8.2 per 100 PY for tocilizumab 8 mg/kg);

- § *Eye Disorders* (5.0 per 100 PY for control and 6.4 per 100 PY for tocilizumab 4 mg/kg and 8.2 per 100 PY for tocilizumab 8 mg/kg);
- § *Blood and Lymphatic System Disorders*, mainly neutropenia (0.4 per 100 PY for control, 1.6 per 100 PY for tocilizumab 4 mg/kg and 4.1 per 100 PY for tocilizumab 8 mg/kg);
- § Hypercholesterolemia (1.0 per 100 PY for control, 0.9 per 100 PY for tocilizumab 4 mg/kg and 2.2 per 100 PY for tocilizumab 8 mg/kg); and
- § Hepatic steatosis (none in control, 0.2 per 100 PY for tocilizumab 4 mg/kg and 0.5 per 100 PY for tocilizumab 8 mg/kg).

In the “All Exposure” population, the rate of AEs leading to withdrawal was 5.8 per 100 PY with the highest AE-related withdrawal rate (11.5 per 100 PY) occurring in the first 6 months of treatment and steadily decreasing thereafter (up to 48 months of follow-up).

A total of 9 serious anaphylactic reactions related to tocilizumab infusion were recorded in the “All Exposure” population – 5 with 4 mg/kg and 4 with 8 mg/kg with most occurring early in the course of treatment.

In the “All Control” population, the rate of SAEs was similar across the 3 treatment groups: control 14.4 per 100 PY, 13.6 per 100 PY for 4 mg/kg and 14.5 per 100 PY for 8 mg/kg.

In the “All Control” population, the overall rate of serious infections was 3.4 per 100 PY for the control group, 3.5 per 100 PY for 4mg/kg and 4.9 per 100 PY for 8 mg/kg. The most commonly reported were pneumonia, cellulitis, urinary tract infection and gastroenteritis. A total of 24 opportunistic infections were reported in 20 patients in the “All Exposure” population. Fourteen of the opportunistic infections were serious. Of the 22 opportunistic infections, 2 (9%) led to a fatal outcome, 9 (41%) led to discontinuation of the tocilizumab treatment and 5 (23%) led to tocilizumab dose modification. One patient with systemic candidiasis also had concomitant staphylococcal sepsis which resulted in death.

Cumulatively, 9 events of TB (8 pulmonary and 1 extra-pulmonary) were reported in the “All Exposure” population, with 3 of the 9 events in the one patient. Twelve infections overall, that is, not just opportunistic and all involving patients receiving tocilizumab 8 mg/kg, led to a fatal outcome in the “All Exposure” population. Serious infections occurred at a higher rate in patients aged more than 65 years, patients weighing more than 100 kg or with BMI >30, subjects with co-morbidities predisposing them to infection and in those who had previously received anti-TNF medication or were taking background corticosteroids. The highest rates were observed for patients on tocilizumab 8 mg/kg.

In the “All Exposure” population, a total of 26 patients experienced GI perforations.

The rate of cardiac disorders was comparable among the 3 treatment populations in the “All Control” dataset – 3.5 per 100 PY for control, 2.7 per 100 PY for 4 mg/kg and 4.0 per 100 PY for 8 mg/kg. In the “All Control” population, the overall rate of hypertension recorded as an AE was 5.8 per 100 PY for the control group, 9.4 per 100 PY for 4 mg/kg and 9.6 per 100 PY for 8 mg/kg.

In the “All Exposure” population a total of 112 malignancies were recorded at an overall event rate of 1.19 per 100 PY which is an incidence similar to that observed for other biological DMARDs used in moderate to severe RA. In the “All Control” population, the rate of malignancy (1.6 per 100 PY – 9 cases made up of 5 solid cancers, 3 non-melanoma skin cancers and 1 other) was higher in the tocilizumab 4 mg/kg group compared with an event rate of 0.7 per 100 PY in both the control (6 cases, 3 each of solid and non-melanoma

skin cancers) and tocilizumab 8 mg/kg treatment groups (8 cases, 4 each of solid cancers and non-melanoma skin cancers).

A total of 50 deaths have been recorded in the “All Exposure” population, the principal causes being cardiac events (13), serious infections (12) and malignancies (8). Of the 50 deaths reported in patients treated with tocilizumab, 1 occurred in a patient on 4 mg/kg and 49 in patients on 8 mg/kg with corresponding mortality rates of 0.97 and 0.53 deaths per 100 PY.

The extended duration safety data from the OLE studies suggest that the incidence and types of AEs occurring in patients for up to 156 weeks is similar to the experience from the controlled trials.

Post-marketing experience

The Marketing Authorisation Holder in Japan provided the EMA with an update as of 25 March 2009 of 27 fatal cases of tocilizumab-treated patients from the Japanese RA database. The estimated death rate in this setting was 10.12 per 1000 PY which is similar to that in the Japanese RA database for anti-TNF medications (10.9 and 11.0 per 1000 PY for etanercept and infliximab, respectively). This event rate is significantly higher when compared to the mortality rate in the initial 6 month controlled periods of the Phase III trials (4.1 per 1000 PY for tocilizumab + MTX and 8.8 per 1000 PY for placebo + MTX). It was argued that the higher death rate observed in tocilizumab-treated patients with RA in the Japanese post-marketing setting reflects patient selection in the real-world clinical experience as opposed to the highly controlled setting of clinical trials. This argument does have merit particularly also when one considers that comparator clinical trial setting was for a relatively short period. Infection was a significant contributor to the deaths.

The sponsor provided a brief summary of the only PSUR which has so far been lodged with the EMEA. This PSUR summarised data collected globally by Roche and Chugai (the Japanese MAH) between 11 October 2008 and 10 April 2009. There were no new particular safety signals of concern.

Late breaking information

On 19 August 2010, the sponsor informed the TGA of a planned safety update to the Actemra (tocilizumab) PI which concerned a post-marketing case of fatal anaphylaxis reported in a patient with rheumatoid arthritis treated with Actemra in the USA. The case involved a 67-year old woman with a 16 year history of RA. Concomitant and/or prior treatments for the RA included prednisone, leflunomide, hydroxychloroquine, sulfasalazine, azathioprine, etanercept, rituximab and abatacept. Other medical history included hypertension treated with a beta blocker and an ACE inhibitor. In May 2010, during her fourth infusion of 4 mg/kg Actemra the patient experienced light-headedness resulting in discontinuation of her infusion. A decrease in systolic BP below 90 mm Hg was noted and medical management at the infusion centre was followed by an emergency room evaluation. Two weeks later, the patient received her fifth infusion of Actemra after pre-medication with steroids and antihistamines. Moments after the start of the infusion, the patient experienced dizziness and hypotension. Despite prompt medical intervention, she became apnoeic and unresponsive. She died within 24 hours of the anaphylactic event. This is the first reported case of fatal anaphylaxis in a patient treated with Actemra. Clinically significant hypersensitivity reactions associated with Actemra and requiring treatment discontinuation have been reported in 0.3% of all patients receiving tocilizumab in clinical trials. The preceding information has been extracted from a Dear Healthcare Professional Letter which has been distributed by the sponsor to all rheumatologists in Australia. A safety-related notification has also been lodged

with the TGA. The Delegate requested advice from the Advisory Committee on Prescription Medicines (ACPM) (which has succeeded ADEC) on the need for a statement in the PI that the infusion is only to be administered in a hospital environment with full resuscitation facilities immediately available.

Risk Management Plan (RMP)

The sponsor submitted a Risk Management Plan (RMP, version 6.0, developed for the EMA and dated September 2009). In this plan, the sponsor has identified three important risks: serious infections (including reactivation of chronic hepatitis B infection), serious hypersensitivity reactions (that is, acute infusion reactions) and complications of diverticular disease including GI perforation. In addition, seven potential risks that require ongoing surveillance or evaluation have been identified. These are neutropenia (and the potential risk of infection), thrombocytopenia (and the potential risk of bleeding), liver enzyme and serum bilirubin elevations (and the risk of hepatotoxicity), elevated lipid levels (and the impact on cardiovascular and cerebrovascular disease), malignancy, demyelination disorders and the potential for interaction with cytochrome P450 substrates. With regard to the latter, inflammatory cytokines such IL-6 have the potential to down-regulate the activity of CYP450 enzymes involved in drug metabolism. Hence, normalization of this mechanism can result in decreased exposure of medicines metabolized by CYP450 enzymes. A drug-drug interaction study (WP18663) in 23 patients with RA found that levels of simvastatin (metabolised by CYP3A4) were decreased by 57% one week after a single dose of tocilizumab. This latter study was part of another application to make changes to the PI, which has recently been evaluated by the TGA. The Delegate requested that the sponsor confirm that the findings of the drug-drug interaction study, WP18663, are to be reported in the proposed Product Information (PI). The clinical evaluator expressed some concern that this potential risk of the normalisation of CYP450 enzyme activity does not appear to be actively addressed in the RMP. The sponsor was asked to comment on this and indicate how it does in fact intend to address this particular issue.

Initial Risk-Benefit Analysis

Delegate Considerations

Radiographic progression

Treatment with tocilizumab 8 mg/kg + MTX resulted in less progression of joint damage compared with placebo + MTX, as indicated by the mean change in the total Sharp-Genant score from baseline to Week 52. These 52-week results are now in the approved PI. This rate of inhibition was maintained in tocilizumab-treated patients (from baseline to Week 104) and supported by corresponding consistently favourable changes in both the erosion and joint space narrowing scores. Also the proportion of patients with no radiographic progression (defined as \leq zero change in the total Sharp-Genant score) was significantly higher in the tocilizumab 8 mg/kg + MTX group compared with the placebo + MTX group and increased in Year 2 compared with Year 1.

Because of the consistency of all results – those for mTSS, erosion scores, joint space narrowing scores and for absence of radiographic progression, the Delegate agreed with the clinical evaluator that the submission is approvable. Also it is most important that there be acknowledgement in the extension of indications for the radiographic endpoint that tocilizumab was given in combination with methotrexate, not as monotherapy.

Physical Function

Patients treated with tocilizumab 8 mg/kg + MTX had a significant improvement in physical function at Week 52 compared with placebo + MTX, as shown by the AUC of the change in

HAQ-DI and these improvements were maintained at Week 104. The clinical evaluator goes on to say that this finding is supported by the high proportion of patients achieving the clinically important improvement of 0.3 at Weeks 52 and 104. However, as has already been noted, there was no significant difference in the proportions of patients in each of the original randomised groups who achieved a clinically important improvement of at least 0.30 units from baseline in the HAQ-DI at Week 104 – 62.3% (144/231) for tocilizumab 8 mg/kg + MTX, 63.3% (138/218) for tocilizumab 4 mg/kg + MTX and 58.3% (74/127) for placebo + MTX. This lack of difference between the three treatment groups for this outcome is said to be explained by the fact that most patients had switched to open-label tocilizumab 8 mg/kg + MTX at Week 52. The data concerning improvement in physical function is also supported by the results of other patient-reported outcomes such as the FACIT-fatigue and SF-36 physical function scores.

