Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Abatacept (rch)

Proprietary Product Name: Orencia

Sponsor: Bristol-Myers Squibb Australia Pty Ltd

June 2011

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The TGA is a division of the Australian Government Department of Health and Ageing, and is responsible for regulating medicines and medical devices.
- TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
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About AusPARs

- 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.

Contents

I. Introduction to Product Submission

Submission Details

Type of Submission	Extension of Indications
Decision:	Approved
Date of Decision:	23 March 2011
Active ingredient(s):	Abatacept (rch)
Product Name(s):	Orencia
Sponsor's Name and Address:	Bristol-Myers Squibb Australia Pty Ltd 556 Princes Highway Noble Park Vic 3174
Dose form(s):	Powder for IV infusion
Strength(s):	250 mg
Container(s):	Single-use vial with a silicone-free disposable syringe
Pack size(s):	Individually packaged
Approved Therapeutic use:	Orencia in combination with methotrexate is indicated for the treatment of moderate to severe active rheumatoid arthritis in adult patients who have had an insufficient response or intolerance to other disease modifying anti-rheumatic drugs (DMARDs), such as methotrexate or tumour necrosis factor (TNF) blocking agents. A reduction in the progression of joint damage and improvement in physical function have been demonstrated during combination treatment with Orencia and methotrexate. Orencia in combination with methotrexate is also indicated in the treatment of severe, active and progressive rheumatoid arthritis in adults not previously treated with methotrexate. Orencia is indicated for reducing signs and symptoms in paediatric patients 6 years of age and older with moderately to severely active polyarticular juvenile idiopathic arthritis who had an inadequate response to one or more disease-modifying anti-rheumatic drugs (DMARDS). Orencia may be used as monotherapy or concomitantly with methotrexate (MTX). Orencia should not be administered concurrently with other biological DMARDs (eg, TNF inhibitors, rituximab, or anakinra).
Route(s) of administration:	IV infusion
Dosage:	Following the initial administration, Orencia should be given at 2 and 4 weeks after the first infusion, then every 4 weeks thereafter, 500 mg, 750 mg or 1 g, depending on body weight.
ARTG Number (s)	130100

Product Background

This AusPAR describes the evaluation of a submission from the sponsor, Bristol-Myers Squibb Australia Pty Ltd for an extension of indications for abatacept (Orencia). An extension of indications for Orencia to allow treatment of paediatric patients with moderately to severely active polyarticular juvenile idiopathic arthritis was recently approved by the TGA.[1] The submission also proposes the updating of the product information with long-term efficacy and safety data for the use of Orencia in rheumatoid arthritis.

Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disease characterized by progressive inflammatory synovitis manifested by polyarticular joint swelling. Activation of T-lymphocytes is an important mediator in the pathogenesis of RA, particularly early in the disease process, because it results in amplification of the pro-inflammatory disease cascade. Abatacept is a selective co-stimulation modulator which inhibits T-cell activation by binding to CD80 and CD86, thereby blocking a crucial interaction with CD 28.

The sponsor submitted that consistent with contemporary practice, early treatment of RA (particularly in those with poor prognostic factors such as the presence of autoantibodies and early radiographic erosion) is considered to offer the best outcomes. In addition, combination therapy involving biological and conventional disease modifying anti-rheumatic drug (DMARD) treatment is considered to offer the best opportunity to achieve favourable outcomes in adult patients with early aggressive RA.

The extended indication proposed by the sponsor is:

Orencia in combination with methotrexate is also indicated in the treatment of severe, active and progressive rheumatoid arthritis in adults not previously treated with methotrexate.

This paragraph is to be an additional insert between the first and second paragraphs of the current approved indication for Orencia which are as follows:

Orencia in combination with methotrexate is indicated for the treatment of moderate to severe active rheumatoid arthritis in adult patients who have had an insufficient response or intolerance to other disease modifying anti-rheumatic drugs (DMARDs), such as methotrexate or tumour necrosis factor (TNF) blocking agents. A reduction in the progression of joint damage and improvement in physical function have been demonstrated during combination treatment with Orencia and methotrexate.

Orencia is indicated for reducing the signs and symptoms in paediatric patients 6 years of age and older with moderately to severely active polyarticular juvenile idiopathic arthritis who have had an inadequate response to one or more disease modifying anti-rheumatic drugs (DMARDs). Orencia may be used as monotherapy or concomitantly with methotrexate (MTX).

Orencia should not be administered concurrently with other biological DMARDs (e.g. TNF inhibitors, rituximab or anakinra).

The route of administration is per intravenous (IV) infusion over a 30 minute period. A weight tiered dosing of 10 mg/kg is currently approved and was utilized in all of the Phase III efficacy studies. The approved dosing regimen is 0, 2 and 4 weeks and every 4 weeks thereafter.

[1] TGA. AusPAR for Abatacept (rch), April 2010. Available at http://www.tga.gov.au/pmeds/auspar/auspar-orencia.pdf.

Regulatory Status

Abatacept has been registered in Australia since August 2007 for the treatment of patients with moderate to severe active RA. The drug was first approved globally for the treatment of adult patients with RA in December 2005 in the USA, where it was originally restricted to patients who were either MTX or anti-TNF inadequate responders (IR). A similar approval has been obtained in the European Union, Canada, Russia, Japan and Latin America.

A similar application for the extension of indication in RA to include the treatment of MTX naïve patients with early aggressive disease characteristics has been approved in the USA in August 2009, Canada in February 2010, the European Union (EU) in May 2010 and Switzerland in October 2010 as well in India and various countries in Latin America. A similar application submitted to the regulatory authorities in the Asia-Pacific region (such as Singapore and New Zealand) remains under review.

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 Product

The formulation of abatacept contains 250 mg of antibody per vial which is reconstituted with 10 mL of sterile Water for Injection resulting in a concentration (after reconstitution) of 25 mg/mL.

Quality Summary and Conclusions

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

III. Nonclinical Findings

Nonclinical Summary and Conclusions

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

IV. Clinical Findings

Introduction

The submission included 16 studies. The original RA treatment indication approval in Australia was based on five Phase II-III studies that investigated the efficacy and safety of abatacept in adult patients with moderately-severely active RA over 6-12 months. In two of these studies (IM101-100 and IM101-102) abatacept in combination with MTX was given to subjects that had an inadequate response to MTX (MTX-IR) and in one study (IM101-029) abatacept + MTX was given to patients who had an inadequate response to anti-TNF therapy (TNF-IR). The other two key studies in the original submission involved adult subjects that received a broad range of concurrent DMARDs (Study IM101-031) or concomitant etanercept (Study IM101-101). In this submission, efficacy and safety data from the open-label extension (OLE) periods of up to 7 years were included for review.

Three new clinical studies presented in this submission are of particular relevance because their details have been added to the proposed product information (PI) and form the basis of the extended indication in RA. A new pivotal Phase III study (IM101-023) was

presented to support the new claim of initiating abatacept in adult patients with active RA who are MTX naïve. This study had a one year double-blind controlled period followed by a second year of open-label treatment with abatacept + MTX. Two other studies supported the proposed updating of the product information with long-term efficacy and safety data for the use of Orencia in rheumatoid arthritis. An uncontrolled, open-label trial (Study IM101-064) of up 2.5 years duration assessed the efficacy and safety of abatacept in combination with non-biological DMARDs in adult patients who are TNF-IR and with limited future treatment options. The third new study (IM101-043) had an active biological DMARD (bDMARD) comparator (infliximab versus abatacept) in the first 12 months followed by an open-label extension period of up to 2.5 years. This study recruited MTX-IR adult patients with active RA. Studies IM101-023 and IM101-064 were not included in the original Australian licensing application as they were still in progress at the time of original submission.

Another 8 "new" studies were also presented in this submission which can be summarized as: -

- Study IM101-015: a 4 month exploratory study assessing the changes in synovial immune response following abatacept in patients with active RA (TNF-IR) on background DMARD,
- Studies IM101-013 and IM101-063: two trials which principally examined the pharmacokinetics of subcutaneously administered abatacept in healthy individuals (IM101-013) and adult patients with RA (IM101-063),
- Study IM101-128: a follow-up of immunogenicity development at 3 years in healthy individuals given a single subcutaneous dose of abatacept 3 years earlier in Study IM101-013,
- Study IM101-034: a short-term (57-127 days) safety follow-up trial of adult patients with RA given either single or multiple doses of open-label abatacept in a dose escalation manner (2, 8 and 16 mg/kg),
- Study IM101-071: an efficacy report at 6 months of 2 doses of abatacept (2 and 10 mg/kg) given on multiple occasions to adult patients with active RA who were MTX-IR,
- Study IM101-129: a 6 month safety follow-up of patients involved in Studies IM101-034 and IM101-071, as well as other subjects with active RA who had an inadequate response to DMARDs (DMARD-IR) and
- Study IM101-046: a 2 year exploratory study of abatacept versus placebo in preventing the development of RA in adult patients with undifferentiated inflammatory arthritis.

In the RA clinical trial program, a total of 4632 subjects representing 12,375 patient-years (PY) of exposure have received at least part of one infusion of abatacept in a controlled setting as of the data cut-off date (31 October 2008). For the integrated study population of adult patients with RA receiving abatacept, 483 have been MTX naïve (717 PY of exposure; Study IM101-023), 1280 have been MTX-IR (4465 PY of exposure), 1419 have been TNF-IR (1986 PY of exposure) and 1450 have received other background treatments (5206 PY of exposure). The overall drug exposure provides a significantly larger database for the evaluation of safety, including relatively uncommon events, compared to that available at the original licensing application assessment.

Pharmacodynamics

The pharmacodynamic (PD) effects of abatacept in adults with RA have been previously characterized and are summarized in the current PI document. Two PD aspects will be considered in this evaluation – the effect of abatacept on disease related biomarkers and the development of immunogenicity.

Within this submission, additional PD data relating to changes in biomarkers were collected in the pivotal Study IM101-023, Study IM101-043 and Study 101-015, which was an exploratory short-term study examining the changes in synovial immune response following abatacept in adult patients with active RA and prior anti-TNF failure.

For the review of immunogenicity, the results of Study IM101-023 (MTX naïve subjects), Study IM101-043 (bDMARD comparator trial) and the studies involving subcutaneous administration of abatacept (Study IM101-013 and IM101-063) will be considered separately. However, for data obtained from other trials, many of which were included in the original licensing application, the results will be presented as an integrated summary according to prior treatment characteristics – MTX-IR subjects (Studies IM101-102 and IM101-100), TNF-IR patients (Studies IM101-029 and IM101-064), uncontrolled open-label populations (Studies IM101-031 and IM101-101) and trials with drug-free periods and then re-exposure to abatacept (Studies IM101-034, IM101-071 and IM101-129). The submission also contained a report for Study IM101-128 which is 3 year follow-up of healthy individuals given a single dose of abatacept 3 years earlier for the development of anti-drug antibodies.

Effect on Biomarkers

All subjects randomized into **Study IM101-023** were to be positive at screening for at least one of the two serological assays (Rheumatoid Factor [RF] or anti-cyclic citrullinated peptide [CCP2] antibodies) associated with RA.[2] The proportion of patients who were positive at baseline and subsequently became negative at study Days 169 and 365 was examined. More subjects treated with abatacept + MTX (17.0% [39/230] at Day 169 and 18.5% [41/222] at Day 365) had a positive to negative seroconversion of RF (determined by a concentration > or < 15 IU/mL) compared with subjects treated with placebo infusions + MTX (9.5% [22/231] at Day 169 and 14.6% [32/219] at Day 365). Following a similar trend, the proportion of subjects treated with abatacept + MTX (6.6% [15/227] at Day 169 and 7.1% [15/212] at Day 365), who had a positive to negative seroconversion of anti-CCP2 antibody (lower limit of detection is 2 IU/mL) was higher compared with patients treated with placebo infusions + MTX (2.9% [6/208] at Day 169 and 4.5% [9/198] at Day 365).

At Day 169, the mean concentration of RF decreased from baseline by 133 IU/mL for patients treated with abatacept + MTX (n=239; baseline mean 305 IU/mL to 172 IU/mL at Day 169 [95% confidence intervals (CI) -209, -57 IU/mL]), compared to patients receiving placebo infusions + MTX where RF levels declined by a mean of 142 IU/mL (n=238; baseline mean 273 IU/mL to 131 IU/mL [95% CI -169, -116 IU/mL). However, changes from baseline to Week 24 in the median anti-CCP2 antibody concentrations followed a

[2] Rheumatoid factor (RF) has been the primary blood test used to detect RA and distinguish it from other types of arthritis and other inflammatory processes. However, the sensitivity and specificity of RF are not ideal; it can be negative in patients who have clinical signs of RA and positive in patients who do not. CCP can be useful in diagnosing early RA. An elevated CCP can be found in a significant number of patients who have a negative RF, the classic test for RA, and therefore can help to make a diagnosis. According to the American College of Rheumatology, CCP antibodies may be detected in about 50-60% of patients with early RA (as early as 3-6 months after the beginning of symptoms). The second generation test (CCP2) has a greater sensitivity.

different trend. The median baseline concentration of anti-CCP2 antibody was 271.9 IU/mL for placebo + MTX (n=241) and 304.8 IU/mL for abatacept + MTX (n=243). The corresponding median 24 Week levels of anti-CCP2 antibodies were 223.3 IU/mL (lower by a mean of 48.6 [95% CI -95.2, -1.98 IU/mL]) for placebo + MTX and 196.3 IU/mL (lower by a mean of 108 [95% CI -138, -79.3 IU/mL) for abatacept + MTX. A similar observation was observed at Day 365 for the median changes (reductions from baseline) in disease associated autoantibodies. Other biochemical markers known to correlate with RA disease activity and progression show that abatacept 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.

The study report for IM101-023 also contained PD information in relation to biochemical markers of cartilage and bone matrix turnover (such as Receptor Activity of NF-κβ Ligand [RANKL], anti-Osteoprotegrin-1 [OPG-1], C-Telopeptide Type I collagen [CTX-1] and Matrix Metalloproteinase -1 [MMP-1]) which are important supporting elements for the biological plausibility of abatacept in its claim of inhibiting structural joint damage in RA. The mean changes from baseline to 6 and 12 months in all 3 bone biomarkers (OPG-1, MMP-1 and CTX-1) for both treatment groups were small in magnitude and inconsistent. As such, no conclusion about a treatment effect with abatacept can be made. In addition, the results for RANKL were subsequently not analysed by the sponsor as more than 90% of data collected for this measure was below the lower limit of assay detection (<0.32).

In **Study IM101-043**, which involved a comparison between placebo infusions + MTX and two active bDMARD groups (abatacept and infliximab), serum levels of inflammatory cytokines such as Interleukin (IL)-6 and RANKL, disease associated autoantibodies (RF) and serum inflammatory markers (ESR and CRP) were assessed at 6 and 12 months. After 6 months of treatment, greater reductions in the mean levels of all biomarkers except RANKL were seen in those who received abatacept + MTX compared to placebo infusions + MTX. When infliximab + MTX was compared to placebo + MTX at 6 months, greater mean reductions in CRP and IL-6 levels were identified but not for any of the other biomarkers (ESR, RANKL or RF levels).

At 12 months of follow-up in Study IM101-043, patients treated with abatacept + MTX had a greater mean reduction in ESR and CRP compared to infliximab + MTX but the opposite observation was seen for the mean decrease in RF levels. No difference in treatment effect was identified for IL-6 and RANKL.

Study IM101-015 was a single centre exploratory study undertaken in England which was an open-label, multiple dose trial conducted over 4 months. Adult subjects with active RA (DAS28 > 5.1 at baseline) and at least one swollen knee joint at screening were given abatacept 10 mg/kg for up to 6 doses.[3] The patients were required to have RA of at least 1 year duration and have a history of inadequate response to anti-TNF drugs. Subjects remained on a stable dose of their background DMARD (mainly MTX) during the study follow-up period of 4 months. A total of 16 subjects were enrolled and 15 received at least

[3] 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.

5 doses of abatacept, which was the requirement for inclusion in the analysis. Following treatment with abatacept, significant decreases in the number of synovial B-cells (median decrease of 71% for CD20 cells and 100% for CD79 cells), macrophages (median decrease of 12%) and intracellular adhesion molecule (ICAM) (median decrease of 21%) were observed. However, no significant changes in the numbers of synovial T-cells (CD 3 or 4) were seen. Abatacept treatment also resulted in significant reductions (geometric mean % change of -52%) in the synovial tissue expression of Interferon γ (IFN γ), which is an important disease related cytokine produced by Th1 T-cells. Abatacept therapy also produced significant median percentile reductions in various serum inflammatory markers including MMP-3 (-44%), IL-6 (-73%) and TNF (-40%). Similar median reductions were seen for both CRP (-67%) and RF (-18%). The reductions in these serum inflammatory markers were more consistently observed and to a greater magnitude in clinical responders than non-responders. For example, the median percent decrease for CRP was 80% in clinical responders and 22% in non-responders. The Dynamic Enhanced MRI (DEMRI) data demonstrated significant reductions in the volume of synovitis following treatment with abatacept: median percent decrease from baseline of 35% for IRE (initial rate of enhancement) and 28.5% for ME (maximal enhancement). The reduction in synovitis was observed in the regions of interest (for example, the cartilage-pannus junction) and was more marked in clinical responders.