The Delegate was not as convinced by the robustness of the data. There were statistically significant improvements in the AUC of the change from baseline in the HAQ-DI at Week 104. However, very similar proportions of patients in each of the three treatment groups achieved what is recognised to be a clinically important improvement, that is, a change of 0.30 units from baseline in the HAQ-DI score, at the same time point. Part of the problem is that the populations being considered for each parameter are different. Nevertheless, the change of 0.30 units has been well validated as a clinically significant threshold. Furthermore, the TGA has, for some time, adopted a position of not permitting such parameters as improvement in function in the Indications section of the PI for any of the treatments for RA. While the HAQ-DI is an often-used device used to describe physical function and is a well validated instrument, it is nonetheless one based on subjective patient reporting. It is well validated as a patient reporting mechanism. It is by no means a direct measure of actual physical function. This is where the HAQ-DI differs from such endpoints as the mTSS and the ACR which both contain substantial physical elements. Furthermore, these elements are measurable by an independent observer. It is also evident that the principal drive for the determination of sample size was the mTSS parameter. At this stage the Delegate suggested that the proper place for dealing with such parameters as improvement in function and quality of life is the Clinical Trials section and the Delegate had no objection to their being reported on in that location. In the view of the Delegate the Indications should, at all times, be confined to reported clinical outcomes which describe for the reader as accurately and succinctly as possible both the disease and the clinical trial population being treated. Terms such as “improvement in function” are inherently vague and have no place in the Indications section. The Delegate requested the sponsor to provide the relevant data relating to the proportions achieving the clinically important 0.30 change in HAQ-DI.

The Delegate proposed to approve the submission for inclusion of the claim of inhibition of the progression of joint damage as an extension of indication and for placement of the claim of improvement in physical function in the Clinical Trials section of the PI. The recommended extension of indication is as follows:

Actemra, when given in combination with methotrexate, has been shown to inhibit the progression of joint damage, as measured by X-ray.

As recommended above, the claim of improvement in physical function should be placed in the Clinical Trials section.

The Delegate also proposed that the implementation of the latest version of the Risk Management Plan be a specific condition of registration of Actemra resulting from the approval of this current application.

The sponsor should address the following issues in their Pre-ACPM response:

- § The provision of an update and accurate summary of the data generated by the Japanese PMDA since Actemra was first approved in Australia.
- § Comment on the deficiency identified in the submission with regard to the absence of any data on biochemical markers of cartilage and bone matrix turnover.
- § Comment on the finding that the mean trough tocilizumab concentrations for those receiving 4 mg/kg declined between Weeks 24 and 104.
- § Confirmation and comment on the differential rates of neoplasms observed in the various treatment groups in the “All Control” population.
- § Specific comment on the types of eye disorders seen with tocilizumab. There is evidence of a clear dose-response. If there is a specific type of eye disorder with a demonstrated dose-related incidence, this is to be noted under an appropriate heading in the Precautions section.
- § Clarification on the number and types of opportunistic infections observed.
- § Comment on the clinical evaluator’s concern that the potential risk of the normalisation of CYP450 enzyme activity does not appear to be actively addressed in the RMP.

The Delegate also directed the following questions to the ACPM.

- § Does the ACPM agree with the Delegate that, even although improvement in physical function as measured by HAQ-DI was pre-defined as a primary endpoint in the pivotal study, the Indications should not contain the wording, “*and to improve physical function*”?
- § Does the ACPM agree with the Delegate that the extension of indications for the radiographic endpoint should specifically mention that the regimen was tocilizumab in combination with methotrexate?
- § Does the ACPM agree with the Delegate that there should be more specific precautionary statements in the PI concerning the more atherogenic lipid profile and the increased rates of hypertension observed with tocilizumab?
- § In the light of the recent fatal case of anaphylaxis following tocilizumab infusion, the Delegate requested advice on whether there should be a statement in the PI that infusions of tocilizumab are only to be given in a hospital environment with full resuscitation facilities immediately available.

Response from the Sponsor

The sponsor concurred with the Delegate’s proposed recommended indication. The sponsor proposes to reword the order of slightly text to:

Actemra has been shown to inhibit the progression of joint damage, as measured by X-ray, when given in combination with methotrexate.

The sponsor also concurred with the Delegate’s proposal to place the physical function claim in the Clinical Trials section.

The sponsor requested deferral of implementation of the Risk Management Plan as a specific condition of registration since the version of the RMP included with this current application is the EU-RMP and contains specific labelling references to the EU Summary of Product

Characteristics and the Patient Information Leaflet, as well as other EU-specific commitments such as a patient alert card.

The sponsor indicated it was currently generating an Australian-specific RMP which will be included with the next Actemra Category 1 application. The sponsor requested that the Australian-specific RMP be the version of the RMP to which a condition of registration is applied.

The sponsor addressed the questions directed by the Delegate as follows:

An up-to-date and accurate summary of the data from the Japanese Post-Marketing Surveillance (JPMS) program is the most recent PSUR which was provided to the TGA on 7 June 2010. The PSUR incorporates the data from the JPMS.

As noted by the evaluator, the sponsor agreed that the submission does not contain data in relation to biochemical markers of cartilage and bone matrix turnover. These data were not included in the submission because these are surrogate markers that are not primary or secondary clinical or radiographic endpoints in the pivotal trials. Changes in biochemical markers of cartilage and bone matrix turnover have been studied with tocilizumab in the OPTION trial (WA17822), with findings recently published.¹¹ As is consistent with the clinical evaluator's comment, the findings do support the effect of tocilizumab on reducing systemic bone resorption and cartilage turnover. The findings supported the hypothesis that tocilizumab has beneficial effects on skeletal structure in patients with established RA, and this was confirmed in the pivotal study that was the basis for this submission (LITHE, WA17823), which confirmed that Actemra inhibits the progression of joint damage, as measured by X-ray. Exploratory studies of bone and cartilage turnover biochemical markers from additional clinical trials are ongoing.

Mean trough concentration from patients receiving 4 mg/kg was shown in the sponsor's *Clinical Study Report*. The mean \pm SD trough was 1.02 ± 6.14 $\mu\text{g/mL}$ at Week 24 and 1.09 ± 2.77 $\mu\text{g/mL}$ at Week 104. The intersubject PK variability was high (600% at Week 24 and 254% at Week 104). Considering the high PK variability, the trough concentrations from Week 24 to Week 104 are not meaningfully different.

As noted by the evaluator, the following event rates were observed in the *Neoplasms System Organ Class (SOC)*: 1.7 per 100 PY for control, 5.1 per 100 PY for 4 mg/kg, and 2.6 per 100 PY for 8 mg/kg. The *Neoplasms SOC* is a collection of event terms based on MedDRA classification that contains malignancies, as well as benign lesions, cysts and polyps. Due to the clinically variable nature of the events that classify to this SOC, it is considered not clinically useful for determining rates of malignancy or other specific potential risks.

Because malignancy is an event of interest for any immunomodulatory therapy, an analysis of malignancy rates was separately performed and was contained in the submission. A basket of terms which represents preferred adverse event terms of potential malignancies was defined. Findings were divided into solid cancers, non-melanoma skin cancers, haematologic cancers, and other. Other cancers are defined as those where the primary site or histology type is not specified.

¹¹ Garnero P, Thompson E, Woodworth T, Smolen JF. Rapid and sustained improvement in bone and cartilage turnover markers with the anti-interleukin-6 receptor tocilizumab plus methotrexate in rheumatoid arthritis patients with an inadequate response to methotrexate: results from a substudy of the multicenter double-blind placebo-controlled trial of tocilizumab in inadequate responders to methotrexate alone. *Arthritis Rheum* 2010; 62: 33-43.

The solid cancers reported in the “All Control” population included two events of colon cancer and one event of prostate cancer in the control group, two events of prostate cancer and one event each of cervix carcinoma Stage III and lung squamous cell carcinoma Stage III in the Actemra 4 mg/kg group, and one event each of dermatofibrosarcoma, endometrial cancer, gastric cancer and rectal cancer in the Actemra 8 mg/kg group. In the Actemra 4 mg/kg group, the “other” represents a skin cancer of unspecified histology.

For the “All Exposure” population, the standardised incidence ratio (SIR) compared to SEER (Surveillance, Epidemiology and End Results statistics data) for malignancy was 0.799 (95% CI: 0.775, 0.829) indicating the rate of malignancy seen in the Actemra clinical trials is consistent with that seen in the general population.

As noted by the evaluator the rates for the *Eye Disorders* SOC are 5.0 per 100 PY for control, 6.4 per 100 PY for 4 mg/kg, and 8.2 per 100 PY for 8 mg/kg. Differences between groups were primarily driven by events of conjunctivitis (control, 1.0 per 100 PY; Actemra 4 mg/kg, 1.1 per 100 PY; Actemra 8 mg/kg, 1.8 per 100 PY) and episcleritis (none in control; Actemra 4 mg/kg, 0.4 per 100 PY; Actemra 8 mg/kg, 0.3 per 100 PY). Events rates were low and a clinically meaningful difference cannot be concluded. Of all the events reported in the *Eye Disorders* SOC, only one was assessed as serious by the investigator (one event of retinal detachment in the 8 mg/kg group) and no events led to withdrawal. The other events seen in the *Eye Disorders* SOC were variable and consistent with those expected in adult patients with rheumatoid arthritis (for example, keratoconjunctivitis sicca), and treated with glucocorticoids (for example, cataracts). In summary, the data do not support a clinically significant dose related incidence and the sponsor did not believe a Precaution in the Actemra Product Information is warranted at this time.

As described in the sponsor’s *Clinical Summary of Safety* for this submission, in the “All Exposure” population, a total of 22 opportunistic infections were reported in 20 patients. Opportunistic infections were defined based on a broad glossary of infection adverse event terms considered relevant for immunosuppressed patients, although some of the infections can also occur in patients with normal immune systems (for example, pulmonary tuberculosis). Of the 22 opportunistic infections observed, 14 were SAEs, of which two were fatal, and the others were non-serious AEs. Most of the events were fungal or mycobacterial.

CYP 450 drug-drug interaction is identified as a potential risk and risk mitigation activities are outlined in the RMP.

The sponsor noted that in light of the fatal case of anaphylaxis following an Actemra infusion, the Delegate has requested ACPM advice on inclusion of an additional statement in the PI concerning the administration of Actemra in a hospital environment with full resuscitation facilities immediately available.

In response to the fatal case the sponsor has revised the current hypersensitivity Precaution in the PI via a safety-related notification. In addition, to ensure rheumatologists are kept informed, the sponsor issued a Dear Healthcare Provider Letter (DHCP) during September 2010 informing of the fatal case of anaphylaxis. The sponsor believed the revised wording in the PI and the publication of the DHCP are appropriate risk minimisation activities and that further PI updates are not warranted at this time

Advisory Committee Considerations

The ACPM, having considered the evaluations and the Delegate’s overview, as well as the sponsor’s response to these documents, recommended approval to include the indication:

For the treatment of moderate to severe active rheumatoid arthritis (RA) in adult patients:

in combination with methotrexate (MTX) or other non-biological disease-modifying anti-rheumatic drugs (DMARDs) in case of either an inadequate response or intolerance to previous therapy with one or more DMARDs; or

as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate.

ACTEMRA in combination with MTX has been shown to inhibit the progression of joint damage, as measured by X-ray.

In making this recommendation the ACPM agreed with the Delegate that there was sufficient evidence to support the inclusion of a statement on the radiographic endpoint when used in combination with MTX in the new indication. The ACPM also agreed that there was evidence to support a claim for benefit in physical function but agreed with the Delegate that the inclusion of reference to a physical function endpoint should not appear in the Indication but that such reference could be included in the Clinical Trials section of the PI.