Immunogenicity

As abatacept is a protein, it has the potential to elicit an antibody response to itself. The formation of anti-drug antibodies may result in alterations in the drug's pharmacokinetic profile that cause increased clearance, or prevent the drug from binding to its pharmacologic target, both of which may reduce efficacy. Furthermore, the formation of anti-drug antibodies may also cause immune-mediated side-effects such as infusion reactions.

In **Study IM101-023**, serum samples from the subjects who received abatacept + MTX (n=249 for Year 1) were collected at several time points for analysis by enzyme-linked immunosorbent assay (ELISA) to detect antibodies directed against the whole molecule (n=795; both the cytotoxic T-lymphocyte antigen 4 (CTLA4) and the immunoglobulin (Ig) portion, so named "anti-abatacept antibodies") or solely the CTLA4 portion (n=798; called "anti-CTLA4 antibodies"). In total, 4 of 249 subjects (1.6%) tested positive for anti-abatacept antibodies, 3 of which had specificity for IgG portion and 1 of which was positive (on 2 occasions – Days 56 and 85 following their last dose) for the anti-CTLA4 region. The latter patient also demonstrated neutralizing activity for the anti-CTLA4 antibody and withdrew on study Day 29 due to an adverse event. Twelve other subjects treated with abatacept + MTX during the first 12 months of the study also prematurely discontinued but none of these patients had detectable anti-drug antibodies. Of the 3 other patients who developed anti-abatacept antibodies, 2 did so by 6 months and the other case was only recorded at 12 months. Two of these subjects achieved the primary efficacy endpoints (ACR50 response or DAS28-CRP remission) during the study and the other patient experienced a severe adverse event (moderate depression) that was unrelated to her treatment.[4] In the open-label phase (second year) of Study IM101-023, 6.1% (28/456) of

[4] The **ACR response** criteria are a standard instrument used in RA trials. The ACR criteria of 20%, 50%, 70% or 90% improvement in clinical manifestations are an attempt to quantify response to therapy. Thus, a patient with an ACR 20 response to an intervention has demonstrated a 20% decrease in the combined number of swollen and tender joint counts, and a 20% improvement in any 3 of the 5 core-set measures which include Patient's Global Assessment, Physician's Global Assessment of disease activity (on 10cm visual analog scale [VAS]), Patient's Assessment of Pain score (on 10cm VAS), HAQ-DI, and acute phase reactants (ESR or CRP). The achievement of an ACR 20 response by an individual subject is considered to be the minimally achieved level of response that is of clinical relevance.

subjects demonstrated anti-abatacept antibodies, 13 (2.9%) of which were directed against the IgG region and 16 (3.5%) were positive for the anti-CTLA4 antibody response (including 1 subject positive for both antibody types). The majority of subjects (60.7%; 17 of 28) were only identified as seropositive after discontinuation of abatacept in the open-label period, typically at the visit performed 85 days following their last dose. Only 3 of the patients were found to have antibodies with neutralizing activity. No correlation between efficacy or safety outcomes (or original treatment in the double-blind phase) and development of anti-drug antibodies was established at 2 years of follow-up.

The rates and clinical effects of immunogenicity were also assessed in **Study IM101-043**. During the 12 month double-blind (DB) study period, none of the subjects who received abatacept + MTX or placebo infusions + MTX developed antibodies to either the whole abatacept molecule or the CTLA4 region. In contrast, most of the patients (62.0%, 101/163) who received infliximab + MTX recorded positive antibodies to infliximab. This event rate is significantly higher than that reported in the literature (typically ~10%) and appears to be influenced by several factors, particularly the sensitivity and specificity of the assay used in this analysis. There was a trend to a higher overall rate of discontinuation in those subjects treated with infliximab that developed anti-drug antibodies but no specific safety concern (such as an increased rate of infusion reactions) was identified.

The effect of subcutaneous (SC) administration of abatacept was assessed in two studies (**IM101-013** [healthy individuals] and **IM101-063** [adult patients with active RA]) that were mainly designed to determine pharmacokinetic parameters. In Study IM101013, 11 of the 40 healthy subjects developed antibodies to the CTLA4 binding portion of the abatacept molecule: 8 of 30 subjects (26.7%) who received the SC formulation (osmolality 386 mOsm/kg) including 1 with neutralization activity, and 3 of 10 subjects who received the IV formulation (osmolality 900 mOsm/kg) by the SC route. The earliest detected seroconversion was 43 days after initiation of abatacept. Endpoint study titres in healthy individuals followed for 71 days ranged from 33-106 μg/mL in those given the SC formulation and 62-872 μg/mL in those who received the IV formulation. In conclusion, Study IM101-013 showed that the SC formulation was no more immunogenic than the IV formulation given by the SC route and no dose dependent relationship was observed. In Study IM101-063, only 1 of the 51 abatacept treated subjects tested positive for anti-abatacept antibodies and this patient had experienced no significant adverse events.

Study IM101-128 was a 3 year immunogenicity follow-up of healthy individuals given a SC dose of abatacept in Study IM101-013. Of the 48 subjects originally involved in Study IM101-013, 31 (26 who received abatacept and 5 given placebo injections) were analysed for immunogenicity potential 3 years later. None of the 31 subjects tested positive for either type of anti-drug antibody.

In the **integrated MTX-IR population** (Studies IM101-100, IM101-102 and IM101-043), a total of 81 of 1236 subjects became seropositive while receiving abatacept treatment – 74 of 1201 (6.2%) for anti-abatacept antibodies and 7 of 1236 (0.6%) for anti-CTLA4 antibodies. In the **integrated TNF-IR cohort** (Studies IM101-029 and IM101-064), 26 of 1266 (2.1%) subjects were seropositive – 23/1252 (1.8%) for anti-abatacept antibodies and 4/1266 (0.3%) for anti-CTLA4 antibodies. In the uncontrolled open-label population (Studies IM101-101 and IM101-031), a total of 80 subjects (5.8% of 1374) became seropositive – 4.8% (63/1309) for anti-abatacept antibodies and 1.5% (21/1374) for anti-CTLA4 antibodies. In all of these populations, immunogenicity data has been collected for up to 5 years after exposure. The cumulative dataset shows that the annual incidence rate on-therapy for anti-abatacept antibody formation is 0.68 per 100 patient-years (95% CI 0.43, 1.03) during the first year and 1.52 per 100 patient-years (95% CI 1.07, 2.09) during

the second year. For the 3 years thereafter, the annual incidence of anti-abatacept antibody formation appears to remain stable with values of 1.93 per 100 PY (95% CI 1.36, 2.65) in year 3, 1.68 per 100 PY (95% CI 1.11, 2.44) in year 4 and 2.07 per 100 PY (95% CI 1.44, 2.88) in year 5. The annual rates of formation of anti-CTLA4 antibodies showed a similar trend with a peak in year 3 of exposure (0.54 per 100 PY [95% CI 0.27, 0.97]). Using the integrated dataset of all types of study populations, a relationship between immunogenicity and safety (infusion reactions, infections, discontinuations, autoimmune disease and anti-dsDNA antibody formation) or efficacy (such as DAS28, ACR or HAQ response) is not evident in patients who develop antibodies to either abatacept or the CTLA4 region of the molecule.[5]

Results from studies in Japanese subjects with RA suggest that compared to the overall incidence, patients left untreated for periods of 2-5 months had a higher incidence of immunogenicity, particularly if those subjects received only a single dose of abatacept. Seven of 21 (33%) patients in **Study IM101-034** demonstrated a positive antibody response to the CTLA4 region. This study was a Phase I dose escalation trial conducted in Japan whereby patients could receive either a single or multiple doses of abatacept (2, 8 or 16 mg/kg) depending upon clinical response. The median time to identification of anti-drug antibodies was 17 weeks (range: 13-20 weeks). In **Study IM101-129** (an open-label uncontrolled trial of abatacept in Japanese patients, some of whom were enrolled at the conclusion of Study IM101-034 and others from another forerunner trial in Japan [Study IM101-071]), a total of 7 of 101 subjects (6.9%) developed anti-CTLA4 antibodies. Five of these 7 subjects had significant drug-free transition periods (mean 2.1 years; range 1.3-3.1 years) between the studies suggesting that interrupted exposure to abatacept may play a role in increasing the likelihood of developing anti-drug antibodies.

Conclusion

In summary, abatacept therapy in a heterogeneous group of adult patients with RA produces desirable effects on reducing systemic levels of various disease related biomarkers and synovial changes associated with the disease. Abatacept is associated with a relatively low incidence of immunogenicity and the formation of anti-drug antibodies does not appear to be significantly associated with safety issues or loss of efficacy. Patients who have extended drug free exposure periods may have a higher incidence of immunogenicity which appears to peak in the second or third year after drug exposure.

Pharmacokinetics

The pharmacokinetics (PK) of intravenous (IV) abatacept in healthy adults and those in patients with RA were presented in the original licensing application and summarized in the current PI. Apart from Study IM101-015, which was primarily a PD outcome focused trial, blood samples for further evaluation of the PK of IV abatacept were not collected in the studies supporting this submission. Serum samples for abatacept concentrations were obtained from 15 patients during the end of the **Study IM101-015** (that is, 7-14 days after

[5] 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 score for that activity remains 2. A total score of between 0 and 3 is obtained from the mean of each activity.

the last dose of abatacept). Serum abatacept concentrations ranged from 16.0-57.0 µg/mL, which is within expectations from the known dataset. Attempts were also made to obtain synovial fluid for abatacept concentration at the end of the trial as well, however the specimens were only obtained from 2 participants and were contaminated with blood. However, the sponsor did provide the reports of 2 studies (IM101-013 and IM101-063) whereby the PK of subcutaneous (SC) administered abatacept were evaluated.

In healthy subjects, C_{max} and AUC increased in a dose proportional relationship over the tested range of 50-150 mg of SC abatacept. Expectedly, drug clearance appears to be increased in those subjects who develop antibodies to abatacept. In Study IM101-063 whereby adult patients with RA were evaluated, the effect of weight on a fixed SC dosing strategy was revealed. The results indicate that patients with a weight > 100 kg will require a weight based dosing regimen (rather than fixed dose approach) in order to control for inter-individual variability of exposure to abatacept.

Efficacy

Introduction

The data for the extended indication in MTX naïve patients with active RA at high risk of disease progression is based on a single Phase III study (IM101-023) which provided 2 year outcome data for clinical, radiographic, physical functioning and quality of life outcomes which are pivotal to the assessment of the sponsor's claim. The study had a 1 year double-blind (DB) controlled period followed by a second year of open-label treatment with abatacept. The two treatment periods for this pivotal study will be considered consecutively in this report.

Study IM101-043 which involved adult patients with RA who were MTX-IR also had a 1 year DB period followed by a second year open-label extension (OLE). For the first 12 months of this trial, patients had 3 treatment options, 2 of which were bDMARDs (infliximab or abatacept).

The sponsor also provided long term follow-up reports of efficacy from the OLE periods in 3 of the 5 original licensing studies which will be considered in an integrated manner depending on the pre-treatment characteristics of the subjects – MTX-IR population (Studies IM101-102 and IM101-100) and TNF-IR population (Study IM101-029). Studies IM101-031 and IM101-101 recruited adult patients with other DMARD treatment background but no efficacy updates were included for this submission. Study IM101-064, which had an uncontrolled open-label design, will be considered independently from the other OLE trials as it is a newly presented trial. This study involved adult subjects with active RA who were TNF-IR.

Additional efficacy data from 2 studies was also presented in the submission and these trials will be presented independently because of their heterogeneity. Study IM101-046 was an exploratory study in 56 adult patients with recent onset undifferentiated inflammatory arthritis which was at high risk of progression to RA (for example, positive anti-CCP2 antibodies at baseline). Study IM101-071 was a 6 month, placebo-controlled, Phase II, dose response study (abatacept 2 and 10 mg/kg) conducted in adult Japanese subjects with active RA who were MTX-IR.

Study IM101-023 (12 month status)

Study IM101-023 was a prospective, multicentre, randomized, double-blind, placebo-controlled study of 1 year duration with 2 treatment groups: placebo infusions + MTX and abatacept infusions (weight tiered dosing at 10 mg/kg) + MTX. It was planned that 500 subjects with early onset, erosive RA were to be randomly assigned in a ratio of 1:1 to each

of the treatment groups. Randomization was administered by a central randomization centre.

Study IM101-023 was designed with a 1 year double-blind controlled period followed by a second year of open-label treatment with abatacept 10 mg/kg + MTX. During the first year of the trial, patients received an infusion of either abatacept or placebo on Days 1, 15 and 29 and then every 28 days thereafter, for a total of 14 infusions. The dose of abatacept (10 mg/kg) used in this study was based on the results from previous dose-ranging studies and is consistent with the current approved dosing regimen in Australia. The abatacept dose assigned to each subject was determined by the patient's body weight (that is, 2 vials [500 mg] if less than 60 kg, 3 vials [750 mg] if 60-100 kg, or 4 vials [1000 mg] if greater than 100 kg). Concurrent administration of usual therapeutic doses of MTX were utilized in the trial with all patients receiving once weekly MTX (oral or parenteral) at a dose of at least 15 mg but not exceeding 20 mg. Subjects enrolled in this study were required to be MTX naive, or have very limited prior exposure to MTX (that is, they must have received MTX at a dose no greater than 10 mg/week for no more than 3 weeks in total and to have received no MTX in the 3 months prior to study entry). Subjects received MTX at a commencement dose of 7.5 mg/week and this was increased to 15 mg/week at Week 4, then to 20 mg/week at Week 8, where it was to be maintained until study completion. 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 to a minimum dose of 15 mg/week was permitted. All subjects were to receive concomitant oral folic or folinic acid to minimize MTX side effects.

Background corticosteroids (oral prednisone <10 mg/day or equivalent doses) and NSAIDs were allowed if use had been stable for at least 6 weeks prior to baseline. No adjustments in the dosing of MTX or corticosteroid were permitted for the first 6 months of the study except for the protocol specified titration changes in MTX dose. After 6 months, adjustments in MTX or corticosteroid therapy as well as the addition of one conventional DMARD (chloroquine, hydroxychloroquine, sulfasalazine, gold or azathioprine) were allowed at the investigator's discretion depending on the patient's disease status as assessed by tender and swollen joint counts. In addition to subjects being allowed to take a stable low dose of oral corticosteroids (oral prednisone <10 mg/day or equivalent doses), additional corticosteroid treatment was permitted in a limited manner. Simple analgesics like paracetamol were also allowed but were not to be taken within 12 hours of a joint assessment.

Assessment of clinical efficacy parameters was collected at screening; Days 1, 15 and 29; and every 28 days thereafter until Day 365. Radiographs of the hands, wrists and feet for the assessment of the primary radiographic 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. Radiographs were obtained at screening, and 6 and 12 months (or upon early withdrawal if not taken within the last 3 months). If no erosion on the screening x-rays was identified by the central readers, then the subject was not randomized into the study. All radiographs were scored by 2 radiologists according to the Sharp method, modified by Genant.[6]

[6] 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.

Eight amendments were made to the protocol during the study conduct, one of which is noteworthy as it influenced the recruited trial population. In particular, following implementation of the sixth study protocol amendment (17 May 2006), the inclusion criterion value of CRP was reduced from equal to or greater than 8 mg/L, to equal to or greater than 4.5 mg/L. In addition, the fifth amendment (dated 4 March 2006) changed the definition of remission in the primary outcome variable to include the use of the DAS28-CRP score rather than the original DAS score calculation methodology (ESR or CRP). The sponsor did a sensitivity analysis of the DAS28 remission outcome using ESR (rather than CRP) as the serum inflammatory marker which supported the outcome of the primary analysis.

Study Population Characteristics

Study IM101-023 was conducted in 99 (of a possible 113) study sites in North, Central and South America, as well as Europe, South Africa, Korea and Australia between July 2005 and February 2008. Subjects were required to be >18 years of age with RA of less than 2 years duration and typically MTX naïve. Limited previous exposure to MTX was permitted (as outlined previously) but a history of intolerance to MTX was an exclusion criterion. At study entry, patients were required to have active disease as defined by the 1987-revised ACR criteria which included >10 swollen joints out of 66 joints assessed, >12 tender joints out of 68 joints assessed, raised serum inflammatory markers (CRP>4.5 mg/L) and have at least one joint erosion on plain x-ray attributable to RA as determined by the central reading facility. In addition, subjects at screening were to be either positive to serum rheumatoid factor or have elevated levels of anti-CCP2 antibodies on blood testing. Significant patient exclusion characteristics limiting the external validity of the study population included: - history of severe chronic or recurrent bacterial infection, clinical or laboratory evidence of active or latent tuberculosis, Herpes zoster infection that resolved less than 2 months prior to enrolment, positive hepatitis B virus surface antigen or hepatitis C antibody, history of non-cutaneous malignancy within the last 5 years, significant underlying cardiac or pulmonary disease, history of alcohol or substance abuse, renal impairment (serum creatinine > x 2 upper limit of normal [ULN]), baseline serum aminotransferases > x 2 ULN and haematological abnormalities (for example platelet count < 100 x 10^9/L).

The studied population was clearly delineated and the 2 treatment groups were well matched with respect to demographic characteristics. Subjects had a median age of 51 (range: 18-79) years and were predominantly female (76.6-78.7% across the 2 treatment groups). Caucasians (82.7%) accounted for the major racial background followed by subjects of Asian ethnicity (7.9%). Patients were recruited from a diversity of geographical sites: 40.3% from South America, 36.0% from Europe, 16.9% from North America and 6.9% from the rest of the world.

Baseline disease characteristics of the participants were similar for the 2 treatment groups. Patients had a mean duration of RA of 6.5 (median 3.0, range: 0 – 39) months. Nearly two-thirds (63.7%, 324/509) of all subjects had RA for less than 6 months, while 13.8% (70/509) had RA for 6-12 months and 22.6% (115/509) had RA for > 12 months. Over 96% 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. A slightly higher proportion of subjects in the abatacept treatment group had positive anti-CCP2 antibodies (92.2% [236/256] for abatacept + MTX compared to 85.8% [217/253] for placebo + MTX).

Baseline disease parameters reflect severely active disease and were comparable among the 2 treatment groups. The baseline median tender joint count was 28 (of a possible maximum of 68) and the median swollen joint count was 20 (of a possible maximum of

66). The overall activity score, as measured by the mean DAS28-CRP score, was 6.2-6.3, indicating high disease activity. As a validated marker of disease progression, CRP values were high (mean 31-36 mg/L). In addition, the mean HAQ-DI scores were high at 1.7 which is consistent with a significant functional impairment due to a severely active disease state. Because the study aimed to recruit patients with early disease duration, subjects in general had a modest quantity of established joint damage (mean mTSS of 7.1 [range: 0 - 57.3], mean erosion score of 5.1 [range: 0 - 36.9] and mean joint space narrowing (JSN) score of 2.0 [range: 0 - 28.2]).

The treatment groups were well-balanced with respect to previous and concomitant treatments for RA. Oral corticosteroid therapy (mean dose of 3.4 mg/day) at baseline was recorded in 36.7% (94/256) of subjects in the abatacept + MTX group and 32.8% (83/253) of patients in the placebo + MTX arm at study entry. Most patients (82%) in both treatment groups were taking NSAID medication at study entry. In the second 6 months of the 1 year study, the utilization of NSAID reduced to 73% for both treatment groups. More than half of the study population had at least 1 medical problem other than RA with the most common concurrent conditions being hypertension (34.8%), depression (9.6%) and gastro-oesophageal reflux disease (7.3%). At baseline, similar proportions of patients in each treatment group had significant risk factors for atherosclerosis including tobacco use (24.8%) and diabetes mellitus (6.4%).

Primary Efficacy endpoints

The 2 co-primary endpoints in Study IM101-023 were: -

- Clinical – proportion of subjects in each of treatment groups who achieved DAS28-CRP remission (score < 2.6) at Week 52,
- Radiographic – the mean change in the Genant-modified Total Sharp Score (mTSS) from screening to Week 52 between the 2 treatment groups.

Secondary Efficacy endpoints

Secondary efficacy endpoints compared between the 2 treatment groups at 12 months included:

- Clinical signs and symptoms - proportion of subjects achieving an ACR50 response, the proportion of subjects achieving major clinical response (MCR, as defined by an ACR70 response maintained for at least 6 consecutive months) and the mean change from baseline in the DAS28-CRP score;
- Radiographic – mean change from baseline in the erosion score and Joint Space Narrowing (JSN) score and the proportion of subjects with no x-ray progression (defined as a change in the erosion score of zero or lower);
- Functional - proportion of patients achieving an improvement of at least 0.30 units in the HAQ-DI; and
- Quality of Life - the mean change from baseline in the Physical and Mental Health Components of the SF-36.

Supporting or Exploratory Endpoints

Several supporting or exploratory parameters relating to the assessment of clinical, radiographic and quality of life outcomes were also included in the study report. In particular, the proportion of patients achieving an ACR20, ACR70 or ACR90 response at 12 months was also explored, as well as the proportion of subjects who achieved a complete articular response (CAR, defined as a continuous 6 month period of 100% improvement in

both the tender and swollen joint counts at 12 months) and extended major clinical response (EMCR, defined by 9 months of consecutive ACR70 response at 12 months). Additional quality of life outcomes were also assessed such as changes in the level of fatigue and activity limitation.

Explanation and validity of the major efficacy variables

In general, the selected endpoints in Study IM101-023 use well-accepted, validated metrics that have served as the basis of previous published studies, prior regulatory approvals and are consistent with published guidelines. 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 in disease activity have been validated.

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 IM101-023 pre-specified both of these variables as efficacy endpoints.

There are 3 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 -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 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.

In addition to the mTSS score, this study has evaluated the proportion of subjects with no radiographic deterioration (defined as change from baseline of equal to or less than 0 in the mTSS) over 104 weeks of therapy. This secondary radiographic endpoint is an important supporting analysis for the evaluation of the drug's 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 relevant EMA document states that for agents claiming to prevent structural joint damage, it is recommended to explore 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. Hence, the design of Study IM101-023 does not meet the minimum requirement for this indication in that the maintenance of treatment effect should be demonstrable to 2 years of follow-up, in addition to a double-blind data collection period for a minimum of 1 year. Furthermore, the FDA has 2 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.

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.

Statistical methods

A total of 500 randomized subjects allocated in 1:1 ratio yielded 99% power to detect a difference of 20% in the DAS28-CRP remission rate at 12 months between the 2 treatment groups at the 5% level (2-tailed test). The power calculation anticipated a response rate of 15% in the placebo + MTX group and an overall patient drop-out rate of 15%. Based on the hierarchical testing procedure for the co-primary endpoints, this sample size also allowed the detection of a treatment difference of 1.6 units (standard deviation of 5 units) at 90% power between the control group and abatacept arm for the mean change in mTSS at 12 months.

The analysis of clinical efficacy variables was performed with the intent to treat (ITT) population, defined as all randomized patients who received at least a part of any study infusion. Comparison at 12 months of the DAS28-CRP remission rate, ACR 50 response, MCR and HAQ response rate was performed with continuity corrected Chi-square test. Point estimates of the remission rates for the 2 treatment groups and the corresponding 95% confidence intervals (CI) were provided. For patients who prematurely withdrew from the study, categorical clinical variables were recorded as non-responder status for all time points thereafter in the study. For patients with missing values (not due to premature discontinuation), a response was imputed for the current visit according to pre-defined rules which either incorporated the data from the immediately prior and subsequent visit to generate a response, or the 2 previous visits if the missing value was the 12 month visit. For a positive response to be recorded both data points had to have a positive result, otherwise the missing value was imputed as negative. Three sensitivity analyses for the DAS28-CRP remission rate were also performed accounting for missing data using alternative imputation assumptions that were biased in favour of the placebo + MTX group (for example “worst case sensitivity analysis”).

The analysis of the mean change from baseline to Week 52 in the DAS28-CRP score and SF-36 values was performed using an analysis of covariates (ANCOVA) model adjusted for treatment group. Missing data for these variables were handled by the Last Observation Carried Forward (LOCF) methodology.

Radiographic endpoints were primarily analysed on the modified intention-to-treat (mITT) population principle which included all randomized patients with a screening and at least 1 post-baseline set of x-rays in the first year of follow-up (either at 26 or 52 weeks, or the discontinuation visit). A non-parametric ANCOVA was employed for the primary radiographic analysis. Baseline radiographic scores and changes from baseline were ranked and the model included the rank score for change from baseline as the dependent variable with treatment group as a main effect and the rank score for baseline as an additional covariate. 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. Again, sensitivity analyses were also performed accounting for missing data using alternative imputation assumptions (for example using percentile and inter-quartile rules).

Patient Disposition and Completion Status

Of the 1052 patients who consented to participate in Study IM101-023, a total of 511 were randomized but 2 subjects did not receive any study medication and were not included in the ITT analysis. Hence, the final efficacy population of 509 patients was comprised of 253 who were randomized to and received at least 1 dose of infusion study treatment with placebo infusions + MTX and 256 allocated to abatacept + MTX therapy. In addition to the enrolled subjects, 541 patients underwent screening but were not subsequently randomized to study treatment because they either failed to meet eligibility criteria (such

as insufficient elevation in baseline CRP or failure to show joint erosion on x-ray) or they subsequently withdrew consent. At 1 year of follow-up, 90.6% (232/256) of patients randomized to abatacept + MTX and 89.7% (227/253) of subjects randomized to placebo + MTX completed treatment to this time point. In total, 5.1% (13/253) of patients assigned to placebo infusions + MTX and 4.3% (11/256) of subjects in the abatacept treatment group withdrew for non-safety reasons prior to Week 52. Withdrawal of consent was the most common reason for premature withdrawal for non-safety reasons in the abatacept arm (7 subjects versus 3 placebo + MTX patients). Insufficient therapeutic response led to the discontinuation of 8 patients (3.1% of 253) in the placebo + MTX group but no patients in the abatacept group withdrew because of lack of efficacy. The mean duration of exposure for the abatacept + MTX was 350 days which is similar to that observed in the placebo + MTX group (345 days). In addition, similar proportions of patients in both groups received 14 infusions (76% for abatacept + MTX versus 74% for placebo + MTX) as well those who received 3 or fewer infusions (3% for both groups).

Result for primary efficacy variables

Clinical

The primary clinical endpoint of the percentage of subjects achieving remission (defined as DAS28-CRP < 2.6) at 12 months was significantly higher for patients in the abatacept + MTX treatment group (41.4% [106/256]; 95% CI 35.4, 47.4) compared with the placebo + MTX arm (23.3% [59/253]; 95% CI 18.1, 28.5; estimated treatment difference of 18.1 [95% CI 9.6, 26.6]; p<0.001) (Table 1). Subgroup analyses of DAS28-CRP remission rate according to age, gender, ethnicity, geographic region, duration of RA and baseline CRP were consistent with the primary result although not sufficiently powered to be of statistical significance. However, patients who were negative for RA autoantibodies (RF or anti-CCP2) did not demonstrate any differences in response between the 2 treatment groups, although the absolute number of seronegative subjects involved in the trial was very small. The results of the sensitivity analyses (using the worst case sensitivity model) were consistent in demonstrating that treatment with abatacept + MTX resulted in a significantly higher rate of DAS28-CRP remission compared with placebo + MTX therapy.

Table 1: Study IM101-023

Efficacy Endpoints at Month 12	ABA + MTX N = 256	PLA + MTX N = 253	Estimate of/Adjusted Difference (95% CI)	p-value
Primary Endpoints:				
Remission rate (DAS 28-CRP < 2.6); n (%)	106 (41.4)	59 (23.3)	18.1 (9.6, 26.6)	< 0.001
Mean change from baseline in radiographic total score (SD)	0.63[a] (1.74)	1.06[a] (2.45)	NA	0.040
Signs and Symptoms:				
Proportion of subjects with ACR 50 response; n (%)	147 (57.4)	107 (42.3)	15.1 (6.0, 24.2)	< 0.001
Proportion of subjects with MCR; n (%)	70 (27.3)	30 (11.9)	15.5 (8.2, 22.8)	< 0.001
Adjusted mean change from baseline in DAS 28-CRP (SE)	-3.22[b] (0.09)	-2.49[c] (0.09)	-0.73 (-0.98, -0.48)	< 0.001
Structural Damage:				
Mean change from baseline in radiographic erosion score	0.50[a] (1.39)	0.89[a] (2.24)	NA	0.033
Mean change from baseline in radiographic JSN	0.13[a] (0.53)	0.17[a] (0.54)	NA	0.353
Physical Function:				
Proportion of subjects with HAQ response rate; n (%)	184 (71.9)	157 (62.1)	9.8 (1.3, 18.4)	0.024
Health-related Outcomes:				
Adjusted mean change from baseline in PCS (SE)	11.68[d] (0.62)	9.18[e] (0.63)	2.50 (0.77, 4.23)	0.005
Adjusted mean change from baseline in MCS (SE)	8.15[f] (0.64)	6.34[g] (0.64)	1.81 (0.03, 3.60)	0.046

[a] n = 242; [b] n = 253; [c] n = 251; [d] n = 254; [e] n = 249

Radiographic

Treatment with abatacept + 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 52 with a mean change in mTSS of 0.63 (standard deviation [SD] 1.74; Baseline mean 7.50) for abatacept + MTX versus 1.06 (SD 2.45; Baseline mean 6.67) for placebo infusions + MTX; p=0.040) (Table 1). The primary analysis of radiographic data included x-ray assessments for 95.7% (242/253) of patients in the control group and 94.5% (242/256) in the abatacept arm. For patients with incomplete datasets, linear extrapolation was used as an imputation method. The sponsor did not specify the relative proportions of subjects in the primary x-ray analysis that had observed change as opposed to imputed data, which is an important consideration in interpreting the robustness of the analysis.

The favourable radiological result for abatacept + MTX treatment versus MTX alone was seen across some of the explored subgroups (consisting of at least 10% of the total study population) including baseline CRP and ethnicity. However, for patients aged > 65 years and in the upper quartile for disease duration, a higher total mean change in mTSS was observed for those who received abatacept + MTX. Moreover, a comparable mean change

in the mTSS was observed between the 2 treatment groups for subjects recruited from South America and women aged < 50 years. The inconsistency in favourable outcome for abatacept + MTX for all of the patient subgroups with sufficient numbers diminishes the validity of the primary analysis as a treatment related effect. However, similar results for the primary radiological efficacy outcome were obtained for the sensitivity analyses performed using different imputation rules, such as utilizing a series of upper and lower percentiles of the observed changes from baseline in total mTSS, erosion scores and JSN scores.

Results for secondary efficacy variables

Clinical

At 12 months, an ACR50 response was achieved by a significantly higher proportion of subjects in the abatacept + MTX group (57.4% [147/256]; 95% CI 51.4, 63.5) compared with the placebo + MTX arm (42.3% [107/253]; 95% CI 36.2, 48.4; estimated treatment difference of 15.1 [95% CI 6.0, 24.2]; p<0.001) (Table 1).

Major clinical response (MCR) by Month 12 (as defined by an ACR70 response maintained for at least 6 consecutive months) was seen in a higher proportion of patients treated with abatacept + MTX (27.3% [70/256]; 95% CI 21.9, 32.8) than patients treated with placebo + MTX (11.9% [30/253]; 95% CI 7.9, 15.8; estimated treatment difference of 15.5 [95% CI 8.2, 22.8]; p<0.001) (Table 1).

Treatment with abatacept + MTX resulted in greater reductions in disease activity compared with MTX monotherapy as evaluated by the mean change from baseline in the DAS28-CRP at Week 52 with a mean change in DAS of -3.22 (Baseline mean 6.30; 12 month mean 3.07; n=253) for abatacept + MTX versus -2.49 (Baseline mean 6.25; 12 month mean 3.78; n=251) for placebo infusions + MTX (p<0.001 for the adjusted treatment difference of -0.73 [95% CI -0.98, -0.48]) (Table 1).

Radiographic

Analysis of the radiographic data at 12 months using the components of the mTSS demonstrated a treatment effect in favour of abatacept + MTX compared with MTX alone for the mean change in erosion score only. The mean change from baseline to 52 weeks in erosion score and JSN score is presented in Table 2. In the mITT population (n=242 for both groups), patients treated with abatacept + MTX had a statistically significant reduction (p=0.033) in erosion score at 12 months (mean change of 0.50; baseline mean 5.48) compared with subjects randomized to placebo + MTX (mean change at 12 months of 0.89; baseline mean 4.81).