The specific conditions of registration should include:

- Development and implementation of the new Risk Management Plan to the satisfaction of the Delegate.
- Changes to the Product Information (PI) and Consumer Medicines Information (CMI) which should be made prior to approval include:
 - Reference to the studies that demonstrate the inhibition of the progression of joint damage, as measured by X-ray and to the improved physical function, when combined with MTX, in the Clinical Trials section of the PI;
 - Reference in the Dosage and Administration section to require administration of infusion in the clinical context where full resuscitation facilities are immediately available;
 - Inclusion of more specific information about the risks of anaphylaxis, increased lipid profile and hypertension in the appropriate section of the PI, to the satisfaction of the delegate.

Further Risk-Benefit Analysis

In response to this resolution, the sponsor submitted a letter with some further information which pointed out that access to Actemra would be severely restricted for many patients since the majority of patients currently receive their infusions in dedicated infusion clinics and not in hospitals.

Sponsor's response to the particular request for the immediate availability of full resuscitation facilities

Clinically significant hypersensitivity reactions have occurred in 0.3% of all patients receiving Actemra in clinical trials. The one fatal case of anaphylaxis in the USA occurred in a patient who had already experienced a previous hypersensitivity reaction. In other words, this case occurred when the patient was rechallenged with Actemra. The currently approved Australian PI contraindicates the continued or repeated use of Actemra after a hypersensitivity reaction to the drug ("*Actemra is contraindicated in patients with known hypersensitivity to any component of the product...*"). Presently, in the USA, there are no contraindications to treatment with Actemra (continued, repeated or otherwise).

Currently, Actemra infusions are performed either in a hospital or a dedicated infusion centre. The sponsor estimates that approximately 80% of all patients receiving Actemra in Australia

do so in a dedicated infusion centre. The sponsor described the operation and staffing of these centres.

Four cases of hypersensitivity, including anaphylaxis, have been reported to Roche in Australia. In three of these four cases, the indication was RA. In the fourth case, the indication was not reported. Of these four cases, one case was from a clinical study and was attributed to a food allergy while a second case in a patient with RA was reported as non-serious. The remaining two cases, one in a patient with RA and one in a patient with an unknown indication, were spontaneous reports of serious hypersensitivity to Actemra.

Since the commencement of the sponsor's ACTiv Infusion Management Program (operated by Lifescreen) in September 2009, Lifescreen's nurses have administered more than 2500 Actemra infusions to 589 patients who have been enrolled by 99 rheumatologists. The one spontaneous serious case of anaphylaxis reported on the program involved a patient who experienced an anaphylactic reaction during her seventh infusion with symptoms of epigastric pain, facial swelling, cough, urticaria and chest tightness. The episode was managed by the nurse by administering adrenaline and hydrocortisone and summoning the paramedics via 000. The patient was transported to the nearest hospital, the reaction resolving within 48 hours. Treatment of this patient with Actemra has been discontinued.

A search of the Actemra global safety database identified 104 serious potential hypersensitivity events which were then medically reviewed. Of these 104 serious events, 90 were assessed as related to Actemra exposure (68 in RA). As of April 2010, a total of 34,012 patients have been exposed to Actemra.

In support of the tocilizumab infusion program, the sponsor also provided a copy of a letter written by a consultant rheumatologist. The rheumatologist indicated that the program offers significant benefits for his patients including easy regional access to the monthly infusions in a setting where they are monitored appropriately for infusion reactions and where there is excellent communication between the program managers, infusion nurses and the consultant. He also indicated that access to the medication would be extremely limited if he used the hospital infusion service which he reported as being overloaded and not taking any new patients.

Delegate Considerations

The one fatal case of anaphylaxis was that reported in a patient in the USA treated with Actemra for RA. The episode occurred when the patient was rechallenged with Actemra despite previously experiencing a hypersensitivity reaction. The current Australian-approved PI would contraindicate any future use of Actemra in the patient (the current US PI has no listed contraindications).

Since its inception a little over a year ago, more than 2500 Actemra infusions have been given to 589 patients enrolled by 99 rheumatologists in the dedicated infusion centres. There has been one serious hypersensitivity reaction which was appropriately managed and reported. The reaction successfully resolved and the patient will now be contraindicated from receiving any further treatment with Actemra. This gives a rate of such events per patient of approximately 0.17% [1/589] which compares favourably with the global rate of 0.26% [90/34,012].

There would almost certainly be serious problems of equity of access to this important treatment if the sponsor was not able to continue facilitating the infusion service.

Recognising that a requirement for infusions to take place only in a clinical setting where full resuscitation facilities are immediately available may be unnecessarily burdensome and in

many instances impractical, the Delegate proposed to recommend a number of alternative amendments to the PI. These include statements in the Dosage and Administration section concerning close monitoring of patients, initiation of appropriate emergency responses and treatments, protocols which clearly set out the latter and continuing education and training for those health care professionals who administer the infusions.

The sponsor should address the following issues in their Pre-ACPM response:

The sponsor was requested to give a summary of how the Risk Management Plan for Actemra deals with the issue of administration of infusions and the monitoring and treatment of patients who may develop hypersensitivity reactions during an infusion of Actemra. Does the Risk Management Plan need amendment in the light of the proposed amendments of the Delegate? The sponsor was requested to give an undertaking to enter into discussions with the Office of Product Review as to how the risks of serious hypersensitivity reactions to Actemra infusions may be mitigated and whether the RMP may require amendment in this regard. This undertaking will form a condition of registration.

The Delegate noted that the pathology collection centres are accredited to the relevant standard which ensures quality and competence in medical laboratories. While this standard may regulate such activities as venepuncture, it was questioned whether this same standard also regulates the administration of medical treatments to patients?

The sponsor was requested to explain precisely what is meant by approval by Medicare Australia under sub-section 23DNBA(1) of the Health Insurance Act 1973. Does this particular legislation refer to the administration of medical treatments to patients?

The sponsor was requested to provide a summary of any hypersensitivity or other serious reactions which may have occurred in the estimated 20% of Actemra patients receiving their infusions in a hospital setting.

The Delegate noted that, of the total of four cases of hypersensitivity reported in Australia, there have been two spontaneous reports of serious hypersensitivity to Actemra. Have all four cases of hypersensitivity been reported to the Office of Product Review?

The Delegate noted that the three pages provided which outline the ACTiv Program does not have a place for the patient's diagnosis. The sponsor was requested to clarify why this is the case.

The sponsor was requested to define what is meant by "*or other serious hypersensitivity reaction*" under the heading Hypersensitivity Reactions in the Precautions section of the currently approved PI.

Sponsor's Pre-ACPM Response

Serious hypersensitivity reactions are classified in the Actemra Risk Management Plan (RMP) as an 'identified risk' of the medicine since clinically significant hypersensitivity reactions associated with Actemra were reported during controlled and open label clinical trials, and experience from the post marketing setting has confirmed this is the case. As reported in the RMP hypersensitivity events presented with the typical symptoms of an anaphylactic reaction, that is, hypotension, dyspnoea, chills, and palpitations.

In clinical trials the symptoms occurred during the second to fifth infusions, were successfully treated with IV corticosteroids and adrenaline, did not require hospitalisation and resolved the same day. The RMP advises that serious outcomes can be prevented by careful observation of patients during the 2nd – 5th infusions, and provision of appropriate medical support and treatment.

The RMP outlines the proactive plans to manage known and potential risks associated with the clinical use of Actemra or those which could be anticipated on the basis of experience with other biological DMARDs, as well as populations in which there are insufficient data to assess risk. Processes and activities for ongoing risk management are described. Key elements of the pharmacovigilance action plan for serious hypersensitivity reactions include:

- Routine pharmacovigilance via Roche's global safety database;
- Use of a guided questionnaire to collect additional data about the adverse event;
- Additional data gathered from the ongoing clinical trial program;
- Regular review by the Roche Pharmaco-epidemiology Board whose responsibilities include ongoing evaluation of the accruing safety data, assessment of the effectiveness of risk minimisation measures and recommendations for actions regarding risk minimisation;
- Epidemiology data obtained from additional sources including the US claims database and the EU registries BSRBR, ARTIS, RABBIT.

The RMP also outlines the risk minimisation activities for identified and potential risks, which includes serious hypersensitivity reactions, as well as identifying where adverse event information is missing. The activities for serious hypersensitivity reactions are split into 2 groups: routine risk minimisation activities and additional risk minimisation activities. The following routine risk minimisation activities for serious hypersensitivity reactions are currently described in the RMP and are in place:¹²

- Contraindication in the Actemra Product Information of use in patients with known hypersensitivity to the medicine. In addition, in the Consumer Medicine Information (CMI) patients are advised that they must not receive Actemra if they have previously suffered an allergic reaction to Actemra or to any of the specific inactive ingredients of the medicine, or to other antibody-based medicines. The signs and symptoms of an allergic reaction are described and the CMI advises patients to contact their doctor immediately or go to Accident and Emergency in the event of any of the signs or symptoms occurring. This is important because the signs and symptoms may occur after the patient has been discharged from the hospital or left the infusion centre;
- Inclusion in the Actemra PI of a specific Hypersensitivity Precaution;
- Inclusion in the PI of infusion reaction adverse effects data from the RA clinical trial program.

The additional risk minimisation activities described in the RMP concern the need to provide prescribers, patients and nurses with additional information and education resource materials. The goal of the training and education program is to minimise the risk of infusion reactions and medication errors by training the medical personnel responsible for preparing and administering the infusion.

Currently Actemra infusions may be performed in either a hospital or a dedicated infusion centre. Outside of the hospital environment Lifescreen Australia Pty Limited conducts Actemra infusions on behalf of Roche under the auspices of the Roche-sponsored ACTiv Infusion Management Program. The manner in which the ACTiv program has been designed supports risk minimisation of clinically important infusion reactions and/or medication errors by personnel involved in the preparation and administration of infusions. (There is no

¹² Routine risk minimisation activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.

financial inducement for a treating physician to use this program, which has been made available to facilitate patients' greater access to treatment.) The following risk minimisation actions are in place as part of the program:

- All nurses employed by Lifescreen are experienced in the administration of infusional drugs, are qualified in cannulation techniques and have current Cardiopulmonary Resuscitation (CPR) certification;
- All nurses receive specific training on the rheumatoid arthritis disease state, the Actemra PI, the Lifescreen Infusion Standard Operating Procedure for Actemra and the management of hypersensitivity reactions;
- All nurses are fully insured with Professional Indemnity insurance and as such meet the criteria to practice in this environment;
- All infusion centres are equipped with, at a minimum, an IV pole, infusion pump and suitable infusion chair or bed. All dispensables and emergency drugs are brought with the registered nurse to each infusion;
- Nurses are equipped with the following emergency provisions: Laerdal resuscitation Pocket Mask, adrenaline injection, promethazine hydrochloride injection, hydrocortisone sodium succinate, 0.9% sodium chloride, 19G needle and 5 mL syringe. When the treating physician signs the ACTiv enrolment form nurses are authorised to administer these medicines in the event of an acute reaction in the absence of the treating physician;
- Lifescreen has agreed to provide oxygen at all infusion centres;
- During infusions nurses have a 1:1 relationship with the patient throughout the entire infusion. A basic medical assessment and medical history check is conducted prior to each infusion to ensure that the patient has not previously experienced a hypersensitivity reaction to Actemra and is fit to receive the infusion. Observations taken include blood pressure, pulse and temperature. Observations are taken prior, during and post the infusion.
- The ACTiv enrolment form asks for information on the patient's specific medical history (prior anaphylaxis is quoted as an example of a previous medical concern);
- The sponsor's field force is regularly trained on Actemra safety matters including the risk of hypersensitivity reactions;
- Educational materials are made available to prescribers and nurses in both the hospital and infusion centres to ensure the appropriate administration of Actemra and the monitoring and treatment of patients who may develop hypersensitivity reactions. These include the Actemra PI and CMI, a training presentation which highlights the potential for hypersensitivity reactions and the actions to take in the event of a reaction, a dosing guide which describes the correct combination of Actemra vials to be administered, an infusion booklet describing how an infusion should be given, a patient information booklet describing the medication to the patient and a leaflet for General Practitioners;
- Adverse events are communicated by the nurse to the treating physician using the Lifescreen Case Management System (CMS). A Roche adverse event form, completed by the nurse is either faxed or emailed to the treating physician. Lifescreen nurses are obliged to report adverse events to Roche within 24 hours. The CMS system also ensures that treating physicians are made aware of any hypersensitivity reaction within 24 hours of the event and can make informed decisions about ongoing treatment on this basis.