Table 2: Study IM101-023 Secondary Radiographic Endpoints at 1 Year

		Abatacept N = 256	Placebo N = 253
Erosion Score	n	242	242
	Baseline Mean (SD)	5.48 (6.15)	4.81 (5.46)
	Baseline Median (Range)	2.94 (0.00, 29.08)	3.15 (0.00, 36.89)
	Mean Change from Baseline (SD)	0.50 (1.39)	0.89 (2.24)
	Median Change from Baseline (25%, 75%)	0.00 (0.00, 0.77)	0.00 (0.00, 1.04)
	p-value	0.033 *	N/A
Joint Space Narrowing Score	n	242	242
	Baseline Mean (SD)	2.03 (3.99)	1.86 (3.95)
	Baseline Median (Range)	0.24 (0.00, 28.17)	0.47 (0.00, 28.01)
	Mean Change from Baseline (SD)	0.13 (0.53)	0.17 (0.54)
	Median Change from Baseline (25%, 75%)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)
	p-value	0.353	N/A

Genant-modified Sharp Scoring System.
n is the number of subjects with baseline and post-baseline measurements.
Change from baseline = Post-baseline - Baseline value.
**p<0.001, ^p<0.01, *p<0.05: probability for comparison of change in radiographic scores between abatacept and placebo.
P-value is based on a nonparametric ANCOVA model.
N/A = not applicable.

The mean change from baseline to 52 weeks in the JSN score demonstrated that patients treated with abatacept + MTX had no statistically significant lower JSN score (mean change of 0.13; baseline mean 2.03) compared with subjects randomized to placebo + MTX (mean change at 12 months of 0.17; baseline 1.86; p=0.353 for treatment difference). No progression of bone erosion was defined as a change from baseline in the erosion score of equal to or less than 0. At 12 months of follow-up, a higher proportion of patients randomized to abatacept + MTX (155/242; 64.0% [95% CI 58.0, 70.1]) demonstrated no erosive progression versus 133 of 242 subjects (55.0%; 95% CI 48.7, 61.2) in the control group but this result did not reach statistical significance. The calculated difference between the 2 treatment groups for this endpoint was 9.1% (95% CI -0.1, 18.3).

Functional

Another secondary endpoint was the proportion of patients in each of the treatment groups who achieved an improvement of at least 0.30 units from baseline in the HAQ-DI at Week 52. A higher percentage of subjects in the abatacept + MTX treatment group achieved this outcome with 184/256 (71.9%; 95% CI 66.4, 77.4) for abatacept + MTX versus 157/253 (62.1%; 95% CI 56.1, 68.0) for placebo infusions + MTX. The estimate of difference between the 2 treatment groups for this outcome is 9.8% (95% CI 1.3, 18.4) which reached statistical significance (p=0.024).

Quality of Life

Regarding the SF-36 results, the mean baseline scores for the Physical Component Score (PCS) and Mental Component Score (MCS) were similar between the 2 treatment groups (mean PCS of 30.70-30.88 and mean MCS of 40.28 - 41.59). The mean PCS improved across both treatment groups during the 52 week study but were higher in those who received abatacept (mean change of 11.68 [SD 0.62]) compared with patients who received placebo + MTX (mean change of 9.18 [SD 0.63]). The adjusted difference for change in the PCS from baseline to 12 months between the treatment groups was 2.50 (95% CI 0.77, 4.23) which reached statistical significance (p=0.005). The submission did not contain an analysis of the proportion of subjects who achieved a clinically significant improvement (defined as a change >5) in the PCS at Week 52. The mean change from baseline to Week 52 in the SF-36 MCS was higher for patients randomized to abatacept + MTX (mean change of 8.15 [SD 0.64]) than for subjects allocated to placebo + MTX (mean change of 6.34 [SD 0.64]). The

adjusted difference for change in the MCS from baseline to 12 months between the treatment groups was 1.81 (95% CI 0.03, 3.60) which reached statistical significance (p=0.046). A clinically meaningful improvement in the SF-36 MCS is considered to be a change from baseline of >5. Again, the sponsor did not present an analysis of those subjects who reached a certain level of clinically significant improvement in MCS.

Supporting or Exploratory Endpoints

A summary of the ACR 20, 50, 70 and 90 response rates at Week 52 is presented in Table 3. The ACR 20 response rate at 12 months was 76.2% (195/256) of subjects who received abatacept + MTX compared to 62.1% (157/253) of patients who received placebo + MTX (p<0.001). The proportion of ACR 70 responses at Week 52 was 42.6% (109/256) of subjects who received abatacept + MTX compared to 27.3% (69/253) of patients who received placebo + MTX (p<0.001). The individual ACR core set parameters (such as the Physician and Patient Global VAS) followed the same results trend as the overall ACR response criteria with greater mean decreases consistently observed for all the variables for subjects in the abatacept + MTX group compared with the placebo + MTX group.

Table 3: Study IM101-023 ACR responses at 52 weeks

		Abatacept N = 256	Placebo N = 253
ACR 20	Number of subjects n (%)	195 (76.2%)	157 (62.1%)
	95% CI for ACR response rate	(71.0, 81.4)	(56.1, 68.0)
	Estimate of difference (95% CI)	14.1 (5.7, 22.5)	N/A
	p-value	<0.001 **	N/A
ACR 50	Number of subjects n (%)	147 (57.4%)	107 (42.3%)
	95% CI for ACR response rate	(51.4, 63.5)	(36.2, 48.4)
	Estimate of difference (95% CI)	15.1 (6.0, 24.2)	N/A
	p-value	<0.001 **	N/A
ACR 70	Number of subjects n (%)	109 (42.6%)	69 (27.3%)
	95% CI for ACR response rate	(36.5, 48.6)	(21.8, 32.8)
	Estimate of difference (95% CI)	15.3 (6.6, 24.0)	N/A
	p-value	<0.001 **	N/A
ACR 90	Number of subjects n (%)	42 (16.4%)	17 (6.7%)
	95% CI for ACR response rate	(11.9, 20.9)	(3.6, 9.8)
	Estimate of difference (95% CI)	9.7 (3.7, 15.6)	N/A
	p-value	0.001 ^	N/A

**p<0.001, ^p<0.01, *p<0.05: probability for testing the difference between abatacept and placebo.
P-value is based on a continuity corrected chi-square test.
N/A = not applicable.

An Extended Major Clinical Response (EMCR) was prospectively defined by the sponsor as maintenance of an ACR70 response over a continuous 9 month period. A higher proportion of patients treated with abatacept + MTX (28/256; 10.9%; 95% CI 7.1, 14.8) compared with those in the placebo + MTX group (12/253; 4.7%; 95% CI 2.1, 7.4), an estimate of difference of 6.2% (95% CI 1.1, 11.3).

Complete Articular Response (CAR) was defined by the sponsor as 100% improvement in both the tender and swollen joint counts for 6 consecutive months. A higher percentage of patients in the abatacept + MTX achieved this outcome by the end of 12 months (16/256; 6.3% [95% CI 3.3, 9.2] for abatacept versus 3/253; 1.2% [-0.1, 2.5] for control, an estimate of difference of 5.1% [95% CI 1.4, 8.8]).

Treatment with abatacept + MTX was associated with a higher proportion of patients achieving low disease activity (defined as a DAS28-CRP score of equal to or less than 3.2) compared to placebo infusions + MTX. At Week 52, 54.3% (139/256; 95% CI 48.2, 60.4) of patients treated with abatacept + MTX reached low disease activity versus 36.8%

(93/253; 95% CI 30.8, 42.7) of subjects in the placebo + MTX group. The estimated difference between the treatment groups for this outcome was 17.5 (95% CI 8.5, 26.6) which reached statistical significance (p<0.001).

Patients in the abatacept + MTX group reported a greater reduction in fatigue (as assessed by a 100 mm fatigue VAS) at Day 365 compared to subjects who received placebo + MTX. At baseline, the mean fatigue scores were similar at 66.29 (SD 23.63) for abatacept + MTX (n=256) and 64.52 (SD 26.07) for placebo + MTX (n=253). At Week 52, the mean change in fatigue score for patients in the abatacept + MTX treatment group was -34.1 (SD 1.58; n=254) and -27.1 (SD 1.59; n=249) for the placebo + MTX group. The adjusted treatment difference was -6.95 (95% CI -11.4, -2.54). The minimal clinically important difference in fatigue score is not defined.

Activity limitation was also measured during the study as the number of days in the past 30 days whereby a subject was unable to perform his or her usual activities because of RA. At Day 365, subjects treated with abatacept + MTX were able to increase their participation in usual activities for a greater time period than patients who received placebo + MTX. The adjusted mean change from baseline to Day 365 for patients in the abatacept + MTX group was -10.4 (baseline mean of 16.10; n=254) compared with -8.22 for subjects in the control arm (baseline mean of 15.08; n=249). The adjusted treatment difference was -2.19 (95% CI -3.63, -0.74) but no formal statistical analysis or definition of clinically important difference in activity was defined.

Efficacy conclusions

> The 12 month efficacy data from Study IM101-023 indicates that abatacept + MTX is statistically superior in a clinically meaningful manner to continued MTX monotherapy in reducing the signs and symptoms of RA (as assessed by ACR and EULAR criteria), including the proportion of patients achieving DAS28-CRP remission criterion, in a group of MTX naïve patients with early RA who had high disease activity at baseline and who were at high risk of disease progression. In addition, the rate of radiographic progression over 52 weeks was significantly less for patients who received abatacept + MTX compared with those given placebo infusions + MTX.

Open-label extension of Study IM101-023 (2 year status)

Patients treated with either abatacept + MTX or placebo + MTX, who completed the 12 month double-blind period of Study IM101-023 were allowed to receive open-label treatment with abatacept (10 mg/kg) thereafter in conjunction with continued MTX (10-20 mg/week). The submission contained a 2 year status report on the open-label extension (OLE) phase. Of the 99 study centres that enrolled subjects in the initial 12 month trial, 87 continued in the OLE period – 43 in Europe, 19 in USA, 7 in Korea, 6 in Canada, 5 in South Africa and 2 in Australia. The primary objective of the OLE study was to assess long-term safety and tolerability; however, efficacy measures (of the same outcome type in the controlled period) were also collected to determine the durability of clinical benefit. Clinical efficacy parameters were assessed every 12 weeks in the second year of the study while additional plain radiographs were obtained only at 24 months after initial randomization.

In the OLE period patients were expected to receive abatacept at a dose of 10 mg/kg every 4 weeks. The body weight recorded at Day 365 (at the end of the first year of Study IM101-023) was used to calculate the abatacept dose throughout the extension phase. Decreases to other treatment (corticosteroids, MTX or other DMARDs) were permissible in the OLE phase if safety concerns developed and efficacy was being maintained. All patients who entered the OLE phase were taking concurrent MTX at a mean weekly dose of 18.5 mg. At

the conclusion of Year 2, 88% of subjects were continuing to receive weekly MTX 15-20 mg (mean weekly dose at 24 months reduced slightly to 17.5 mg).

Subjects were also allowed to continue taking stable background doses of NSAIDs or oral corticosteroids throughout the study. The proportion of patients who continued to receive these adjunctive therapies in Year 2 was comparable for both groups during the OLE phase (80.4% for NSAIDs and 54.7% for low dose corticosteroids), which is also similar to that observed in Year 1. Analgesics were permissible at all times, except within 12 hours before a joint count assessment. Investigators were also allowed to commence one of the following DMARDs: chloroquine, hydroxychloroquine, parenteral gold, sulfasalazine or azathioprine.

Study Population

The characteristics of the patients recruited into the OLE phase of Study IM101-023 are well described in the assessment of the controlled phase of the study. The majority of patients treated in the OLE were Caucasian (82.8%, 380/459) and female (77.1%, 354/459) with a mean age of 49.5 years. The mean duration of RA was 6.5 months. Subjects treated in the OLE originally had a higher level of baseline disease activity at study entry into the double-blind period based on the mean number of tender (30.9) and swollen (22.4) joints. Most patients were seropositive for RF (96.5%) and anti-CCP2 antibodies (90.2%). The mean baseline HAQ-DI score was high at 1.7.

Patient Disposition and Drug Exposure

All 459 subjects (232 on abatacept + MTX and 227 on placebo + MTX in year 1) who completed the double-blind treatment period received at least 1 dose of abatacept in the OLE. Most (94.3%, 433/459) completed the second year of treatment and follow-up, although 5.7% (26/459) prematurely discontinued before the end of Year 2. A small proportion of patients (0.7%, 3/459) discontinued due to insufficient response during the OLE phase. Other non-safety reasons for withdrawal from the OLE population were withdrawal of consent (4 patients) and failure to return for follow-up (4 subjects).

During the combined 2 year treatment period for Study IM101-023, the mean exposure to abatacept was 18.7 (median 17.1; range 1.9 – 25.7) months. On average, patients received 19.4 infusions (range: 1-27) over the 2 year study period. The proportion of patients who had at least 24 months of follow-up was 48.6% (223/459) while another 44.4% (204/459) completed 12-18 months of observation. A total of 20 (4.4% of 459) patients missed 2 infusions during the OLE and 2 patients missed 3 non-consecutive infusions.

Efficacy Parameters

At 24 months of treatment, the 2 original treatment groups were assessed for the following protocol specified secondary outcomes:

1. Proportion of patients achieving clinically significant improvements in HAQ-DI, defined as a reduction of at least 0.30 units from baseline and
2. Mean change from baseline in total mTSS, erosion score and JSN score.

In addition, tertiary defined objectives after 24 months of follow-up included:

1. Proportion of patients achieving DAS28-CRP remission and EULAR defined Low Disease Activity (LDA),
2. Proportion of patients achieving ACR 20, 50, 70 and 90 response,
3. Proportion of patients achieving MCR, EMCR and CAR (as previously defined) and

4. Mean change from baseline in various quality of life outcomes such as the SF-36, Fatigue VAS and activity limitation.

Statistical Analysis and Data Handling Methods

No hypothesis testing or power calculation was done in the OLE of Study IM101-023. Clinical efficacy outcomes such as the proportion of subjects achieving DAS28-CRP remission or various levels of ACR response (20, 50 or 70) were summarized with point estimates and 95% confidence intervals according to the patient's original randomized treatment assignment. For the radiographic analysis, readers remained blinded to the sequence of films and treatment during the second year of the study. In addition, the x-rays taken during the first year of the study (baseline and 6 and 12 months) were re-read as part of a second reading campaign. Changes in mTSS, erosion score and JSN score were summarized descriptively by original treatment group.

Pre-defined rules were used for the handling of missing data depending on the efficacy outcome. For ACR responses (20/50/70) and DAS28 calculation, patients who withdrew were classified as non-responders at all protocol scheduled visits following discontinuation. However, for subjects with missing values at a given visit (but not due to premature discontinuation), responses were imputed depending on their immediately prior and subsequent visit results. For all the radiographic outcomes evaluated at 24 months, no imputation methodology was included in the study report and results were based on observed assessments.

Efficacy results

Secondary

The proportion of patients originally treated with abatacept + MTX during Year 1 who maintained clinically significant improvements in their HAQ-DI score (that is, a reduction of 0.30 units from baseline) during Year 2 was high at 94.7% (178/188) at 18 months and 94.1% (177/188) at 24 months. For patients treated with placebo + MTX during the first 12 months, the rate of categorical HAQ response achievement was maintained but not improved upon with the addition of abatacept to MTX (rather than placebo infusions) in Year 2 of the study. That is, the sustained HAQ response rate was 93.4% (156/167) at 18 months and 92.8% (155/167) at 24 months. The mean improvement from baseline (Day 1) for HAQ-DI was slightly better at 24 months (-1.01) compared to 12 months (-0.81) in subjects who switched from placebo to abatacept infusions in Year 2. Patients treated with abatacept +MTX from the study outset had a similar mean improvement in HAQ-DI at 12 months (-1.01) as they did at 24 months (-1.06).

Analysis of the radiographic data at 24 months using the mTSS and its components indicated that less progression of structural damage following 2 years of treatment with abatacept + MTX compared with subjects initially treated with MTX alone who then changed to abatacept + MTX in Year 2. Of the 459 subjects treated in the OLE, 405 (213 of a possible 232 from the original abatacept + MTX group and 192 of a possible 227 from the initial placebo + MTX arm) had the minimum radiographic dataset (Day 1 and Month 24 x-ray) to be included in this analysis. The mean change from baseline to 104 weeks in total mTSS, erosion score and JSN score is presented in Table 4. Patients originally treated with abatacept + MTX had a mean change from baseline of 0.59 units in erosion score at 24 months (baseline mean 5.91) compared with 1.40 units for subjects randomized to placebo + MTX (baseline mean 5.49). The mean change from baseline to 104 weeks in the JSN score demonstrated that patients treated with abatacept + MTX for 2 years had a slightly lower JSN score (mean change of 0.25; baseline mean 1.83) compared with subjects randomized to placebo + MTX (mean change of 0.24; baseline 1.75). Regarding the total score, patients treated with abatacept + MTX for 2 years had a mean change from

baseline of 0.84 units at 24 months (baseline mean 7.73) compared with 1.75 units for subjects randomized to placebo + MTX (baseline mean 7.24). The result for the total mTSS which reflected a treatment difference for 1 versus 2 years of abatacept + MTX was primarily accounted for by the difference in mean change for erosion score.