The sponsor believed that the actions put in place under the ACTiv program comprehensively align with the request for consideration of amendment to the RMP for additional risk

minimisation activities. With the exception of completion of the ACTiv enrolment form and the CMS reporting system, all the above points would also apply to infusions in the hospital setting.

Nevertheless the sponsor agrees that the RMP needs amendment to account for the risk minimisation activities provided by the ACTiv program since many of these are not currently referenced in the RMP.

In addition the PI wording quoted in the RMP will need to be aligned with the proposed new PI wording requested by the Delegate.

As requested, the sponsor agreed to enter into discussions with the Office of Product Review regarding risk mitigation strategies for serious hypersensitivity reactions to Actemra infusions and whether the RMP requires amendment in this regard.

The NATA standard does not regulate administration of medical treatments to patients. The sponsor included a reference to NATA in its letter to demonstrate that the pathology collection centres have received accreditation from the appropriate regulatory body (NATA) covering these centres.

The relevance of conformance to section 23DNBA(1) of the Health Insurance Act 1973 is that Medicare payment for an infusion performed in a pathology collection centre (the medical treatment) is contingent upon the centre having been granted approval by the Minister. This approval is subject to "Approval Principles" which include the giving of undertakings by the pathology authority (owner) for an eligible collection centre regarding compliance with the Collection Centre guidelines. The pathology authority is also required to undertake to ensure that a properly qualified person supervises the rendering of each service. The service in this case is the administration of the infusion, not the medical treatment per se.

Approval by Medicare Australia ensures that the centres maintain an appropriate level of clinical hygiene and occupational safety standards for both nurses and patients.

Four cases of hypersensitivity reaction, including anaphylaxis, have been reported to Roche in Australia.

Of these, one case occurred in the hospital setting as part of the long-term extension study WA18695 (an extension study investigating safety during treatment with Actemra in patients completing treatment in Actemra core registration studies). Of the other three cases, two occurred in the infusion centre setting whilst the sponsor was unable to ascertain where the third case occurred.

The sponsor confirmed that the case of serious hypersensitivity reported in Australia is the patient to whom the Delegate was referring. Regarding the case in a patient with an unknown indication the sponsor was unable to ascertain where the case occurred.

Only the case referred to above has been submitted to the Office of Product Review (OPR). The other three cases did not qualify for submission to OPR. One case occurred in a clinical trial and was not a suspected unexpected serious adverse reaction, another was a non-serious spontaneous case and the third was not submitted as there was no patient identifier.

Access to the ACTiv program is limited only to patients who are receiving Authority Approved PBS-reimbursed Actemra treatment. The written authority process for all bDMARDs involves acknowledgement and confirmation by the prescribing physician that the patient has a history of severe rheumatoid arthritis (RA). Patients without Authority Approved scripts or patients being treated off-label are not permitted access to the ACTiv Program. As a result there is no need to include the patient's diagnosis on either of the ACTiv

forms since the patient can not be in the program if they haven't been diagnosed with severe RA.

The sponsor noted that there is no precise definition for "other serious hypersensitivity reaction". The statement has been included to ensure the PI covers other forms of serious hypersensitivity reaction in addition to anaphylaxis. The wording acknowledges the value and importance of medical judgment involved in the diagnosis, treatment and management of anaphylaxis

Advisory Committee Considerations

The ACPM reaffirmed its recommendation for approval. The ACPM at the time expressed its concern about appropriate facilities in which to administer the medication.

The ACPM reiterated its concern over the risk of anaphylaxis, as these events were reported well into the course of treatment. However, this risk may be mitigated by:

- The incorporation of this risk into the Risk Management Plan (RMP) following referral to the Advisory Committee on Safety of Medicines (ACSOM) and to the satisfaction of the delegate.
- The sponsor seeking advice from such organisations as the Australian and New Zealand College of Anaesthetists (ANZCA), the Australian Resuscitation Council or from the Australian Immunology Society to develop a suitable safety protocol for administration of the drug.

In the matter of location for administering treatment to patients, the ACPM expressed concern about the statement by the sponsor that full resuscitation facilities are only available in tertiary centres as facilities such as private radiology practices currently include this facility.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Actemra concentrated injection solution containing tocilizumab (rch) 80 mg/4 ml, 200 mg/10 mL and 400 mg/20 ml, for the additional indication:

ACTEMRA has been shown to inhibit the progression of joint damage, as measured by X-ray, when given in combination with methotrexate.

Included among the specific conditions of registration were the following:

- Referral by the Delegate, via the Office of Product Review, to the Advisory Committee on the Safety of Medicines (ACSOM) for the latter's recommendation regarding the extent to which resuscitation facilities should be required during the administration of Actemra to a patient.
- The development and implementation of an Australian-specific Risk Management Plan (RMP), in particular an RMP which addresses, to the satisfaction of the Delegate and the Office of Product Review (OPR), the risk of anaphylaxis with Actemra and the appropriate management of that risk.
- The sponsor is required to write to all three of the following organisations, the Australian and New Zealand College of Anaesthetists, the Australian Resuscitation Council and the Australian Immunology Society, seeking their advice on the development of a suitable safety protocol for the administration of Actemra, a protocol which addresses in particular the risk of anaphylaxis.

- The sponsor is required to provide regular updates on the progress of the consultation process with the three organisations named at the previous dot point, these updates to be provided every two months to both the Prescription Medicines Clinical Unit 3 (PMCU3) of the Office of Medicines Authorisation (OMA) and to the Office of Product Review (OPR) of the TGA.
- A safety protocol, developed by the consultation process referred to under the two points above, will be required to be submitted for review by both the Prescription Medicines Clinical Unit 3 (PMCU3) and to the Office of Product Review (OPR) no later than six months after the date of the approval letter for this application.

Attachment 1. Product Information

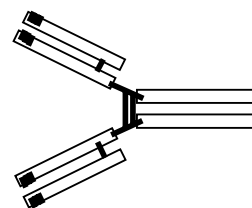
The following Product Information was approved at the time this AusPAR was published. For the current Product Information please refer to the TGA website at www.tga.gov.au.



ACTEMRA

Tocilizumab (rch)

CAS 375823-41-9



Tocilizumab is a recombinant humanised monoclonal antibody of the immunoglobulin (Ig) IgG1 subclass which binds to human interleukin 6 (IL-6) receptors. It is composed of two heterodimers, each of which consists of a heavy and a light polypeptide chain. The light chain contains 214 amino acids and the heavy chain 448 amino acids. The four polypeptide chains are linked intra- and inter-molecularly by disulfide bonds. Tocilizumab has a molecular weight of approximately 148,000 Daltons. Tocilizumab binds to both soluble and membrane-bound IL-6 receptors (sIL-6R and mIL-6R).

DESCRIPTION

ACTEMRA is a clear to opalescent, colourless to pale yellow sterile solution for intravenous (IV) infusion. ACTEMRA is supplied in preservative-free, non-pyrogenic single-use, clear glass vials. ACTEMRA is available in 10 mL and 20 mL vials containing 4 mL, 10 mL or 20 mL of tocilizumab concentrate (20 mg/mL). ACTEMRA also contains polysorbate 80, sucrose, dibasic sodium phosphate dodecahydrate, monobasic sodium phosphate dihydrate and water for injections.

PHARMACOLOGY

Mechanism of Action

Tocilizumab is a recombinant humanised monoclonal antibody of the immunoglobulin (Ig) IgG1 subclass. Tocilizumab binds specifically to both soluble and membrane-bound IL-6 receptors, and has been shown to inhibit sIL-6R and mIL-6R-mediated signaling. IL-6 is a multi-functional cytokine, produced by a variety of cell types involved in local paracrine function as well as regulation of systemic physiological and pathological processes such as induction of immunoglobulin secretion, T-cell activation, induction of hepatic acute phase proteins and stimulation of haematopoiesis. IL-6 has been implicated in the pathogenesis of inflammatory diseases, including rheumatoid arthritis (RA).

The possibility exists for tocilizumab to affect host defences against infections and malignancies. The role of IL-6 receptor inhibition in the development of malignancies is not known.

PHARMACODYNAMICS

In clinical studies with tocilizumab, rapid decreases in C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) and serum amyloid A were observed. Rapid increases in haemoglobin levels (within the first 2 weeks) were also observed, through tocilizumab decreasing the IL-6 driven effects on hepcidin production to increase iron availability.



In healthy subjects administered tocilizumab in doses from 2 to 28 mg/kg, absolute neutrophil counts (ANC) decreased to their lowest levels 3 to 5 days following administration. Thereafter, neutrophils recovered towards baseline in a dose dependent manner. Patients with RA demonstrated a similar pattern of absolute neutrophil counts following tocilizumab administration (see PRECAUTIONS - Haematological Abnormalities).

PHARMACOKINETICS

The pharmacokinetics of tocilizumab were determined using a population pharmacokinetic analysis on a database composed of 1793 RA patients treated with a one hour infusion of 4 and 8 mg/kg every 4 weeks for 24 weeks.

The pharmacokinetic parameters of tocilizumab did not change with time. A more than dose-proportional increase in area under the curve (AUC) and trough concentration (C_{\min}) was observed for doses of 4 and 8 mg/kg every 4 weeks. Maximum concentration (C_{\max}) increased dose-proportionally. At steady-state, predicted AUC and C_{\min} were 2.7 and 6.5 fold higher at 8 mg/kg as compared to 4 mg/kg, respectively.