Table 4: Study IM101-023 Secondary Radiographic Endpoints at 2 Years

		Abatacept N = 232	Placebo N = 227
Erosion Score	n	213	192
	Baseline Mean (SD)	5.91 (6.48)	5.49 (5.85)
	Baseline Median (Range)	3.41 (0.00, 30.41)	3.55 (0.00, 37.32)
	Mean Change from Baseline (SD)	0.59 (2.31)	1.40 (3.08)
	Median Change from Baseline (25%, 75%)	0.00 (0.00, 0.78)	0.25 (0.00, 1.83)
Joint Space Narrowing Score	n	213	192
	Baseline Mean (SD)	1.83 (3.82)	1.75 (3.92)
	Baseline Median (Range)	0.24 (0.00, 25.57)	0.00 (0.00, 23.99)
	Mean Change from Baseline (SD)	0.25 (1.03)	0.34 (0.99)
	Median Change from Baseline (25%, 75%)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)
Total Score	n	213	192
	Baseline Mean (SD)	7.73 (9.50)	7.24 (8.89)
	Baseline Median (Range)	3.91 (0.00, 49.19)	4.17 (0.00, 61.31)
	Mean Change from Baseline (SD)	0.84 (3.22)	1.75 (3.59)
	Median Change from Baseline (25%, 75%)	0.00 (0.00, 1.00)	0.26 (0.00, 2.36)

Genant-Modified Sharp Scoring System.
Analysis includes all subjects with observed assessments collected at baseline and in the Day 729 window.
n is the number of subjects with both baseline and post-baseline measurements.
Change from baseline = Post-baseline - Baseline value.
Treatment groups represent treatment received in the double-blind period.

Within the group who received abatacept + MTX for 2 years, less radiographic progression was observed in the OLE period compared to the double-blind phase. This was assessed using the change in the total score from baseline to 12 months (0.65 units; n=211) versus the change from Month 12 to 24 for the mTSS (0.18 units; n=207; p<0.001).

No progression of bone erosion was defined as a change from baseline in the erosion score of equal to or less than 0. At 24 months of follow-up, a higher proportion of patients randomized to abatacept + MTX (125/213; 58.7% [95% CI 52.1, 65.3]) demonstrated no erosive progression compared with 92 of 227 subjects (47.9%; 95% CI 40.9, 55.0) in the group who first started treatment with placebo + MTX and then switched to abatacept + MTX in Year 2. A similar result was observed for the proportion of patients with no radiographic progression defined by the change in mTSS and JSN, using the same (equal to less than 0 units) or a higher cut-off level of x-ray change (<0.5 units).

Tertiary

The proportion of patients treated with abatacept + MTX who achieved DAS remission (DAS28-CRP < 2.6) and LDA at end of 12 months of therapy was largely maintained with extended treatment duration to 24 months. For example, the proportion of patients maintaining DAS remission was 86.0% (92/107) at Month 18 and 81.3% (87/107) at 24 months. Improved DAS remission and LDA response rates were observed with the original placebo + MTX group after adding abatacept infusions in the OLE, so that by Month 3 (remission rate 40.1% [91/227] and LDA rate 59.0% [134/227]) and Month 12 (remission rate 44.5% [101/227] and LDA rate 60.4% [137/227]) of the OLE this group had response rates similar to that observed with the original abatacept + MTX group. Improvements in the DAS28-CRP score, as reflected by the mean change from baseline (Day 1), were observed at the end of the double blind period (-3.36 at 12 months) and maintained at the end of the OLE phase (-3.79 at 24 months) for patients who received 2 years of therapy with abatacept + MTX. For patients in the original placebo + MTX group, the mean

improvement in DAS28-CRP score was improved when they initiated abatacept in the OLE (-2.58 at Month 12 and -3.52 at Month 24).

In general, patients who continued with a second year of treatment with abatacept + MTX demonstrated either a similar or improved rate of ACR response. For example, the rates of ACR50 response observed with the original abatacept + MTX group at the end of the double-blind period (64.7% [150/232] at 12 months) were improved at the end of Year 2 (74.1% [172/232] at 24 months). Improved rates of ACR response were also seen for the original placebo + MTX group during Year 2 when abatacept was added to MTX. In particular, the rate of ACR50 response improved from 50.2% (114/227) at 12 months to 67.0% (152/227) at 24 months.

The proportion of subjects achieving major clinical response (an ACR70 response for at least 24 consecutive weeks) was significant at 52.2% (121/232) at 24 months for the group who received abatacept + MTX from the study commencement. Improved MCR rates were also achieved for the original placebo + MTX group at 18 (27.3%, 62/227) and 24 months (48.5%, 110/227) once switched to abatacept infusions in Year 2. The MCR response rates at the end of the OLE in this group are similar to the original abatacept + MTX group.

An EMCR was observed at 24 months in 44.8% (104/232) of subjects from the original abatacept + MTX treatment arm. The rates of EMCR for the original placebo + MTX group improved over the second year of follow-up (16.7% [38/227] at 18 months and 38.3% [87/227] at 24 months) and eventually approximated that observed for those allocated to abatacept + MTX from the study outset.

The rate of CAR observed in the abatacept + MTX group was 28.9% (67/232) at 24 months. Improved CAR rates were recorded for the original placebo + MTX group at 18 months (7.9%, 18/227) and 24 months (22.5%, 51/227).

The mean improvements from baseline (Day 1) in the PCS and MCS of the SF-36 Questionnaire achieved at 12 months (mean change of 12.64 from a baseline of 30.71 for PCS and mean change of 8.77 from a baseline of 40.52 for MCS; n=230) for subjects in the original abatacept + MTX group were maintained to the end of the second year of treatment (mean change of 14.22 from a baseline of 30.82 for PCS and mean change of 9.55 from a baseline of 40.20 for MCS; n=218). The mean improvements observed in the original placebo + MTX group at the end of the double-blind period (mean change of 9.67 from a baseline of 30.72 for PCS and mean change of 6.42 from a baseline of 42.03 for MCS; n=227) increased, particularly for the PCS, in the OLE phase when abatacept was added (mean change of 14.38 from a baseline of 30.40 for PCS and mean change of 7.43 from a baseline of 41.90 for MCS; n=205).

Improvements in fatigue, as reflected by mean changes from baseline to 12 months (mean change of -36.1 from a baseline of 65.81; n=231), was maintained to the end of the OLE phase (mean change of -40.2 at 24 months; n=222) for patients who received 2 years of therapy with abatacept + MTX. For patients in the original placebo + MTX group, the mean improvement in the fatigue VAS was additionally improved when they initiated abatacept in the OLE phase (-28.0 at Month 12 [baseline 64.27; n=224] and -37.0 at Month 24 [baseline 64.57; n=206]).

Furthermore, improvements in activity limitation, as evidenced by mean changes from baseline in the score followed the same trend as the other quality of life outcomes. For patients who received abatacept + MTX from the study outset, the mean improvement in the activity limitation score recorded at 12 months (mean change of -11.4 from a baseline of 15.99; n=228) was maintained at the end of the OLE period (mean change of -12.1 from a baseline of 15.70; n=213). For patients in the original placebo + MTX group, the mean

improvement in the activity limitation score at 12 months (mean change of -8.30 from a baseline of 15.36; n=222) was improved upon in the second year of the study (mean change of -11.5 at 24 months from a baseline of 15.62; n=201).

Efficacy conclusions

The efficacy data from the open-label extension experience of Study IM101-023 indicates that continued treatment for up to 2 years with abatacept + 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) with supporting improvements in radiographic and functional outcomes. Patients who initially received placebo + MTX in Year 1 and then were switched to open-label abatacept 10 mg/kg + MTX in Year 2 of the trial showed improvements in disease activity equivalent to that observed in patients who received 12 months of abatacept + MTX.

Study IM101-043 (12 month status)

Study IM101-043 was a prospective, multicentre, randomized, double-blind, active and placebo-controlled study of 1 year duration with 2 treatment periods: Period 1 (Days 1-197) and Period 2 (Days 198-365). Adult subjects with active RA who were inadequate responders to MTX were randomized 3:3:2 into 1 of 3 possible treatment groups for the initial 6 months: abatacept infusions (10 mg/kg) + MTX, infliximab infusions (3 mg/kg) + MTX or placebo infusions + MTX. Randomization occurred at the study site level with each subject assigned a unique sequential subject number via the central randomization system. Treatment with placebo infusions was limited to 6 months to validate the clinical response rates of the 2 bDMARD groups. All patients treated with placebo infusions + MTX in Period 1 were re-allocated to receive abatacept + MTX in Period 2. However, subjects treated with abatacept or infliximab in Period 1, continued with the same treatment in Period 2. Reallocation and study drug administration proceeded in a manner that maintained the blinding for all treatment groups in Period 2. Comparisons of the relative efficacy and safety of bDMARDs used in the treatment of RA are typically extrapolated by indirect trial data comparison as it is uncommon for two bDMARDs to be included as two of the treatment options in a RA study. Hence, the design of Study IM101-043 is relatively unique.

Abatacept dosing was identical to that used in Study IM101-023. Infliximab was given at the licensed dose of 3 mg/kg IV in 250 mL of normal saline over 2 hours, however, prior to that subjects also received 100 mL of normal saline to match the abatacept infusion process. At the time of the study, fixed dosing of infliximab was the standard but more recent evidence indicates that many patients can obtain or maintain durable clinical responses if the dose of infliximab is increased by up to 30% more than the approved weight tiered dose of 3 mg/kg. Because the dosing regimens of abatacept and infliximab are different, subjects received normal saline at some dosing visits to maintain the integrity of the blind. Patients who received infliximab received active doses during the first 12 months at Days 1, 15, 43, 85 and every 56 days thereafter for a total of 8 doses. Concurrent administration of usual therapeutic doses of MTX was utilized in the trial with all patients receiving once weekly MTX (oral or parenteral) at a dose of 15-25 mg. No increase in the dose of MTX was permitted for the first 6 months of the study although decreases were allowed for protocol specified toxicities. No other DMARDs were permitted. Background corticosteroids and NSAID were allowed if their use had been stable for at least 28 days prior to baseline. Additional NSAID therapy or rescue analgesics were not permitted within 12 hours of a joint assessment. After 6 months, adjustments in MTX or corticosteroid therapy were allowed at the investigator's discretion depending on the patient's disease status as assessed by tender and swollen joint counts. Furthermore,

the addition of 1 conventional DMARD (a choice of chloroquine, hydroxychloroquine, sulfasalazine, gold or azathioprine) was also allowed after 6 months.

The assessment of clinical efficacy parameters was undertaken at screening; Days 1, 15 and 29; and every 28 days thereafter until Day 365.

Study Population Characteristics

Study IM101-043 was conducted in 86 study sites in North, Central and South America, as well as Europe, South Africa and Australia between February 2005 and June 2006. Subjects were required to be between 18 and 75 years of age and taking MTX for at least 3 months prior to enrolment (stable dose for 28 days prior to inclusion) at a minimum weekly dose of 15 mg. However, a MTX dose as low as 10 mg/week was permitted for subjects with a history of intolerance to MTX. If patients were taking DMARDs (such as leflunomide) in addition to MTX, then an appropriate wash-out period for the other DMARD was required. At study entry, patients were required to have active disease as defined by the 1987-revised ACR criteria which included >10 swollen joints out of 66 joints assessed, >12 tender joints out of 68 joints assessed and raised serum inflammatory markers (CRP>10 mg/L). Subjects were excluded from enrolment if they had received previous anti-TNF treatment or failed more than 4 DMARDs (including MTX). Significant other patient exclusion characteristics were the same as those described for Study IM101-023.

The 3 treatment groups were well balanced with respect to demographic characteristics. Baseline disease characteristics of the participants were similar for the 3 treatment groups. The baseline disease parameters reflected severely active disease and were comparable among the 3 treatment groups. The treatment groups were well-balanced with respect to previous and concomitant treatments for RA.

Primary Efficacy endpoint

The primary endpoint of Study IM101-043 was the comparison for the mean change from baseline to Day 197 (6 months) in the DAS28 score between the abatacept + MTX treatment group and the placebo infusion + MTX arm.

Secondary Efficacy endpoints

Secondary efficacy endpoints included:

- Comparison between the infliximab + MTX and placebo + MTX group for the mean change from baseline to Day 197 in the DAS28 score,
- Comparison between the infliximab + MTX and abatacept + MTX group for the AUC of DAS28 from baseline to Day 365 (12 months),
- Comparison between the 3 treatment groups for the mean change from baseline to 6 months (Day 197) and 12 months (Day 365) in the HAQ-DI and SF-36,
- The proportion of patients treated with abatacept or infliximab at 12 months who achieved a good, moderate or no EULAR response and
- The proportion of subjects achieving an ACR 20, 50 and 70 response at 6 and 12 months.

Supporting Endpoints

Supporting efficacy parameters included in the study report were the proportion of patients achieving MCR, EMCR or a clinically meaningful reduction in HAQ-DI (that is, a decrease of at least 0.30 units from baseline) at 12 months. However, one of the significant

limitations of the study is that there was no assessment of radiographic outcomes which would have supported the analysis of clinical endpoints.

Statistical methods

A total of 150 abatacept treated subjects and 100 placebo treated patients was estimated to yield over 99% power to detect a difference of 0.88 units in the primary comparison of mean change in DAS28 score at 6 months between the above 2 treatment groups. This assumed a subject drop-out of 20% and calculations being performed at the 5% level of significance (2-tailed test). Post-hoc analysis of Study IM101-100 demonstrated a mean improvement in the DAS28 at 6 months of 0.88 units (standard deviation 1.25 units) in the patients who received abatacept 10 mg/kg + MTX compared with placebo infusions + MTX. If the underlying treatment difference was 0.59 units the study was still powered at 90% for the primary endpoint using the same sample size. The study was not prospectively powered to detect a treatment difference between the abatacept and infliximab groups. A key secondary endpoint was the proportion of patients achieving an ACR20 response at 6 months, as this was considered to demonstrate internal consistency for the response rates of the 2 bDMARD groups. With a sample size of 150, 150 and 100 subjects in the abatacept, infliximab and placebo groups, respectively, the study had 85% power to detect a difference of at least 20% in the ACR20 response rate at 6 months between each of the 2 bDMARD groups versus placebo + MTX (5% level; 2-tailed based on a continuity-corrected Chi-square test). This calculation assumed an ACR20 response rate of 35% for the placebo + MTX, as observed in Study IM101-100.

The primary analysis was performed with the ITT population (defined as all randomized patients who received at least a part of any study infusion) and compared the mean change from baseline to Day 197 in DAS28 score for the abatacept and placebo treatment groups. This analysis was performed using an ANCOVA model, with treatment group as the effect and baseline value as the covariate. No statistical tests were performed for the subgroup analyses and sensitivity tests were only to be performed if the comparative discontinuation rate in either group exceeded 10%. The secondary endpoint of the comparison for the mean change in DAS28 between the infliximab and placebo infusion group used the same ANCOVA model as described above for the primary endpoint. The categorical efficacy endpoints relating to HAQ-DI change of at least 0.30 units and various levels of ACR response were analysed using a continuity corrected Chi-square test.

For patients who prematurely withdrew from the study, categorical clinical variables were recorded as non-responder status for all time points thereafter in the study. The same rule applied for all patients who required an additional DMARD, or an increase in their MTX or corticosteroid dose (including 2 or more rescue therapies within a 6 month period) during Days 198-365.

Patient Disposition and Completion Status

Of the 748 patients enrolled into Study IM101-043, a total of 431 were randomized to receive study medication (156 were randomized to abatacept + MTX, 165 to infliximab + MTX and 110 to placebo infusions + MTX). The commonest reason for screened patients to not be subsequently randomized to study treatment was failure to meet eligibility criteria (usually insufficient elevation in baseline CRP).

During study Period 1 (Days 1-197), the rate of premature discontinuation was low among all 3 treatment groups. Similarly, few subjects withdrew from study Period 2. The overall rates of completion at Day 365 were 89.1% (139/156) for abatacept + MTX, 85.5% (141/165) for infliximab + MTX and 94.5% (104/110) for the original placebo + MTX treatment arm.

Consistent with an overall low incidence of early withdrawal, the mean duration of exposure to study drug for the first 6 months for all 3 treatment groups was close to the planned duration of 197 days (193.8 days for abatacept + MTX, 191.7 days for infliximab + MTX and 194.4 days for the placebo + MTX group). Mean exposure across the entire 12 month DB period was 352.7 days for abatacept + MTX and 347.4 days for infliximab + MTX. In addition, the median number of infusions was 15 for patients in both bDMARD groups and more than 90% of subjects in both groups received treatment for greater than 10 months.

Primary Efficacy Result

The primary endpoint was achieved with the mean reduction in DAS28 score at Day 197 being greater for patients in the abatacept + MTX treatment group (mean decrease of 2.53 from a baseline of 6.86; n=150) compared with the placebo + MTX arm (mean decrease of 1.48 from a baseline of 6.79; n=102; adjusted treatment difference of -1.04 [95% CI -1.42, -0.67]; p<0.001) (Table 5). Subgroup analyses of the mean change from baseline in DAS28 score (according to age, gender, ethnicity, geographic region, duration of RA, baseline CRP value and rheumatoid factor status) were consistent with the primary result although not sufficiently powered to be of statistical significance.

Table 5: Study IM101-023 mean change in DAS28

Mean Change from Baseline in DAS28 (ESR) at Day 197 (LOCF Analysis)

		ABA N = 156	INF N = 165	PLA N = 110
Day 197	n	150	156	102
	Baseline Mean (SD)	6.86 (1.01)	6.79 (0.89)	6.79 (1.02)
	Post-Baseline Mean (SD)	4.31 (1.35)	4.55 (1.76)	5.31 (1.61)
	Adjusted Mean Change from Baseline (SE)	-2.53 (0.12)	-2.25 (0.12)	-1.48 (0.15)
	Difference from Placebo (95% CI)	-1.04 (-1.42, -0.67)	-0.77 (-1.14, -0.39)	N/A
	Comparison with Placebo p-value	<0.001 **	<0.001 **	N/A
	Difference from Infliximab (95% CI)	-0.28 (-0.61, 0.06)	N/A	N/A
	Subjects with Improvement (DAS 28 change >= 1.2)	123 (82.0)	113 (72.4)	53 (52.0)
	Subjects with Low Disease Activity (DAS 28 <= 3.2)	31 (20.7)	40 (25.6)	11 (10.8)
	Subjects in Remission (DAS 28 < 2.6)	17 (11.3)	20 (12.8)	3 (2.9)

Population: All randomized and treated subjects.
ABA: Abatacept, INF: Infliximab, PLA: placebo
Change of >=1.2 units in DAS 28 score was defined as clinically meaningful improvement in disease activity.
** p <0.001, ^ p<0.01, * p<0.05.

Results for secondary efficacy variables

At Day 197, a greater reduction in mean DAS28 score was also observed for patients treated with infliximab + MTX (mean decrease of 2.25 from a baseline of 6.79; n=156) compared with those who received placebo infusions + MTX (mean decrease of 1.48 from a baseline of 6.79; n=102; adjusted treatment difference of -0.77 [95% CI -1.14, -0.39]; p<0.001) (Table 5).

The DAS28 AUC over the Day 1-365 time period was similar for the abatacept (adjusted mean of 1631.6 [SE 31.64]; n=150) and infliximab treatment groups (adjusted mean of 1664.3 [SE 31.03]; n=156; difference of the means = -32.7 [95% CI -119.9, 54.6]).

At Day 197, a greater mean reduction in HAQ-DI from baseline was observed for patients in the abatacept + MTX group (mean change of -0.69 from a baseline of 1.76; n=156; difference from control group of -0.38 [95% CI -0.53, -0.23]; p<0.001) compared with those treated with placebo infusions + MTX (mean change of -0.31 from a baseline of 1.77; n=109). Similarly, patients who received infliximab + MTX (mean change of -0.61 from a

baseline of 1.67; n=164; difference from control group of -0.30 [95% CI -0.45, -0.15]; p<0.001) demonstrated a greater mean reduction from baseline to Day 197 in HAQ-DI compared to those who received placebo + MTX. At the end of the DB period (Day 365), no statistically significant difference for the mean change from baseline in HAQ-DI was demonstrated for patients treated with abatacept + MTX (mean change of -0.67 from a baseline of 1.76; n=156) compared to those who received infliximab + MTX (mean change of -0.59 from a baseline of 1.67; n=164; difference between abatacept and infliximab groups of -0.08 [95% CI -0.22, -0.06]).

The impact of bDMARD therapy on health related quality of life was assessed using the SF-36 questionnaire with higher scores indicating a better quality of life. Subjects who received abatacept + MTX had greater improvements from baseline to Day 197 in both the PCS (mean improvement of 8.36 from a baseline of 31.00; n=154; difference from control of 4.02 [95% CI 1.92, 6.12]; p<0.001) and MCS (mean improvement of 5.14 from a baseline of 39.63; n=154; difference from control of 3.51 [95% CI 1.10, 5.91]; p=0.004) than those who were treated with placebo + MTX (mean improvement in PCS of 4.34 from a baseline of 30.50 and mean improvement in MCS of 1.64 from a baseline of 42.36; n=109). The same trend in favour of bDMARD therapy at 6 months was observed for patients treated with infliximab + MTX for both the PCS (mean improvement of 7.66 from a baseline of 30.69; n=163; difference from control group of 3.32 [95% CI 1.25, 5.40]; p=0.002) and MCS (mean improvement of 4.32 from a baseline of 41.20; n=163; difference from control arm of 2.68 [95% CI 0.31, 5.05]; p=0.027) compared to those who received treatment with placebo infusions + MTX. At Day 365, patients treated with abatacept + MTX (mean improvement of 9.52 from a baseline of 31.00; n=154) had a greater improvement in the PCS compared to those who received infliximab + MTX (mean improvement of 7.59 from a baseline of 30.69; n=163; difference between abatacept and infliximab groups of 1.93 [95% CI 0.02, 3.84]). However, similar improvements were observed between the 2 bDMARD groups with respect to the mean change from baseline in the MCS: - mean improvement of 5.96 from a baseline of 39.63 for abatacept (n=154) versus mean improvement of 4.03 from a baseline of 41.20 for infliximab (n=163). The difference between the abatacept and infliximab groups for the mean change in MCS at 12 months was non-significant at 1.92 [95% CI -0.30, 4.15].

At 1 year, a higher proportion of subjects in the abatacept group compared with the infliximab arm demonstrated the attainment of a “good” EULAR response (32.0% [48/150] for abatacept versus 18.5% [29/157] for infliximab. However, “moderate” EULAR responses were recorded in a similar percentage of patients in each treatment group (40.7% [61/150] for abatacept and 45.2% [71/157] for infliximab) but “no response” was seen in more patients in the infliximab group (36.3% [57/157] for infliximab compared with 27.3% [41/150] for abatacept).

At Day 197, the percentages of subjects achieving an ACR20, 50 or 70 response was higher in the abatacept and infliximab treatment groups compared to placebo + MTX (Table 6). In particular, the 6 month ACR20 response rate (which was pre-defined as a key secondary outcome) were 66.7% (104/156) for abatacept compared to 41.8% (46/110) for placebo + MTX (difference between abatacept and control of 24.8 [95% CI 12.0, 37.7]; p<0.001). For patients who received infliximab the ACR20 response rate at 6 months was 59.4% (98/165) which reflects a treatment difference when compared to the placebo + MTX arm of 17.6 [95% CI 4.8, 30.4] which is also statistically significant (p=0.006). However, when the 2 bDMARD groups were compared for the relative proportion of ACR20, 50 and 70 at 6 months, no significant difference was observed because of wide and overlapping 95% confidence intervals. At Day 365, the percentages of patients achieving an ACR20 response was significantly higher in the abatacept group (72.4% [113/156]) compared with the infliximab arm (55.8% [92/165]) (Table 7). For the ACR20 outcome at 1 year, the

difference between abatacept and infliximab treatment favoured abatacept at 16.7 (95% CI 5.5, 27.8). However, for the higher levels of ACR response (50 or 70), the proportion of responders was higher for those who received abatacept compared to infliximab but these results were not significant as the estimated treatment difference between the 2 treatment groups included zero.

Table 6: Study IM101-043 ACR responses at Day 197

Proportion of Subjects Who Have ACR 20, 50, 70 Responses at Day 197

		ABA N = 156	INF N = 165	PLA N = 110
ACR 20	Number of responders (%)	104 (66.7%)	98 (59.4%)	46 (41.8%)
	Estimate of difference from Placebo (95% CI)	24.8 (12.0, 37.7)	17.6 (4.8, 30.4)	N/A
	Comparison with Placebo p-value	<0.001 **	0.006 ^	N/A
	Estimate of difference from Infliximab (95% CI)	7.3 (-3.9, 18.5)	N/A	N/A
ACR 50	Number of responders (%)	63 (40.4%)	61 (37.0%)	22 (20.0%)
	Estimate of difference from Placebo (95% CI)	20.4 (8.2, 32.5)	17.0 (5.1, 28.8)	N/A
	Comparison with Placebo p-value	<0.001 **	0.004 ^	N/A
	Estimate of difference from Infliximab (95% CI)	3.4 (-7.9, 14.7)	N/A	N/A
ACR 70	Number of responders (%)	32 (20.5%)	40 (24.2%)	10 (9.1%)
	Estimate of difference from Placebo (95% CI)	11.4 (1.7, 21.1)	15.2 (5.1, 25.2)	N/A
	Comparison with Placebo p-value	0.019 *	0.002 ^	N/A
	Estimate of difference from Infliximab (95% CI)	-3.7 (-13.5, 6.0)	N/A	N/A

Population: All randomized and treated subjects.
ABA: Abatacept, INF: Infliximab, PLA: placebo
** p <0.001, ^ p<0.01, * p<0.05: probability for testing the difference in ACR response vs. PLA group.

Table 7: Study IM101-043 ACR responses at Day 365

Proportion of Subjects Who Have ACR 20, 50, 70 Responses at Day 365

		ABA N = 156	INF N = 165	PLA-ABA N = 110
ACR 20	Number of responders (%)	113 (72.4%)	92 (55.8%)	75 (68.2%)
	Estimate of difference from Infliximab (95% CI)	16.7 (5.5, 27.8)	N/A	N/A
ACR 50	Number of responders (%)	71 (45.5%)	60 (36.4%)	56 (50.9%)
	Estimate of difference from Infliximab (95% CI)	9.1 (-2.2, 20.5)	N/A	N/A
ACR 70	Number of responders (%)	41 (26.3%)	34 (20.6%)	32 (29.1%)
	Estimate of difference from Infliximab (95% CI)	5.7 (-4.2, 15.6)	N/A	N/A

Population: All randomized and treated subjects.
ABA: Abatacept, INF: Infliximab, PLA-ABA: placebo to abatacept
Subjects in the PLA-ABA group received placebo for the first 6 months and abatacept for the second 6 months
One additional DMARDs (i.e. hydroxychloroquine, sulfasalazine, gold or azathioprine) could be added on or after Day 197.

Results for Supporting Endpoints

The proportion of subjects with MCR by Day 365 was similar for both bDMARD treatment groups: 10.9% (17/156) for abatacept + MTX and 11.5% (19/165) for infliximab + MTX. Likewise, the percentage of patients achieving EMCR by Day 365 was similar in the abatacept (5.1%, 9/156) and infliximab (6.7%, 11/165) groups. Consistent with the above

results is the proportion of subjects in each of the bDMARD arms that obtained a clinically significant improvement in HAQ-DI (a reduction of at least 0.30 units from baseline) at 1 year – 57.7% (90/156) for abatacept and 52.7% (87/165) for infliximab (estimated treatment difference of 5.0 but with 95% CI [-6.5, 16.5] overlapping zero indicating non-significance).

Interestingly, at 6 months a numerically higher proportion of subjects treated with infliximab achieved LDA (DAS28<3.2) and DAS remission (score <2.6) compared with abatacept. However, at 12 months of follow-up this pattern in favour of infliximab over abatacept reversed once a post-hoc sensitivity analysis adjusting for the addition of further DMARD, or increase in MTX dose, or corticosteroids during Days 198-365 was applied. More subjects in the infliximab group (17.6%, 29/165) compared with abatacept (12.8%, 20/156) underwent the above medication changes in Period 2. The rates of LDA at 12 months were 34.7% (52/150) for abatacept versus 18.7% (29/155) for infliximab. The rates of DAS remission at 12 months were 19.3% (29/150) for abatacept versus 9.7% (15/155) for infliximab.

Efficacy conclusions

> The 6 month efficacy data from Study IM101-043 indicate that both abatacept + MTX and infliximab + MTX are statistically superior in a clinically meaningful manner to continued MTX monotherapy in reducing the signs and symptoms of RA (as assessed by ACR and EULAR criteria) and improving both physical function and quality of life for patients with RA. The 12 month data indicate that the efficacy of abatacept and infliximab is largely maintained and comparable between the 2 bDMARD agents for the major efficacy variables such as the rate of ACR50 and major clinical response. There are some minor differences in bDMARD treatment effect (for example, the ACR20 response rate) seen at 12 months but the clinical significance of these differences is unclear.

Open-label extension of Study IM101-043 (2 year status)

All patients who completed the 12 month double-blind period of Study IM101-043 were allowed to receive open-label treatment with abatacept (10 mg/kg) thereafter in conjunction with continued MTX (15-25 mg/week). Hence, subjects originally randomized to infliximab were re-assigned to abatacept therapy. The submission contained a 2 year (Day 757) status report on the OLE phase. Of the 86 study centres that enrolled subjects in the initial 12 month trial, 62 continued in the OLE period – 18 in South America, 16 in North America, 10 in Europe, 9 in Mexico, 3 in South Africa and 6 in Australia. The primary objective of the OLE study was to assess long-term safety and tolerability; however, efficacy measures (of a similar type in the controlled period) were also collected to determine the durability of clinical benefit. Clinical efficacy parameters were assessed every 12 weeks in the second year of the study.

In the OLE period patients were expected to receive abatacept at a dose of 10 mg/kg every 4 weeks. All patients who entered the OLE phase were taking concurrent MTX at a mean weekly dose of 16.7 mg (range: 10-25 mg). All but 4 (of 372) subjects continued taking MTX during the OLE. Subjects were also allowed to continue taking stable background doses of NSAIDs or oral corticosteroids throughout the OLE. Investigators were also allowed to commence 1 of the following DMARDs: chloroquine, hydroxychloroquine, leflunomide, cyclosporine, sulfasalazine or azathioprine. Approximately 10% of patients in each of the original DB assigned treatment groups received additional DMARDs in the OLE. The addition of other bDMARDs was not permitted by the protocol until 56 days after the last abatacept infusion but 11 patients received anti-TNF medications in this time frame,

Of these 11 subjects, 1 withdrew to commence infliximab, 6 were discontinued due to lack of efficacy and 4 had completed the OLE.

Study Population

The characteristics of the patients recruited into the second and subsequent OLE years of Study IM101-043 were very similar to the controlled phase population.

Patient Disposition and Drug Exposure

Of the 384 subjects (139 on abatacept + MTX, 141 on infliximab + MTX and 104 in the treatment switch group in Year 1) who completed the DB treatment period, 372 (96.9%) received at least 1 dose of abatacept in the OLE. Approximately 2/3 (68.0%, 253/372) completed the OLE at the time of data cut-off (31/10/2008), although 11.6% (43/372) prematurely discontinued before the data cut-off date. The most common reasons for discontinuation from the OLE were withdrawal of consent (3.2%, 12/372), adverse events (2.7%, 10/372) and lack of efficacy (2.4%, 9/372). A total of 76 subjects (20.4%) were "ongoing" at the time of data cut-off for this report.

During the combined DB and OLE treatment periods for Study IM101-043, the mean exposure to abatacept was 30.5 (median 32.3; range 1.9 – 44.1) months. On average, patients received 32.2 infusions (range: 1-50) over the entire study period. The proportion of patients who received at least 24 months of abatacept was 77.2% (287/372) while a total of 94.9% (353/372) completed 12 of abatacept in the OLE.

Efficacy Parameters

During the OLE, the 3 originally assigned treatment groups were assessed for the following protocol specified secondary outcomes up to 2 years (Day 729):

- Proportion of patients achieving DAS28 (ESR) remission and EULAR defined Low Disease Activity (LDA),
- Mean change from baseline in DAS28 (ESR) score,
- Proportion of patients achieving ACR 20, 50 and 70 response,
- Proportion of patients achieving clinically significant improvements in HAQ-DI (defined as a reduction of at least 0.30 units from baseline) and
- Mean change from baseline in health related quality of life (as measured by the SF-36).

Statistical Analysis and Data Handling Methods

No hypothesis testing or power calculation was done in the OLE of Study IM101-043. Clinical efficacy outcomes such as the proportion of subjects achieving various levels of ACR or DAS 28 response were summarized with point estimates and 95% confidence intervals according to the patient's original randomized treatment assignment (abatacept, infliximab or placebo). If data for any efficacy outcome was missing, no imputation was undertaken. The presented efficacy data were limited to assessments taken up to Day 729 (end of first year of OLE). As ESR and CRP were only measured every 6 months (not quarterly) in the OLE, the proportion of patients achieving Major Clinical Response (MCR) was not evaluable despite it being a pre-defined outcome measure. Furthermore, the analyses of ACR and DAS28 responses could only be performed at 6 and 12 months in the OLE.