The following parameters are valid for a dose of 8 mg/kg tocilizumab given every 4 weeks. Predicted mean (\pm SD) steady-state AUC, C_{\min} and C_{\max} of tocilizumab were 35000 ± 15500 h· μ g/mL, 9.74 ± 10.5 μ g/mL, and 183 ± 85.6 μ g/mL, respectively. The accumulation ratios for AUC and C_{\max} were small; 1.22 and 1.06, respectively. The accumulation ratio was higher for C_{\min} (2.35), which was expected based on the nonlinear clearance contribution at lower concentrations. Steady-state was reached following the first administration and after 8 and 20 weeks for C_{\max} , AUC, and C_{\min} , respectively. Tocilizumab AUC, C_{\min} and C_{\max} increased with increase of body weight. At body weight ≥ 100 kg, the predicted mean (\pm SD) steady-state AUC, C_{\min} and C_{\max} of tocilizumab were 55500 ± 14100 h· μ g/mL, 19.0 ± 12.0 μ g/mL, and 269 ± 57 μ g/mL, respectively, which are higher than mean exposure values for the patient population. Therefore, tocilizumab doses exceeding 800 mg per infusion are not recommended in patients ≥ 100 kg (see DOSAGE AND ADMINISTRATION).

The following parameters are valid for a dose of 4 mg/kg tocilizumab given every 4 weeks. Predicted mean (\pm SD) steady-state AUC, C_{\min} and C_{\max} of tocilizumab were 13000 ± 5800 · μ g·h/mL, 1.49 ± 2.13 μ g/mL, and 88.3 ± 41.4 μ g/mL, respectively. The accumulation ratios for AUC and C_{\max} were small; 1.11 and 1.02, respectively. The accumulation ratio was higher for C_{\min} (1.96). Steady-state was reached following the first administration for both C_{\max} and AUC and from 16 weeks for C_{\min} .

Absorption and Bioavailability

Not applicable.

Distribution

Following IV dosing, tocilizumab undergoes biphasic elimination from the circulation. In rheumatoid arthritis patients the central volume of distribution was 3.5 L and the



peripheral volume of distribution was 2.9 L, resulting in a volume of distribution at steady state of 6.4 L.

Metabolism

Not applicable.

Elimination

The total clearance of tocilizumab was concentration-dependent and is the sum of the linear clearance and the nonlinear clearance. The linear clearance was estimated as a parameter in the population pharmacokinetic analysis and was 12.5 mL/h. The concentration-dependent nonlinear clearance plays a major role at low tocilizumab concentrations. Once the nonlinear clearance pathway is saturated, at higher tocilizumab concentrations, clearance is mainly determined by the linear clearance.

The half life ($t_{1/2}$) of tocilizumab is concentration-dependent. The concentration-dependent apparent $t_{1/2}$ is up to 11 days for 4 mg/kg and 13 days for 8 mg/kg every 4 weeks at steady-state.

Pharmacokinetics in Special Populations

Hepatic Impairment: No formal study of the effect of hepatic impairment on the pharmacokinetics of ACTEMRA was conducted.

Renal Impairment: No formal study of the effect of renal impairment on the pharmacokinetics of ACTEMRA was conducted.

Most of the patients in the population pharmacokinetic analysis had normal renal function or mild renal impairment. Mild renal impairment (creatinine clearance based on Cockcroft-Gault < 80 mL/min and ≥ 50 mL/min) did not impact the pharmacokinetics of ACTEMRA. ACTEMRA has not been studied in patients with moderate to severe renal impairment. (See CLINICAL TRIALS and DOSAGE AND ADMINISTRATION).

Other special populations: Population pharmacokinetics in adult rheumatoid arthritis patients showed that age, gender and race did not affect the pharmacokinetics of ACTEMRA. No dose adjustment is necessary for these demographic factors.

CLINICAL TRIALS

The efficacy of ACTEMRA in alleviating the signs and symptoms of rheumatoid arthritis was assessed in five randomised, double-blind, multicentre studies. Studies I-V required patients \geq age 18 with active rheumatoid arthritis diagnosed according to American College of Rheumatology (ACR) criteria who had at least 8 tender and 6 swollen joints at baseline.

ACTEMRA was administered intravenously every 4 weeks as monotherapy (Study I), in combination with methotrexate (MTX) (Studies II, III, V) or with other disease-modifying anti-rheumatic drugs (DMARDs) (Study IV).



Study I (AMBITION) evaluated 673 patients who had not been treated with MTX within 6 months prior to randomisation, and who had not discontinued previous MTX treatment as a result of clinically important toxic effects or lack of response. The majority (67%) of patients were MTX naïve. Doses of 8 mg/kg of ACTEMRA were given every 4 weeks as monotherapy. The comparator group was weekly MTX (dose titrated from 7.5 to a maximum of 20 mg weekly over an 8 week period). The primary endpoint was the proportion of patients who achieved an ACR20 response at week 24.

Study II (LITHE), a 2 year study with a planned interim analysis at week 24 and week 52, evaluated 1196 patients who had an inadequate clinical response to MTX. Doses of 4 or 8 mg/kg of ACTEMRA or placebo were given every 4 weeks as blinded therapy for 52 weeks, in combination with stable MTX (10–25 mg weekly). The primary endpoint at week 24 was the proportion of patients who achieved ACR20 response criteria. At week 52 the co-primary endpoints were prevention of joint damage and improvement in physical function.

Study III (OPTION) evaluated 623 patients who had an inadequate clinical response to MTX. Doses of 4 or 8 mg/kg of ACTEMRA or placebo were given every 4 weeks, in combination with stable MTX (10 – 25 mg weekly). The primary endpoint was the proportion of patients who achieved an ACR20 response at week 24.

Study IV (TOWARD) evaluated 1220 patients who had an inadequate response to their existing rheumatologic therapy, including one or more DMARDs. Doses of 8 mg/kg ACTEMRA or placebo were given every 4 weeks, in combination with the stable DMARD. The primary endpoint was the proportion of patients who achieved an ACR20 response at week 24.

Study V (RADIATE) evaluated 499 patients who had an inadequate clinical response or were intolerant to one or more anti-tumour necrosis factor (TNF) therapies. The anti-TNF agent was discontinued prior to randomisation. Doses of 4 or 8 mg/kg of ACTEMRA or placebo were given every 4 weeks, in combination with stable MTX (10 – 25 mg weekly). The primary endpoint was the proportion of patients who achieved an ACR20 response at week 24.

The percent of patients achieving ACR 20, 50 and 70 responses in Studies I to V are shown in Table 1.



Table 1 ACR Responses in MTX/Placebo-Controlled Trials (Percent of Patients)

	Study I MTX-Naïve		Study II Inadequate Response to MTX		Study III Inadequate Response to MTX		Study IV Inadequate Response to DMARD		Study V Inadequate Response to anti-TNF Agent	
Response Rate	ACT 8 mg/kg n=286	MTX n=284	ACT 8 mg/kg +MTX n=398	Placebo + MTX n=393	ACT 8 mg/kg +MTX n=205	Placebo + MTX n=204	ACT 8 mg/kg + DMARD n=803	Placebo + DMARD n=413	ACT 8 mg/kg +MTX n=170	Placebo + MTX n=158
ACR 20										
Week 24	70%***	52%	56%***	27%	59%***	26%	61%***	24%	50%***	10%
Week 52 [^]			56%***	25%						
ACR 50										
Week 24	44%**	33%	32%***	10%	44%***	11%	38%***	9%	29%***	4%
Week 52 [^]			36%***	10%						
ACR 70										
Week 24	28%**	15%	13%***	2%	22%***	2%	21%***	3%	12%**	1%
Week 52 [^]			20%***	4%						
MCR [†] by Week 52 [^]			7%	1%						

ACT = ACTEMRA

* p < 0.05, ACTEMRA vs. placebo + MTX/DMARD

** p < 0.01, ACTEMRA vs. placebo + MTX/DMARD

*** p < 0.0001, ACTEMRA vs. placebo + MTX/DMARD

† MCR = major clinical response, defined as an ACR70 response maintained for any 24 consecutive weeks or more. Note: the comparison for MCR occurred after the break in the hierarchical ordered testing sequence, so no significance claims can be made. Secondary efficacy endpoints were tested in a fixed sequence approach in order to control for the rate of false positive conclusions.

[^] - based on a protocol-specified interim analysis

In all studies, 8 mg/kg ACTEMRA-treated patients had statistically significant higher ACR20, 50, 70 response rates at 6 months compared to placebo. The treatment effect was similar in patients independent of rheumatoid factor status, age, gender, race, number of prior treatments or disease status. Time to onset was rapid (as early as week 2) and the magnitude of response continued to improve with duration of treatment. Continued durable responses were seen for over 3 years in the on going open label extension studies of studies I - V.

In the 8 mg/kg ACTEMRA-treated patients significant improvements were noted on all individual components of the ACR response: tender and swollen joint counts; pain assessment and CRP normalisation; disability index scores; patients and physician global assessment, compared to patients receiving placebo + MTX/DMARDS in all studies. ACTEMRA 8 mg/kg treated patients had a statistically significant greater reduction in disease activity score (DAS28) than patients treated with placebo + DMARD. The rate of remission (defined as DAS < 2.6) for patients treated with ACTEMRA ranged from



27.5% to 33.6%. ACTEMRA treated patients had a statistically significant greater rate of remission than patients treated with placebo + DMARD. A good to moderate EULAR response was achieved by significantly more ACTEMRA treated patients compared to patients treated with placebo + DMARD (Table 2).

Table 2 Cross-Study Comparison of DAS and EULAR Responses at Week 24

	Study I MTX Naïve		Study II Inadequate Response to MTX		Study III Inadequate Response to MTX		Study IV Inadequate Response to DMARD		Study V Inadequate Response to anti- TNF Agent	
	ACT 8 mg/kg n=286	MTX n=284	ACT 8 mg/kg +MTX n=398	Placebo + MTX n=393	ACT 8 mg/kg +MTX n=205	Placebo + MTX n=204	ACT 8 mg/kg + DMARD n=803	Placebo + DMARD n=413	ACT 8 mg/kg +MTX n=170	Placebo +MTX n=158
Change in DAS28 [mean (Adjusted mean (SE))]										
Week 24	-3.31 (0.12)	-2.05 (0.12)	-3.11 (0.09)***	-1.45 (0.11)	-3.43 (0.12)***	-1.55 (0.15)	-3.17 (0.07)***	-1.16 (0.09)	-3.16 (0.14) ***	-0.95 (0.22)
DAS < 2.6 response (%)										
Week 24	33.6%	12.1%	≠33.3% ***	^3.8%	27.5%***	0.8%	30.2%***	3.4%	30.1% ***	1.6%
EULAR response (%)										
None	18%	35%	26%	65%	20%	65%	20%	62%	32%	84%
Moderate	42%	48%	34%	29%	41%	32%	40%	33%	31%	15%
Good†	40%	17%	41%***	6%	38%***	3%	40%***	4%	37%***	2%

ACT = ACTEMRA

†The p value compares across all the EULAR categories

* p < 0.05, ACTEMRA vs. placebo + MTX/DMARD

** p < 0.01, ACTEMRA vs. placebo + MTX/DMARD

*** p < 0.0001, ACTEMRA vs. placebo + MTX/DMARD

≠ In study II, 47% of patients achieved a DAS28 < 2.6 at 52 weeks compared to 33% of patients at week 24.

^ In study II, 8% of patients achieved a DAS28 < 2.6 at 52 weeks compared to 4% of patients at week 24.

Major Clinical Response

After 2 years of treatment with ACTEMRA + MTX, 14% of patients achieved a major clinical response (maintenance of an ACR70 response for 24 weeks or more)

Radiographic response

In study II (LITHE), in patients with an inadequate response to MTX, inhibition of structural joint damage was assessed radiographically and expressed as change in modified Sharp score and its components, the erosion score and joint space narrowing (JSN) score. Missing week 52 radiographic data was imputed using linear extrapolation. This was performed for any patient who had a baseline assessment and at least one post-baseline radiographic assessment. The change from baseline was then calculated using the extrapolated score. Inhibition of structural joint damage was shown with significantly



less radiographic progression in patients receiving ACTEMRA compared to control (Table 3).

In the open-label extension of study II further improvement in the inhibition of progression of structural damage in ACTEMRA + MTX-treated patients was observed in the second year of treatment. Study II did not investigate the effect of ACTEMRA monotherapy on radiographic endpoints.

Table 3 Radiographic mean changes at 52 and 104 weeks in study II (LITHE)

	Placebo + MTX (+ option of ACT from week 16) [n=393]	ACT 8 mg/kg + MTX [n=398]
Changes from baseline to week 52		
n	294	353
Total Sharp-Genant score	1.17	0.25
Erosion score	0.76	0.15
JSN score	0.41	0.10
Change from week 52 to week 104		
n	294	353
Total Sharp-Genant score	0.79	0.12
Erosion score	0.48	0.07
JSN score	0.31	0.05

ACT = ACTEMRA

JSN = joint space narrowing

The data presented consists of the evaluations of the baseline, week 24, week 52, week 80, week 104 and early withdrawal or escape therapy readings taken up to the week 104 visit.

Following 1 year of treatment with ACTEMRA + MTX, 83% of patients had no progression of structural damage, as defined by a change in the Total Sharp Score of zero or less, compared with 67% of placebo + MTX-treated patients. This remained consistent following 2 years of treatment (83%). Ninety three percent (93%) of patients had no progression between week 52 and week 104.

Quality of Life Outcomes

Clinically significant improvements in disability index (HAQ-DI, Health Assessment Questionnaire Disability Index), fatigue (FACIT-F, Functional Assessment of Chronic Illness Therapy Fatigue) and improvement in both the physical (PCS, Physical Component Summary) and mental health (MCS, Mental Component Summary) domains of the SF-36 (Short Form 36) were observed in patients treated with 8 mg/kg ACTEMRA (monotherapy or combination with DMARDs) compared to patients treated with MTX/DMARDs.

At week 24, the proportion of 8 mg/kg ACTEMRA treated patients showing a clinically relevant improvement in HAQ-DI (defined as an individual total score decrease of > 0.25), was significantly higher than among patients receiving placebo + MTX/DMARDs



in all studies. During the open-label period of study II the improvement in physical function has been maintained for up to 2 years.

At week 52, the mean change in HAQ-DI was -0.58 in the ACTEMRA 8 mg/kg + MTX group compared with -0.39 in the placebo + MTX group. The mean change in HAQ-DI was maintained at week 104 in the ACTEMRA 8 mg/kg + MTX group (-0.61). The percentage of ACTEMRA-treated patients showing a clinically relevant improvement in HAQ-DI (≥ 0.3 units) at weeks 52 & 104 were 63% and 62%, respectively.

Laboratory Evaluations

Treatment with 8 mg/kg ACTEMRA in combination with DMARD/MTX or as monotherapy resulted in a statistically significant improvement in haemoglobin levels compared with placebo + MTX/DMARD ($p < 0.0001$) at week 24. The greatest improvement was observed in patients with chronic anaemia associated with RA; mean haemoglobin levels increased by week 2 and remained within normal range through week 24.

A marked decrease in mean levels of acute phase reactants, CRP, ESR, and serum amyloid A occurred rapidly after ACTEMRA administration. Consistent with the effect on acute phase reactants, treatment with ACTEMRA was associated with reduction in platelet count within the normal range.

INDICATIONS

ACTEMRA is indicated for the treatment of moderate to severe active rheumatoid arthritis (RA) in adult patients:

- in combination with methotrexate (MTX) or other non-biological disease-modifying anti-rheumatic drugs (DMARDs) in case of either an inadequate response or intolerance to previous therapy with one or more DMARDs; or
- as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate.

ACTEMRA has been shown to inhibit the progression of joint damage, as measured by X-ray, when given in combination with methotrexate.

CONTRAINDICATIONS

ACTEMRA is contraindicated in patients with:

- known hypersensitivity to any component of the product or with a history of any reaction consistent with hypersensitivity to any component of the product, Chinese hamster ovary cell products or other recombinant human or humanised antibodies
- active, severe infections (See PRECAUTIONS)



PRECAUTIONS

Infections

Serious and sometimes fatal infections have been reported in patients receiving immunosuppressive agents including ACTEMRA (see ADVERSE EFFECTS). ACTEMRA treatment should not be initiated in patients with active infections (see CONTRAINDICATIONS). If a patient develops a serious infection, administration of ACTEMRA should be interrupted until the infection is controlled. Physicians should exercise caution when considering the use of ACTEMRA in patients with a history of recurring or chronic infection, or with underlying conditions (e.g. diverticulitis, diabetes) which may predispose patients to infections.

Vigilance for the timely detection of serious infection is recommended for patients receiving biologic treatments for moderate to severe RA as signs and symptoms of acute inflammation may be lessened, associated with suppression of the acute phase reaction. The effects of tocilizumab on C-reactive protein (CRP), neutrophils and signs and symptoms of infection should be considered when evaluating a patient for a potential infection. Patients should be instructed to contact a physician immediately when any symptoms suggesting infection appear, in order to assure rapid evaluation and appropriate treatment.

The use of ACTEMRA is not recommended in patients with HIV, positive core antibody for hepatitis B, prior HCV infection, or symptomatic EBV infection. Viral reactivation (e.g. hepatitis B) has been reported with biologic therapies for RA. In clinical studies with ACTEMRA, patients who screened positive for hepatitis were excluded.

In the long term exposure population, the overall rate of serious infections (bacterial, viral and fungal) was 4.7 events per 100 patient years. Reported serious infections, some with fatal outcome, included active tuberculosis, which may present with intrapulmonary or extrapulmonary disease, invasive pulmonary infections, including candidiasis, aspergillosis, coccidioidomycosis and pneumocystis jirovecii, pneumonia, cellulitis, herpes zoster, gastroenteritis, diverticulitis, sepsis and bacterial arthritis. Cases of opportunistic infections have been reported.

Complications of Diverticulitis

Events of diverticular perforation as complications of diverticulitis have been reported. ACTEMRA should be used with caution in patients with previous history of intestinal ulceration or diverticulitis. Patients presenting with symptoms potentially indicative of complicated diverticulitis, such as abdominal pain, should be evaluated promptly for early identification of gastrointestinal perforation.

Tuberculosis

As recommended for other biological treatments in RA, patients should be screened for latent tuberculosis (TB) infection prior to starting ACTEMRA therapy. Patients with latent TB should be treated with standard anti-mycobacterial therapy before initiating ACTEMRA.



Vaccinations

Live and live attenuated vaccines should not be given concurrently with ACTEMRA as clinical safety has not been established.

No data are available on the secondary transmission of infection from persons receiving live vaccines to patients receiving ACTEMRA.

Hypersensitivity Reactions

Serious hypersensitivity reactions have been reported in association with infusion of ACTEMRA in approximately 0.3 % of patients (see ADVERSE EFFECTS – Infusion Reactions). A patient with a previous infusion reaction and premedicated with steroids and antihistamines experienced a fatal anaphylactic reaction during a subsequent treatment with ACTEMRA in the post-marketing setting (see POST-MARKETING EXPERIENCE). Appropriate treatment should be available for immediate use in the event of an anaphylactic reaction during treatment with ACTEMRA. If an anaphylactic reaction or other serious hypersensitivity reaction occurs, administration of ACTEMRA should be stopped immediately and ACTEMRA should be permanently discontinued.

Patients with a history of any reaction consistent with hypersensitivity to any component of the product must not be re-challenged with ACTEMRA (see CONTRAINDICATIONS).

Viral Reactivation

Viral reactivation (e.g. hepatitis B virus) has been reported with biologic therapies for RA. In clinical studies with ACTEMRA, patients who screened positive for hepatitis were excluded.

Active Hepatic Disease and Hepatic Impairment

Treatment with ACTEMRA particularly when administered concomitantly with MTX, may be associated with elevations in hepatic transaminases therefore caution should be exercised when considering treatment of patients with active hepatic disease or hepatic impairment (see ADVERSE EFFECTS – Laboratory Abnormalities and DOSAGE AND ADMINISTRATION – Special Patient Groups).

Viral reactivation (e.g. hepatitis B) has been reported with biologic therapies for RA. In clinical studies with ACTEMRA, patients who screened positive for hepatitis were excluded.

Hepatic Transaminase and Laboratory Effects

In clinical trials, transient or intermittent mild and moderate elevations of hepatic transaminases and bilirubin have been reported with ACTEMRA treatment, without progression to hepatic injury (see ADVERSE EFFECTS). An increased frequency of these elevations was observed when potentially hepatotoxic drugs (e.g. MTX) were used



in combination with ACTEMRA. There is a potential risk of hepatotoxicity with use of ACTEMRA.

Particular caution should be exercised when considering initiation of ACTEMRA treatment in patients with elevated ALT or AST > 1.5 x ULN. In patients with baseline ALT or AST > 5 x ULN, treatment with ACTEMRA is not recommended.

ALT and AST levels should be monitored every 4 to 8 weeks for the first 6 months of treatment followed by every 12 weeks thereafter. For recommended modifications based on transaminases see DOSING AND ADMINISTRATION. For ALT or AST elevations > 3 to 5 x ULN, confirmed by repeat testing, ACTEMRA treatment should be interrupted. Once the patient's hepatic transaminases are below 3 x ULN, treatment with ACTEMRA may recommence at 4 or 8 mg/kg.

Haematological Abnormalities

Decreases in neutrophil and platelet counts have occurred following treatment with ACTEMRA 8 mg/kg in combination with MTX (see section ADVERSE EFFECTS – Laboratory Abnormalities). There may be an increased risk of neutropenia in patients who have previously been treated with a TNF antagonist.

Caution should be exercised when considering initiation of ACTEMRA treatment in patients with a low neutrophil or platelet count (i.e. ANC < 2 x 10⁹/L or platelet count < 100 x 10⁹/L). In patients with an ANC < 0.5 x 10⁹/L or a platelet count < 50 x 10⁹/L treatment is not recommended (See PRECAUTIONS – Effects of Laboratory Tests).

Severe neutropenia may be associated with an increased risk of serious infections, although there has been no clear association between decreases in neutrophils and the occurrence of serious infections in clinical trials with ACTEMRA to date.

Neutrophils and platelets should be monitored 4 to 8 weeks after start of therapy and thereafter according to standard clinical practice. For recommended dose modifications based on ANC and platelet counts, see DOSAGE AND ADMINISTRATION.

Lipid Parameters

Elevations in lipid parameters including total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL) and triglycerides were observed in patients treated with ACTEMRA (see ADVERSE EFFECTS – Elevations in lipid parameters). In the majority of patients, there was no increase in atherogenic indices, and elevations in total cholesterol responded to treatment with lipid lowering agents.

Assessment of lipid parameters should be performed 4 to 8 weeks following initiation of ACTEMRA therapy. Patients should be managed according to local clinical guidelines for management of hyperlipidaemia.