Efficacy results

At Day 729, the proportion of patients treated with an additional year of abatacept + MTX who achieved DAS remission was 26.1% (30/115) and LDA was 41.7% (48/115), which is similar to that observed at 12 months of therapy (19.3% [29/150] for remission and 34.7% [52/150] for LDA). For patients in the original infliximab group, the proportion of patients obtaining DAS remission at 2 years was higher (28.6% [36/126]) than that observed at 12 months (9.7% [15/155]). Furthermore, patients who switched from infliximab to abatacept showed improved LDA response rates at 2 years (45.2% [57/126] at Day 729 versus 18.7% [29/155] at Day 365). Similarly, patients in the original placebo infusion + MTX group who changed to abatacept infusions at 6 months and then continued this therapy in the OLE had high response rates at 24 months (22.0% [22/100] for remission and 34.0% [34/10] for LDA. A similar pattern of outcome was observed when CRP was used as an alternative input into the DAS28 calculation; however, the response rates at all time points and for all treatment groups were generally higher than when ESR was used in the DAS28 score calculation.

Improvement in the DAS28-ESR score, as reflected by the mean change from baseline (Day 1), was observed at the end of the double blind period (-3.12 at 12 months) and maintained at the end of the OLE phase (-3.35 at 24 months) for patients who received 2 years of therapy with abatacept + MTX. In the original infliximab group, the mean reduction in DAS28-ESR was -2.39 at 12 months and this result improved during the OLE treatment period to be comparable to the original abatacept group (-3.29 at 24 months). For patients in the original placebo + MTX group who then switched to abatacept at 6 months, the mean improvement in DAS28-ESR score achieved at 12 months (-2.81) was maintained until the end of the OLE (-2.98 at 24 months).

The rates of ACR response (ACR 20, 50 and 70) observed at Days 365 and 729 in the original abatacept + MTX and placebo + MTX treatment groups were maintained until the end of the OLE (Tables 8 and 9). However, patients in the original control group of placebo + MTX were switched to abatacept at 6 months. Patients who continued with a second year of treatment with abatacept + MTX demonstrated either a similar or improved rate of response. For example, the rates of ACR50 response observed with the original abatacept + MTX group at the end of the DB period (55.0% [72/131] at 12 months) were similar at the end of year 2 (60.7% [71/117] at 24 months). However, improved rates of ACR response were observed for the infliximab + MTX group during Year 2 when abatacept was substituted for infliximab. In particular, the rate of ACR50 response improved from 43.4% (59/136) at 12 months to 70.9% (90/127) at 24 months.

Table 8: Study IM101-043 ACR responses at Day 365

Proportion of Subjects with ACR Response by Visit - As-observed Analysis:
Day 365
All Treated Subjects in the Open-label Period

		Abatacept N= 132	Infliximab N= 136	Placebo N= 104
ACR 20	Number of Subjects n/m (%)	115/130 (88.5%)	94/136 (69.1%)	78/103 (75.7%)
	95% CI	(83.0, 94.0)	(61.4, 76.9)	(67.4, 84.0)
ACR 50	Number of Subjects n/m (%)	72/131 (55.0%)	59/136 (43.4%)	56/102 (54.9%)
	95% CI	(46.4, 63.5)	(35.1, 51.7)	(45.2, 64.6)
ACR 70	Number of Subjects n/m (%)	41/131 (31.3%)	32/136 (23.5%)	32/102 (31.4%)
	95% CI	(23.4, 39.2)	(16.4, 30.7)	(22.4, 40.4)

Table 9: Study IM101-043 ACR responses at Day 729

Proportion of Subjects with ACR Response by Visit - As-observed Analysis:
Day 729
All Treated Subjects in the Open-label Period

		Abatacept N= 132	Infliximab N= 136	Placebo N= 104
ACR 20	Number of Subjects n/m (%)	103/119 (86.6%)	107/127 (84.3%)	78/102 (76.5%)
	95% CI	(80.4, 92.7)	(77.9, 90.6)	(68.2, 84.7)
ACR 50	Number of Subjects n/m (%)	71/117 (60.7%)	90/127 (70.9%)	50/101 (49.5%)
	95% CI	(51.8, 69.5)	(63.0, 78.8)	(39.8, 59.3)
ACR 70	Number of Subjects n/m (%)	49/120 (40.8%)	57/127 (44.9%)	33/100 (33.0%)
	95% CI	(32.0, 49.6)	(36.2, 53.5)	(23.8, 42.2)

Within each of the 3 original DB treatment groups, the majority of subjects who demonstrated either an ACR50 or 70 response at Day 365 continued to maintain the same level of response at 24 months (Table 10).

Table 10: Proportion of subjects with a sustained ACR response at Day 365

		Abatacept N= 132	Infliximab N= 136	Placebo N= 104
Sustained ACR 50 at Day 729	Number of Subjects n/m (%)	50/ 72 (69.4%)	52/ 59 (88.1%)	41/ 56 (73.2%)
	95% CI	(58.8, 80.1)	(79.9, 96.4)	(61.6, 84.8)
Sustained ACR 70 at Day 729	Number of Subjects n/m (%)	32/ 41 (78.0%)	29/ 32 (90.6%)	22/ 32 (68.8%)
	95% CI	(65.4, 90.7)	(80.5, 100.0)	(52.7, 84.8)

n = Number of subjects with Sustained ACR Response, m = Number of subjects with ACR Response at Day 365.
Treatment groups represent treatment received in the double-blind period.

Subjects in original abatacept group received abatacept 10 mg/kg throughout double-blind (Days 1 to 365) and open-label periods. Subjects in original placebo group received placebo during first 6 months (Days 1 to 197) of double-blind period and abatacept 10 mg/kg during second 6 months (Days 198 to 365) of double-blind period and during open-label period. Subjects in original infliximab group received infliximab 3 mg/kg during double-blind period (Days 1 to 365) and abatacept 10 mg/kg during open-label period.

All 3 treatments groups were observed to have a similar maintenance rate of subjects with clinically significant improvements in categorical HAQ-DI response (a reduction of 0.30 units from baseline) during 2 years of follow-up. The proportion of patients in the original abatacept + MTX group who improved their HAQ-DI score by at least 0.30 units at 12 months was 70.8% (92/130) and this rate of response was maintained at 24 months (74.6%, 91/122). For patients treated with placebo infusions + MTX during the first 6 months and then switched to abatacept, the rate of categorical HAQ response achievement was 61.2% (63/103) at 12 months and maintained at 2 years (63.1%, 65/103). For patients in the infliximab arm the rate of significant HAQ-DI response at 12 months was 67.6% (92/136) and this increased to 78.0% (99/127) at 24 months following the change to abatacept treatment in Year 2.

The mean improvements from baseline (Day 1) in the PCS and MCS of the SF-36 Questionnaire achieved at 12 months (mean change of 10.24 from a baseline of 30.87 for PCS and mean change of 7.95 from a baseline of 38.67 for MCS; n=130) for subjects in the original abatacept + MTX group were maintained to the end of the second year of treatment (mean change of 10.94 from a baseline of 30.90 for PCS and mean change of 6.63 from a baseline of 38.76 for MCS; n=121). The mean improvements observed in the infliximab + MTX group at the end of the DB period (mean change of 8.17 from a baseline of 30.13 for PCS and mean change of 5.14 from a baseline of 41.06 for MCS; n=134) increased, particularly for the PCS, in the OLE phase when abatacept was substituted for

infliximab (mean change of 11.16 from a baseline of 30.10 for PCS and mean change of 6.79 from a baseline of 40.82 for MCS; n=125). For the treatment switch group (placebo → abatacept at 6 months), the mean improvements at 12 months (mean change of 8.88 from a baseline of 30.57 for PCS and mean change of 5.67 from a baseline of 42.50 for MCS; n=102) were maintained to the end of the OLE for the PCS (mean change of 8.49 from a baseline of 30.43; n=101) but not the MCS (mean change of 3.23 from a baseline of 42.73 for MCS; n=101).

Efficacy conclusions

The efficacy data from the open-label extension experience of Study IM101-043 indicates that continued treatment for up to 2 years with abatacept + MTX results in significant proportions of patients either maintaining or continuing to improve in the signs and symptoms of RA (ACR and DAS responses) with supporting improvements in health-related outcomes. Patients who initially received infliximab + MTX in Year 1 and then were switched to open-label abatacept 10 mg/kg + MTX in Year 2 of the study showed improvements in disease activity and health outcomes equivalent to those observed in patients who received abatacept + MTX from the study outset.

Long-term efficacy updates (Studies IM101-102, IM101-100 and IM101-029)

The primary objective of the OLE phases was to assess long-term safety and tolerability; however, efficacy measures were also collected to determine the durability of clinical benefit. In general, efficacy parameters were assessed every 12 weeks up to the data cut-off date of 31 October 2008. The 2 trials involving MTX-IR subjects had 12 month core phases and the TNF-IR study had a 6 month core observation period. In the 3 OLE studies, patients were expected to receive abatacept at a dose of 10 mg/kg (with weight determined annually) every 4 weeks. The majority of OLE patients continued with adjunctive conventional DMARD therapy (typically MTX). Other permitted DMARDs included hydroxychloroquine, sulfasalazine and leflunomide. In all 3 OLE studies, stable background doses of oral corticosteroids and NSAIDs were allowed at initial entry to the controlled studies and could be continued if the patient did not achieve a satisfactory improvement. In reality, most subjects remained on background treatment during the OLE: >99% for MTX, 88-94% for concomitant NSAID and 79-86% for low dose corticosteroids.

A total of 219 subjects (of a possible 235) who completed the core phase of Study IM101-100 enrolled into the OLE. For the other MTX-IR trial (Study IM101-102), 539 of a possible 547 patients contributed to the OLE experience. The OLE of Study IM101-029 (TNF-IR cohort) recruited 317 (of a possible 322) patients who completed the 24 week DB treatment phase.

Patient Characteristics

The recruited patient population for subjects involved in the 3 original Phase III controlled studies with reported OLE phases had moderately-severely active RA at baseline as evidenced by a mean swollen joint count of 18.6-22.4, mean tender joint count of 26.2-33.0, as well as raised serum inflammatory markers (mean CRP of 25-46 mg/L). For 2 of the studies (IM101-102 and IM101-100) patients had previously failed MTX and for Study IM101-029 subjects had failed at least 1 anti-TNF medication. The minimum duration of RA at entry was 12 months for all 3 core studies. However, the mean duration of RA was significantly longer than this at 8.2-12.1 years indicating that patients had established disease which had been refractory to many other treatment options.

Statistical Analysis and Data Handling Methods

Because of the non-comparative, open-label design of these trial extension periods, no formal hypothesis testing was undertaken. Results were analysed on an as observed basis with no imputation rules for the handling of missing data.

Patient Disposition and Drug Exposure

Across both populations (MTX-IR and TNF-IR), the discontinuation rates at 4 years (including the core study periods) ranged from 27.6% (149/539) for Study IM101-102 to 47.9% (105/219) for Study IM101-100 and 52.1% (165/317) for Study IM101-029. The majority of patients (21.8% [69/317] for Study IM101-029) who discontinued before 4 years in the long-term follow-up studies did so because of lack of efficacy. This reflects a higher discontinuation rate for the TNF-IR cohort, which is expected given the more refractory nature of their RA. Beyond 4 years of follow-up, the subject continuation rate was low ranging from 23.0% (73/317) for Study IM101-029 to 35.8% (193/539) for Study IM101-102 and 52.1% (114/219) for Study IM101-100. At this time point, most patients elected to formally withdraw from the studies once abatacept became commercially available in their countries. As such, meaningful numbers of continuing patients beyond this time point are not available for interpretation of efficacy outcomes.

Efficacy results

At the end of the 12 month core study periods in the 2 MTX-IR trials, the comparative ACR50 response rates between abatacept and control treatment were 39.9% versus 16.8% for Study IM101-102 and 36.5% versus 11.8% in Study IM101-100 ($p<0.001$). For the original abatacept treatment group in Study IM101-102, the majority of patients who achieved and then maintained a significant ACR response for up to 5 years (1 year of DB treatment and 4 years of OLE) with continuous abatacept were 72.0-83.7% for ACR50 and 62.6-73.0% for ACR70. For the original control group in Study IM101-102, increases in ACR20, 50 and 70 response rates during the OLE were observed after the start of abatacept and were of a magnitude similar to that seen in the original abatacept group by approximately 3 months after starting abatacept. A similar degree of maintaining ACR 50 and 70 response rates was observed in Study IM101-100 for up to 7 years of follow-up. Patients recruited into the OLE of Study IM101-029 (TNF-IR group) showed high rates of sustained response for ACR50 (66.7-78.8%) and ACR70 (40.0-69.6%) during the 4.5 years of follow-up. At the end of the 6 month core period, the rates of ACR50 response were 20.3% for abatacept compared with 3.8% for control treatment ($p<0.001$).

The long-term analysis of subjects involved in Study IM101-102 showed that the proportion of patients who achieved and maintained DAS remission (DAS28<2.6) and LDA over 5 years of follow-up was 60.3-72.3% and 61.2-75.9%, respectively. For the TNF-IR population (Study IM101-029), the rates of sustained DAS remission over 4.5 years of observation were 50.0-61.9% and the rates of LDA were similar. DAS remission and low disease activity were not assessed in Study IM101-100.

The rates of continuing categorical HAQ-DI response (an improvement of at least 0.30 units from baseline) were assessed in the long term follow-up of Studies IM101-102 and IM101-029. Over 4 years of follow-up in Study IM101-102, the percentage of patients who maintained a significant improvement in their HAQ-DI was high at 90.5-92.3%. The rates of HAQ-DI response in the core 12 month part of Study IM101-102 was 49.6% for patients treated with abatacept and 38.1% for subjects from the control group ($p<0.005$). At the end of 6 months in Study IM101-029, the rates of categorical HAQ-DI response were 47.3% for abatacept compared with 23.3% for patients in the control arm ($p<0.001$). Over the OLE period of 4.5 years in Study IM101-029, the rates of maintenance of categorical HAQ-DI response were 62.1-67.6%.

Study IM101-102 (MTX-IR) was the only trial of 3 in this long-term efficacy dataset that collected radiographic outcomes. Plain x-rays were taken annually over the extended follow-up period of 4 years (that is, a total of 5 years when the core phase is added). At the end of 12 months, patients treated with abatacept had a significant improvement in x-ray outcomes compared to those who were in the control group – mean mTSS change of 1.21 versus 2.32 ($p<0.012$), mean erosion score change of 0.63 versus 1.14 ($p<0.29$) and mean change in JSN score of 0.58 versus 1.18 ($p<0.009$). A lower score indicates less radiographic progression. Based on the year-to-year assessment, a decrease in x-ray progression was seen for all 3 scores (mean change from baseline) with the most noticeable change being seen in Year 2. Furthermore, at 4 years of follow-up, 45.1% (106/235) subjects in the original abatacept group and 39.1% (45/115) patients in the original control group who then switched to open-label abatacept had no x-ray progression (as judged by change from baseline in their mTSS).

Efficacy conclusions

The efficacy data from the open-label extension experience of 3 of the core RA studies involving a mixture of adult patients with MTX-IR and TNF-IR RA indicates that treatment with abatacept (often in combination with MTX) results in significant proportions of patients maintaining a clinically significant response (for example ACR 50 and 70 responses and DAS clinical remission or low disease activity) for up to 5 years of follow-up.

Study IM101-064

Adult patients with active RA despite background non-biologic DMARDs were treated with open-label abatacept and continued a non-biologic DMARD in Study IM101-064. Enrolment was controlled such that both previous (off therapy for at least 2 months) and current users of anti-TNF medications were adequately represented (that is, either group had to be at least 1/3 of all recruited subjects). The submission contained a 6 month status report and, as the study is ongoing until commercial drug launch in each country, an addendum of long-term experience (up to ~2.5 years of exposure) as of the data cut-off date of 31 October 2008. The short term phase of the trial commenced in April 2005 and ended in January 2007. A total of 137 sites worldwide enrolled subjects in the trial, 103 in USA, 32 in Europe and 2 centres in Mexico. The primary objective of the study was to assess long-term safety and tolerability; however, efficacy measures were also collected to determine the durability of clinical benefit. Clinical efficacy parameters were assessed with every infusion (~ every 28 days). Patients were expected to receive abatacept at a dose of 10 mg/kg every 4 weeks in conjunction with their continued non-biologic DMARD. At study commencement, patients had taken a mean of 1.5 previous non-biologic DMARDs and 1.8 previous anti-TNF medications indicating significant prior treatment in a disease refractory RA population. The most common prior conventional DMARDs were MTX (77%, 805/1046), leflunomide (23%, 235/1046), anti-malarials (22.5%, 235/1046) and sulfasalazine (14%, 146/1046). Regarding prior or concurrent bDMARDs, 61.4% (642/1046) of subjects had or were receiving etanercept, 63.4% (663/1046) infliximab, 51.0% (533/1046) adalimumab and 15.3% (160/1046) anakinra.