Demyelinating Disorders

Physicians should be vigilant for symptoms potentially indicative of new-onset central demyelinating disorders. The potential for central demyelination with ACTEMRA is currently unknown.

Malignancy

The risk of malignancy is increased in patients with RA. Immunomodulatory medicinal products may increase the risk of malignancy.

Infusion Reactions

Infusion reactions have been observed during and within 24 hours of treatment with ACTEMRA (see ADVERSE EFFECTS – Infusion Reactions).

Cardiovascular Risk

RA patients have an increased risk for cardiovascular disorders and should have risk factors (e.g. hypertension, hyperlipidaemia) managed as part of usual standard of care (see PRECAUTIONS – Lipid Parameters). Elevations in LDL and HDL lipids have been observed, with no clinical consequences identified. No data are available concerning cardiovascular outcomes with long-term use of ACTEMRA.

Combination with TNF Antagonists and/or other Biological Therapies

There is no experience with the use of ACTEMRA with TNF antagonists or other biological treatments for RA. ACTEMRA is not recommended for use with other biological agents including TNF antagonists, anakinra, rituximab and abatacept.

Sodium

This medicinal product contains 1.17 mmol (26.55 mg) of sodium per maximum dose of 1200 mg. This should be taken into consideration by patients on a controlled sodium diet. Doses below 1025 mg of ACTEMRA contain less than 1 mmol of sodium (23 mg) and can essentially be considered 'sodium free'.

Effects on Fertility

Preclinical data do not suggest an effect on fertility under treatment with a murine analogue of tocilizumab. Effects on endocrine active organs or on organs of the reproductive system were not seen in a chronic cynomolgus monkey toxicity study, nor was reproductive performance affected in IL-6 deficient male and female mice.

Use in Pregnancy - Category C

ACTEMRA should not be used during pregnancy unless clearly necessary. There are no adequate data from the use of ACTEMRA in pregnant women. The potential risk for humans is unknown. Women of childbearing potential should be advised to use adequate contraception during and for several months after therapy with ACTEMRA.



In an embryo-foetal toxicity study conducted in cynomolgus monkeys, a slight increase of abortion/embryo-foetal death was observed with high systemic cumulative exposure in the 10 mg/kg/day mid-dose group (> 35 times human exposure) and in the 50 mg/kg/day high-dose group (> 100 times human exposure) compared to vehicle control and low-dose groups. It cannot be excluded that this finding is related to ACTEMRA treatment. Placental transfer of both tocilizumab and anti-tocilizumab antibodies to the foetus was seen in cynomolgus monkeys.

Use in Lactation

It is unknown whether ACTEMRA is excreted in human breast milk and its efficacy and safety in lactating women has not been established. However, it is known that endogenous immunoglobulins of the IgG isotype are excreted into human milk. A decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with ACTEMRA should be made taking into account the benefit of breast-feeding to the child and the benefit of ACTEMRA therapy to the woman.

Transfer of a murine analogue of tocilizumab into the milk of lactating mice has been observed.

Use in Children

The safety and efficacy of ACTEMRA in children have not been established.

Use in the Elderly

Population analyses evaluated the potential effects of demographic characteristics on the pharmacokinetics of ACTEMRA in adult rheumatoid arthritis patients. Results of these analyses showed that no adjustment of the dose is necessary for age, gender, or race.

No dose adjustment is required in elderly patients.

Carcinogenicity

A carcinogenicity study of ACTEMRA has not been conducted. Proliferating lesions were not observed in a chronic cynomolgus monkey 6-month toxicity study.

Genotoxicity

Standard genotoxicity studies with ACTEMRA in both prokaryotic and eukaryotic cells were negative.

Interactions with Other Medicines

Population pharmacokinetic analyses did not detect any effect of MTX, non-steroidal anti-inflammatory drugs or corticosteroids on tocilizumab clearance



Concomitant administration of a single dose of 10 mg/kg tocilizumab with 10-25 mg MTX once weekly had no clinically significant effect on MTX exposure.

ACTEMRA has not been studied in combination with other biological DMARDs.

The expression of hepatic CYP450 enzymes is suppressed by cytokines that stimulate chronic inflammation, such as IL-6. Thus suppression of CYP450 expression may be reversed when potent cytokine inhibitory therapy, such as tocilizumab, is introduced.

In vitro studies with cultured human hepatocytes demonstrated that IL-6 caused a reduction in CYP3A4 and to a lesser extent CYP1A2, CYP2C9 and CYP2C19 enzyme messenger RNA (mRNA) expression. Tocilizumab was shown to normalise expression of the mRNA for these enzymes.

This is clinically relevant for CYP450 substrates with a narrow therapeutic index, and/or where the dose is individually adjusted.

In a study in RA patients, levels of simvastatin and its acid metabolite (CYP3A4 substrates) were decreased by 57% and 39%, respectively, one week following a single dose of tocilizumab, to a level similar or slightly higher than those observed (in other studies) in healthy subjects.

When starting or stopping therapy with ACTEMRA, patients taking medicinal products which are individually adjusted and are metabolised via CYP450 3A4, 1A2, 2C9 or 2C19 (e.g. atorvastatin, calcium channel blockers, theophylline, warfarin, phenytoin, cyclosporin or benzodiazepines) should be monitored as doses may need to be adjusted to maintain therapeutic effect. The degree of dose up-titration upon initiation of therapy or dose down-titration when stopping therapy with ACTEMRA should be based on the therapeutic response and/or adverse effects of the patient to the individual medicine. Given a relatively long elimination half-life ($t_{1/2}$), the effect of tocilizumab on CYP450 enzyme activity may persist for several weeks after stopping therapy.

Effects on Laboratory Tests

Caution should be exercised when considering initiation of ACTEMRA treatment in patients with a low neutrophil count. Decreases in neutrophil counts below $1 \times 10^9/L$ occurred in 3.4%, with counts $< 0.5 \times 10^9/L$ occurring in 0.3%, of patients on ACTEMRA 8 mg/kg + DMARD without clear association with serious infection (see PRECAUTIONS – Haematological Abnormalities; ADVERSE EFFECTS - Laboratory Abnormalities). In patients with an absolute neutrophil count $< 0.5 \times 10^9/L$ treatment is not recommended.

Ability to Drive and Use Machines

No studies on the effects on the ability to drive and use machines have been performed. However, there is no evidence from the available data that ACTEMRA treatment affects the ability to drive and use machines.



ADVERSE EFFECTS

The safety of ACTEMRA has been studied in 5 phase III, double-blind controlled trials and their extension periods.

The *all control* population includes all patients who received at least one dose of ACTEMRA in the double-blind controlled period of the 5 studies. The control period in 4 of the studies was 6 months and in 1 study was up to 2 years. In the double-blind controlled studies 774 patients received ACTEMRA 4 mg/kg in combination with MTX, 1870 patients received ACTEMRA 8 mg/kg in combination with MTX/other DMARDs and 288 patients received ACTEMRA 8 mg/kg monotherapy.

The *all exposure* population includes all patients who received at least one dose of ACTEMRA either in the double-blind control period or open label extension phase in studies. Of the 4009 patients in this population, 3577 received treatment for at least 6 months, 3296 for at least one year; 2806 received treatment for at least 2 years and 1222 for 3 years. The mean duration of exposure to ACTEMRA in the *all exposure* population was 2.14 years.

The most commonly reported AEs in controlled studies up to 2 years (occurring in $\geq 5\%$ of patients treated with ACTEMRA monotherapy or in combination with DMARDs) were upper respiratory tract infections, nasopharyngitis, headache, hypertension, increased ALT and bronchitis. In study II the rate of AEs (including deaths, serious AEs and AEs leading to treatment withdrawal or dose modification) after 2 years, calculated as a function of exposure (i.e. events per 100 patient years), had not increased in comparison with the AE profile observed after 1 year of study II.

Table 4 Adverse Events occurring in at least 2% or more of patients on 8 mg/kg ACTEMRA + DMARD and at least 1% greater than that observed in patients on placebo + DMARD

Preferred Term	All Control Study Population				
	ACTEMRA 8 mg/kg monotherapy n=288 (%)	MTX n=284 (%)	ACTEMRA 4 mg/kg + MTX n=774 (%)	ACTEMRA 8 mg/kg + DMARDs n=1870 (%)	Placebo + DMARDs n=1555 (%)
Upper Respiratory Tract Infection	7	5	9	9	7
Nasopharyngitis	7	6	5	7	5
Headache	7	2	6	6	4
Hypertension	6	2	6	5	3
Cough	3	0	3	3	2
ALT increased	6	4	3	3	1
Diarrhoea	5	5	5	4	4
Back Pain	2	1	3	4	3
Peripheral Oedema	2	0	2	3	1
Dizziness	3	1	2	3	2
Bronchitis	3	2	4	3	3
Rash	2	1	4	3	1



Mouth Ulceration	2	2	1	2	1
Abdominal Pain Upper	2	2	3	3	2
Gastritis	1	2	2	2	1
Transaminase increased	1	5	3	3	1

Other infrequent and medically relevant adverse events occurring at an incidence of less than 2% in rheumatoid arthritis patients treated with ACTEMRA in controlled trials were:

Infections and infestations: cellulitis, oral herpes simplex, herpes zoster, diverticulitis

Gastrointestinal disorders: stomatitis, gastric ulcer

Skin and subcutaneous tissue disorders: pruritus, urticaria

Investigations: weight increased, total bilirubin increased

Blood and lymphatic system disorders: leucopenia, neutropenia

Metabolism and nutrition disorders: hypercholesterolaemia, hypertriglyceridaemia

General disorders and administration site conditions: hypersensitivity reaction

Respiratory, thoracic and mediastinal disorders: dyspnoea

Eye disorders: conjunctivitis

Renal disorders: nephrolithiasis

Endocrine disorders: hypothyroidism

Infections

In the 6 month controlled clinical trials, the rate of all infections reported with ACTEMRA 8 mg/kg + DMARD treatment was 127 events per 100 patient (pt) years compared to 112 events per 100 pt years in the placebo + DMARD group. In the *all exposure* population the overall rate of infections with ACTEMRA was 108 events per 100 pt years exposure.

In the 6 month controlled clinical trials, the rate of serious infections (bacterial, viral and fungal) with ACTEMRA 8 mg/kg + DMARD was 5.3 events per 100 pt years exposure compared to 3.9 events per 100 pt years exposure in the placebo + DMARD group. In the monotherapy study the rate of serious infections was 3.6 events per 100 pt years of exposure in the ACTEMRA group and 1.5 events per 100 pt years of exposure in the MTX group.

In the *all exposure* population the overall rate of serious infections was 4.7 events per 100 pt years. Reported serious infections, some with fatal outcome, included pneumonia, cellulitis, herpes zoster, gastroenteritis, diverticulitis, sepsis and bacterial arthritis. Cases of opportunistic infections have also been reported.

Gastrointestinal Perforation

During the 6 month controlled clinical trials, the overall rate of gastrointestinal (GI) perforation was 0.26 events per 100 pt years with ACTEMRA therapy. In the *all exposure* population the overall rate of gastrointestinal perforation was 0.28 events per 100 pt years. Reports of gastrointestinal perforation were primarily reported as



complications of diverticulitis including generalised purulent peritonitis, lower GI perforation, fistula and abscess.

Infusion Reactions

In the 6 month controlled trials adverse events associated with infusion (selected events occurring during or within 24 hours of infusion) were reported by 6.9% of patients in the ACTEMRA 8 mg/kg + DMARD and 5.1% of patients in the placebo + DMARD group. Events reported during the infusion were primarily episodes of hypertension. Events reported within 24 hours of finishing an infusion were headache and skin reactions (rash, urticaria). These events were not treatment limiting.

In the 6 month controlled clinical trials, the rate of anaphylactic reactions in those receiving the lower dose of 4 mg/kg was 3/744 (0.4%) and in the higher dose of 8 mg/kg was 3/1870 (0.2%). As anaphylactic reactions tend to occur early in the course of treatment, the overall rate of anaphylaxis cumulatively in the long term extensions remained at 6/3778 or 0.2%.

Clinically significant hypersensitivity reactions associated with ACTEMRA and requiring treatment discontinuation, were reported in a total of 13 out of 3778 patients (0.3%) treated with ACTEMRA during the controlled and open label clinical trials. These reactions were generally observed during the second to fifth infusions of ACTEMRA.

Immunogenicity

A total of 2876 patients have been tested for anti-tocilizumab antibodies in the 6 month controlled clinical trials. Forty six patients (1.6%) developed positive anti-tocilizumab antibodies of whom 5 had an associated medically significant hypersensitivity reaction leading to withdrawal. Thirty patients (1.1%) developed neutralising antibodies.

Laboratory Abnormalities

Haematology abnormalities

Neutrophils

In the 6 month controlled trials decreases in neutrophil counts below $1 \times 10^9/L$ occurred in 3.4% of patients on ACTEMRA 8 mg/kg + DMARD compared to < 0.1% of patients on placebo + DMARD. Approximately half of the patients who developed an ANC < $1 \times 10^9/L$ did so within 8 weeks after starting therapy. Decreases below $0.5 \times 10^9/L$ were reported in 0.3% patients receiving ACTEMRA 8 mg/kg + DMARD (see PRECAUTIONS – Effects on Laboratory Tests).

There was no clear relationship between decreases in neutrophils below $1 \times 10^9/L$ and the occurrence of serious infections.



In the *all control* and *all exposure* population, the pattern and incidence of decreases in neutrophil counts remained consistent with what was seen in the 6 month controlled clinical trials.

Platelets

In the 6 month controlled trials decreases in platelet counts below $100 \times 10^9/L$ occurred in 1.7% of patients on ACTEMRA 8 mg/kg + DMARDs compared to < 1% on placebo + DMARDs. These decreases occurred without associated bleeding events. (See DOSAGE AND ADMINISTRATION and PRECAUTIONS – Haematological Abnormalities.)

In the *all control* and *all exposure population*, the pattern and incidence of decreases in platelet counts remained consistent with what was seen in the 6 month controlled clinical trials.

Liver enzyme elevations

During the 6 month controlled trials transient elevations in ALT (alanine transaminase)/AST (aspartate transaminase) $> 3 \times ULN$ (Upper Limit of Normal) were observed in 2.1% of patients on ACTEMRA 8 mg/kg compared to 4.9% of patients on MTX, and in 6.5% of patients who received ACTEMRA 8 mg/kg + DMARD compared to 1.5% of patients on placebo + DMARD. The addition of potentially hepatotoxic drugs (for example MTX) to ACTEMRA monotherapy resulted in increased frequency of these elevations. Elevations of ALT/AST $> 5 \times ULN$ were observed in 0.7% of ACTEMRA monotherapy patients and 1.4% of ACTEMRA + DMARD patients, the majority of whom were discontinued from ACTEMRA treatment. These elevations were not associated with any clinically relevant increases in direct bilirubin, nor were they associated with clinical evidence of hepatitis or hepatic insufficiency. During routine laboratory monitoring, the incidence of indirect bilirubin $> ULN$ is 6.2% in patients treated with 8 mg/kg ACTEMRA + DMARD in the *all control* population.

In the *all control* and *all exposure* population, the pattern and incidence of elevations in ALT/AST remained consistent with what was seen in the 6 month controlled clinical trials.

Elevations in lipid parameters

During routine laboratory monitoring in the 6 month controlled clinical trials, increases of lipid parameters such as total cholesterol, triglycerides, LDL cholesterol, and/or HDL cholesterol have been reported commonly. Approximately 24% of patients receiving ACTEMRA in clinical trials experienced sustained elevations in total cholesterol > 6.2 mmol/L (240 mg/dL), with 15% experiencing a sustained increase in LDL to ≥ 4.1 mmol/L (160 mg/dL). Elevations in lipid parameters responded to treatment with lipid-lowering agents.

In the *all control* and *all exposure* population, the pattern and incidence of elevations in lipid parameters remained consistent with what was seen in the 6 month controlled clinical trials.



Malignancies

The clinical data are insufficient to assess the potential incidence of malignancy following exposure to tocilizumab. Long-term safety evaluations are ongoing.

Post-Marketing Experience

The safety profile in post-marketing experience is consistent with clinical trial data with the exception of a case of fatal anaphylactic reaction which has been reported during post-marketing experience (see PRECAUTIONS – Hypersensitivity Reactions).

Globally, serious hypersensitivity reactions related to ACTEMRA exposure reportedly occur at a rate of approximately 0.26%. In Australia this rate is approximately 0.17%. The one fatal anaphylactic reaction, which has been reported, occurred when the patient was re-challenged with ACTEMRA despite previously experiencing a hypersensitivity reaction to ACTEMRA (see CONTRAINDICATIONS).

DOSAGE AND ADMINISTRATION

Treatment should be initiated by healthcare professionals experienced not only in the diagnosis and treatment of RA but also in the use of biological therapies for this condition.

The recommended dose of ACTEMRA for adult patients is 8 mg/kg given once every 4 weeks as an IV infusion.

For individuals whose body weight is more than 100 kg, doses exceeding 800 mg per infusion are not recommended (see PHARMACOLOGY – PHARMACOKINETICS).

The calculated dose of ACTEMRA should be diluted to 100 mL and administered as an IV infusion over a period of 1 hour.

ACTEMRA can be used alone or in combination with MTX and/or other non-biological DMARDs.

During IV infusion with ACTEMRA the patient must be closely monitored at all times for any signs or symptoms of a hypersensitivity reaction. Should any such reaction occur then appropriate urgent responses and treatments are to be initiated. The necessary equipment, treatments and protocols sufficient to initiate the management of acute anaphylaxis are to be in place along with the availability of appropriately trained personnel. There must be continued education and training of the health care professionals who administer the infusions. As part of the informed consent process patients should be made aware of the risk of anaphylaxis and the equipment, treatments and protocols in place to manage this risk.



Dose Modification Recommendations

- Liver enzyme abnormalities

Lab Value	Action
> 1 to 3 x ULN	Dose modify concomitant DMARDs if appropriate For persistent increases in this range, reduce ACTEMRA dose to 4 mg/kg or interrupt ACTEMRA until ALT/AST have normalised Restart with 4 mg/kg or 8 mg/kg, as clinically appropriate
> 3 to 5 x ULN (confirmed by repeat testing, see PRECAUTIONS - Hepatic Transaminase Elevations)	Interrupt ACTEMRA dosing until < 3 x ULN and follow recommendations above for > 1 to 3 x ULN For persistent increases > 3 x ULN, discontinue ACTEMRA
> 5 x ULN	Discontinue ACTEMRA

- Low absolute neutrophil count (ANC)

Lab Value (cells x 10 ⁹ /L)	Action
ANC > 1	Maintain dose
ANC 0.5 to 1	Interrupt ACTEMRA dosing When ANC > 1 x 10 ⁹ /L resume ACTEMRA at 4 mg/kg and increase to 8 mg/kg as clinically appropriate
ANC < 0.5	Discontinue ACTEMRA

- Low platelet count

Lab Value (cells x 10 ⁹ /L)	Action
50 to 100	Interrupt ACTEMRA dosing When platelet count is > 100 x 10 ⁹ /L resume ACTEMRA at 4 mg/kg and increase to 8 mg/kg as clinically appropriate
< 50	Discontinue ACTEMRA

Special Patient Groups

Children: The safety and efficacy of ACTEMRA in children below 18 years of age have not been established.

Elderly: No dose adjustment is required in elderly patients aged 65 years and older.



Renal impairment: No dose adjustment is required in patients with mild renal impairment (see PHARMACOLOGY – Pharmacokinetics in Special Populations). ACTEMRA has not been studied in patients with moderate to severe renal impairment.

Hepatic impairment: The safety and efficacy of ACTEMRA has not been studied in patients with hepatic impairment (see PRECAUTIONS – Active Hepatic Disease and Hepatic Impairment) and therefore no dose recommendations can be made.

Preparing the Infusion

Parenteral medications should be inspected visually for particulate matter or discolouration prior to administration.

Only solutions which are clear to opalescent, colourless to pale yellow and free of visible particles must be infused.

From a 100 mL infusion bag, withdraw a volume of 0.9% sodium chloride solution equal to the volume of the ACTEMRA solution required for the patient's dose, and discard. Withdraw the required amount of ACTEMRA (0.4 mL per kg of the patient's body weight) under aseptic conditions and add to the infusion bag. To mix the solution, gently invert the bag to avoid foaming.

OVERDOSAGE

There are limited data available on overdose with ACTEMRA. One case of accidental overdose was reported in which a patient with multiple myeloma received a single dose of 40 mg/kg. No adverse drug reactions were observed. No serious adverse drug reactions were observed in healthy volunteers who received a single dose up to 28 mg/kg, although dose-limiting neutropenia was observed.

Treatment of overdose should consist of general supportive measures.

Contact the Poisons Information Centre for advice on management of overdose.

PRESENTATION AND STORAGE

ACTEMRA is available as:

*(not marketed)

- Single use vial containing 80 mg of ACTEMRA in 4 mL (20 mg/mL). Packs of 1 and 4* vials.
- Single use vial containing 200 mg of ACTEMRA in 10 mL (20 mg/mL). Packs of 1 and 4* vials.
- Single use vial containing 400 mg of ACTEMRA in 20 mL (20 mg/mL). Packs of 1 and 4* vials.



Store vials at 2°C – 8°C. (Refrigerate. Do not freeze.) Keep the container in the outer carton in order to protect from light.

ACTEMRA does not contain any antimicrobial agent; therefore care must be taken to ensure the sterility of the prepared solution. Product is for single use in one patient only. Discard any residue.

The prepared infusion solution of ACTEMRA is physically and chemically stable in 0.9% w/v sodium chloride solution at 30°C for 24 hours. To reduce microbiological hazard, the prepared infusion should be used immediately. If storage is necessary, hold at 2°C – 8°C for not more than 24 hours.

Do not use after the expiry date (EXP) shown on the pack.

Disposal of Medicines

The release of medicines into the environment should be minimised. Medicines should not be disposed of via wastewater and disposal through household waste should be avoided. Unused or expired medicine should be returned to a pharmacy for disposal.

POISON SCHEDULE

Prescription Only Medicine (S4)

SPONSOR

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ABN 70 000 132 865
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AUSTRALIA

Customer enquiries: 1800 233 950

Distributed in New Zealand by:
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TGA Approval Date: 13 January 2011

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