During the study, all but 8 patients received a conventional DMARD which was principally MTX (70.6%, 738/1046). The study report did not specify the mean or median weekly dose of MTX, which is important in verifying the adequacy of adjunctive therapy.

Study Population

The characteristics of the patients recruited into the study were well described and consistent with expectations: age > 18 years, baseline DAS28 of at least 5.1 and RA of at least 1 year duration. The exclusion criteria were identical to the other Phase III studies.

The majority of patients were Caucasian (92.6%) and female (81.3%) with a mean age of 54.7 years. The mean duration of RA was 11.7 years. Subjects treated in the trial had a high level of baseline disease activity at study entry with the mean number of tender and swollen joints being 17.5 and 13.4, respectively. The mean baseline CRP was 23 mg/L and the mean baseline DAS28 was 6.2 indicating severe disease activity. Just over half of all patients were seropositive for RF (61.5%).

Patient Disposition and Drug Exposure

A total of 1286 subjects were enrolled into Study IM101-064 and 1046 received at least 1 dose of abatacept (42.9% [449] were previous anti-TNF users and 57.1% [597] were current anti-TNF users). Most subjects (82.2%, 860/1046) completed the initial 6 months of treatment and follow-up, although 17.8% (186/1046) prematurely discontinued mainly because of insufficient response. The frequencies of reasons for discontinuation were similar between past and current anti-TNF users, except for lack of efficacy which was more common in the current anti-TNF users (12.2% [73/597] versus 7.1% [32/449]).

A total of 530 patients entered into the long-term treatment period of the study and 25 (4.7% of 530) patients from Belgium and Mexico are on-going at data cut-off. The main reason for the high drop-out rate of subjects in the extension period was the commercial availability of abatacept to these patients. During the combined short and long term treatment periods, the mean exposure to abatacept was 13.7 (range: 7.3 – 34.5) months.

Efficacy Parameters

Patients were assessed for the following specified efficacy outcomes at 6 months and on a continual basis in the extension period beyond 6 months:

- Proportion of patients achieving clinically significant improvements in DAS28 (that is, reduction of at least 1.2), as well as the proportion of patients achieving DAS28 remission and EULAR defined Low Disease Activity (LDA – DAS < 3.2),
- Proportion of subjects with a change from baseline in their HAQ-DI score of at least 0.22,
- Changes from baseline in health-related quality of life outcomes such as the SF-36 and Fatigue VAS.

Statistical Analysis and Data Handling Methods

No formal statistical testing was performed on the data. All efficacy analyses were conducted on the as-observed data. Point estimates and 95% confidence intervals were determined for the efficacy variables.

Efficacy results

At 6 months of therapy, the proportion of treated patients who achieved DAS improvement (change of >1.2), DAS remission (DAS28 < 2.6) and LDA (DAS28 < 3.2) was 56.1% (597/1046; 95% CI 53.1, 59.1), 22.4% (234/1046; 95% CI 19.8, 24.9) and 13.0% (136/1046; 95% CI 11.0, 15.0), respectively. The proportion of patients who achieved at least a 0.22 unit reduction from baseline in their HAQ-DI score at 6 months was 46.7% (499/1046; 95% CI 43.7, 49.8) and the mean improvement in HAQ-DI at 6 months was -0.38 units (95% CI -0.42, -0.34; baseline mean = 1.71; n=841). The mean improvements from baseline in the PCS and MCS of the SF-36 achieved at 6 months were 5.82 (95% CI 5.21, 6.44) and 5.15 (95% CI 4.38, 5.92) respectively. The mean baseline PCS was 28.78 and the mean baseline MCS was 42.44 (n=826 for both assessments). Improvements in fatigue, as reflected by mean changes from baseline to 6 months in the fatigue VAS was -19.4 (95% CI -21.2, -17.6; baseline of 72.97; n=831).

During the extended treatment phase of Study IM101-064, improvements in efficacy outcomes were largely maintained to 24 months of follow-up, which is the latest time point whereby sufficient on-going subject participation was observed because of commercial availability of the drug. The proportion of patients maintaining DAS improvement at Day 365 and 729 was 76.9% (163/212) and 86.2% (50/58). Regarding the 12 and 24 month rates of LDA, these were 32.9% (70/213) and 37.3% (22/59) respectively. DAS remission was observed in 14.6% (31/213) at 12 months and 18.6% (11/59) at 24 months. The corresponding rates of categorical HAQ-DI response were 57.7% (124/215) at 12 months and 60.3% (38/63) and 24 months. The mean change from baseline in HAQ-DI was -0.46 at 12 months and -0.51 at 24 months. Furthermore, improvements in health related quality of life outcomes (SF-36 and fatigue VAS) followed the same trend to 2 years with regard to maintenance of improvement.

Efficacy conclusions

The efficacy data from the short-term (6 month) and long-term open-label extension experience of Study IM101-064 indicates that continued treatment for up to 2 years with abatacept results in significant proportions of patients maintaining clinically significant improvements in disease activity (for example changes in DAS28 scores) with supporting improvements in functional and health related quality of life outcomes.

Study IM101-046

Study IM101-046 was a multinational, randomized, double-blind exploratory study of abatacept monotherapy (weight tiered 10 mg/kg) versus placebo infusions in preventing the development of RA in adult patients with undifferentiated inflammatory arthritis (UA) at high risk of progression to RA over the next year (that is, anti-CCP2 antibody positive at baseline). Up until recently, the standard universal diagnostic criteria for RA (1987 ARA criteria) had limited sensitivity and specificity when applied to patients with recent onset inflammatory arthritis compared to subjects with established RA. However, up to 40% of patients referred to hospital based rheumatology centres with recent onset polyarthritis meet the criteria for RA. In addition, no evidence based standard of care exists for patients with UA and the disease has a variable natural history (that is, remission, progression to RA or remaining undifferentiated). However, with an increasing emphasis being placed upon early diagnosis and treatment of RA, these types of studies are useful in guiding clinical practice. The entire duration of the study was 24 months which involved a screening period, a 6 month DB treatment period (randomized 1:1 to either abatacept of placebo infusions on 8 occasions) followed by an 18 month untreated observation phase in those individuals who did not meet the criteria for RA. Subjects with UA were required to have symptomatic clinical synovitis in at least 2 peripheral joints at baseline as well as be positive for anti-CCP2 antibodies. Randomization was stratified by the presence or absence of radiographic erosions of the hands or feet on plain x-rays at baseline, as determined by a central expert reader. Concomitant treatments with corticosteroids and/or NSAIDs were allowed if stable for at least 25 of 28 days immediately prior to baseline. No concurrent DMARDs were permitted for the first 6 months of the study except in those who developed RA. In addition, up to 2 courses of high dose oral corticosteroids were allowed in any 6 month period of the study. Analgesics like paracetamol or tramadol were also allowed but were not to be taken within 12 hours of a joint assessment. Clinical efficacy parameters were collected at screening; monthly in the first 6 months; and then 3-monthly thereafter until 2 years.

Study Population Characteristics

Study IM101-046 was conducted in 21 study sites (4 in North America, 13 in Europe and 4 in Mexico) between September 2005 and April 2008. Subjects were required to be >18 years of age with UA of less than 18 months, positive anti-CCP2 antibodies, clinical synovitis in at least 2 joints and no other rheumatic condition. Significant patient exclusion characteristics were similar to previous RA studies.

The studied population was clearly delineated and the 2 treatment groups were well matched with respect to demographic and baseline disease characteristics. Subjects had a median age of 44.8 years and were predominantly female (71.4%) and Caucasian (85.7%) in racial background. Patients involved in Study IM101-046 had a mean duration of UA of 7.9 months and approximately half (55.4%) had radiographic erosions at baseline. Most patients had a symmetrical pattern of arthritis (87.5%) involving the hands (60.7%) and a total of 2-4 involved joints (78.6%). The mean DAS28-CRP score was 3.5 and CRP values were elevated (mean 11.0 mg/L). In addition, the mean HAQ-DI score was 0.8 which is consistent with a moderate functional impairment. Because the study aimed to recruit patients with early disease duration, subjects in general had a limited quantity of established joint damage: - mean mTSS of 3.6, mean erosion score of 3.5 and mean JSN score of 0.2.

Primary Efficacy Endpoint

The primary efficacy endpoint was the proportion of subjects in each of treatment groups who developed RA within 1 year of commencing blinded study medication.

Secondary Efficacy Endpoints

Secondary efficacy endpoints compared between the 2 treatment groups included:

- The proportion of subjects developing RA or another rheumatic disorder within 2 years,
- The proportion of patients with symptomatic clinical synovitis at 6, 12 and 24 months,
- Mean change from baseline in the DAS28-CRP score and the proportion of subjects with DAS28 < 2.6 at 6, 12 and 24 months,
- Mean change from baseline in inflammation and structural joint damage of the hands and feet as measured by erosion, oedema and synovitis scored by gadolinium MRI at 6, 12 and 24 months,
- Mean change from baseline in the serum levels of anti-CCP2 antibody and the proportion of subjects who became anti-CCP2 antibody negative at 6, 12 and 24 months,
- Proportion of patients achieving an improvement of at least 0.30 units in the HAQ-DI as well as the mean change from baseline in HAQ-DI at 6, 12 and 24 months and
- The mean change from baseline in the Physical and Mental Health Components of the SF-36 at 6, 12 and 24 months.

Additional Efficacy Endpoints

These included assessment at 6, 12 and 24 months of further radiographic outcomes (that is, the mean change from baseline in mTSS, erosion score and JSN score) and clinical endpoints such as the mean percent improvement from baseline in each individual component of the ACR RA composite variable over time.

Statistical Considerations

As this was an exploratory study, analyses were descriptive in nature and no formal statistical comparisons between the 2 treatment groups were planned or conducted. A power calculation estimated that 25 subjects per treatment group would be required. This assumed the incidence of RA at 12 months would be 80% in the placebo group and 40% in the abatacept arm. It was estimated that 625 subjects with early arthritis would need to be screened, 40% [250] of whom would meet the definition of UA and then 20% of those with UA (n=50) were expected to be anti-CCP2 antibody positive.

Patient Disposition and Completion Status

A total of 184 patients were screened, of whom 57 were enrolled and randomized in Study IM101-046 to DB treatment with either abatacept (n=29) or placebo (n=28). One patient randomized to receive abatacept withdrew before any study drug was given, so 28 patients in each treatment group were part of the efficacy analysis. The 6 month completion rate was 78.6% (22/28) for abatacept and 60.7% (17/28) for placebo. The most common reason for premature withdrawal before 6 months was lack of efficacy which affected 28.6% (8/28) of subjects in the placebo group and 10.7% (3/28) patients in the abatacept arm. The completion rate to the primary endpoint (12 months) was 50% (14/28) for patients in the abatacept group and 32.1% (9/28) for subjects in the placebo arm. In total, 11 patients (7 for abatacept and 4 on placebo) completed 24 months of follow-up. The main reason for withdrawal prior to 24 months was lack of efficacy: 50% (14/28) for patients in the abatacept group and 71.4% (20/28) for subjects in the placebo group.

Despite the high premature discontinuation rate in the placebo group, most subjects (75%, 21/28) received at least 6 infusions in the defined treatment period. For those randomized to abatacept therapy, most patients (89.3%, 25/28) had at least 6 infusions in the first 6 months.

Result for primary efficacy variable

The proportion of subjects with UA who developed RA within 1 year was lower for the abatacept group (12/26, 46.2% [95% CI 26.6, 66.6]) compared with the placebo arm (16/24, 66.7% [95% CI 44.7, 84.4]). This results in an estimated treatment difference of -20.5% (95% CI -47.4, 7.8). The primary analysis excluded 1 patient in the placebo group who in retrospect had RA at baseline and another 5 subjects (2 in the abatacept group and 3 in the placebo arm) that withdrew prior to 12 months for reasons other than a lack of efficacy.

Results for secondary efficacy variables

At 24 months, fewer patients with UA initially who then were given abatacept (73.9%, 17/23) developed RA compared to subjects who received placebo therapy (87.5%, 21/24). The magnitude of the treatment difference (-13.6% [95% CI -37.6, 10.8]) was less than that seen at 12 months. No patients evolved into other discernible rheumatic disorders.

The presence of symptomatic synovitis was required at baseline for enrolment. At 6 months, a similar proportion of patients treated with abatacept had persistent synovitis (80%, 4/5) compared with placebo (100%, 12/12). The number of evaluable patients was small because only subjects with consistent evaluations at both time points were included in the analysis. At 12 months, the proportion of subjects with persistent clinical synovitis was comparable between the 2 treatment groups (10 of 11 patients for abatacept versus 7 of 7 patients for placebo).

At the end of the study drug treatment period (6 months), the mean DAS28 (CRP) score was reduced from baseline for patients who received abatacept (n=20; mean change of -1.13 [95% CI -1.56, -0.71] from a baseline of 3.38) but remained unchanged for patients given placebo infusions (n=20; mean change of 0.01 [95% CI -0.55, 0.56] from a baseline of 3.29). The rate of remission (defined as DAS28-CRP < 2.6) at 6 months was higher for patients in the abatacept treatment group (71.4%, 15/21) compared with the placebo arm (35%, 7/20).

Evaluations of DAS28 at 12 and 24 months showed continued but waning improvements in inflammatory activity for the abatacept group (mean change from baseline of -0.50 [95% CI -0.97, -0.03] at 12 months [n=18] and -0.33 [95% CI -1.19, 0.52] at 24 months [n=6]) and either unchanged or worsened disease for the placebo group (mean change from baseline of -0.05 [95% CI -0.98, 0.87] at 12 months [n=13] and 0.69 [95% CI -3.02, 4.39] at 24 months [n=4]). Of the 11 subjects who had DAS28 scores at 24 months, 4 of 7 abatacept patients and 2 of 4 placebo subjects had DAS remission.

A total of 11 subjects in the abatacept group and 10 in the control arm had gadolinium enhanced MRI assessments of the hands and feet by protocol design (only done in European sites) at baseline and then again at 6 months. Mean changes from baseline in MRI bone erosion and synovitis scores at 6 months indicated minimal disease progression in the abatacept group (mean change of 0.45 [95% CI -0.36, 1.27] from a baseline of 3.18 for erosion score; and 0.27 [95% CI -0.97, 1.51] from a baseline of 1.00 for synovitis score) compared with larger changes indicative of disease progression in the placebo group (mean changes of 1.20 [95% CI -1.27, 3.67] from a baseline of 2.40 for erosion score; and 1.60 [95% CI -1.18, 4.38] from a baseline of 1.30 for synovitis score). Mean changes from baseline in MRI bone oedema scores at 6 months indicated an improvement with abatacept (mean change of -1.64 [95% CI -4.94, 1.67] from a baseline of 2.36) but worsening with placebo (mean change of 1.40 [95% CI -2.19, 4.99] from a baseline of 3.40). A similar pattern of results with respect to all 3 MRI scores was seen at 12 and 24 months, albeit very small patient numbers (9 abatacept and 6 placebo subjects at 12 months; and 5 abatacept and 2 placebo patients at 24 months).

Consistent with protocol, all subjects were positive for anti-CCP antibodies at baseline. The mean change from baseline in anti-CCP2 titres was -94.5 U/L at 6 months (n=21; baseline 227.6 U/L) and -6.46 U/L at 12 months (n=14; baseline 270.0 U/L) for those given abatacept. In the placebo group, levels of anti-CCP at 6 and 12 months increased relative to baseline (mean change of 16.32 U/L at 6 months [n=19; baseline 145.5 U/L] and 149.5 U/L at 12 months [n=10; baseline 212.9 U/L]). No patient in the placebo group became seronegative over the 24 month study but 2 patients given abatacept did so from Day 169 through to Day 729.

The proportion of patients in each of the treatment groups who achieved an improvement of at least 0.30 units from baseline in the HAQ-DI was greater for the abatacept group than for the placebo arm at 6, 12 and 24 months. At the end of the drug treatment phase (6 months), 16 of 26 subjects (61.5%; 95% CI 40.6, 79.8) given abatacept achieved this outcome versus 6 of 25 patients (24.0%; 95% CI 9.4, 45.1) in the control group. The estimate of difference between the 2 treatment groups for this outcome at 6 months is 37.5% (95% CI 9.9, 61.4). The proportion of patients in the abatacept group who had a clinically significant improvement in HAQ-DI after a further 6 and 18 months of untreated follow-up (36.0% [9/25] at 12 months and 14.3% [3/21] at 24 months) was less than that observed at 6 months but numerically higher than the placebo group (12.0% [3/25] at 12 months and 4.2% [1/24] at 24 months).

Regarding the SF-36 results, larger mean improvements from baseline PCS and MCS were seen for those received abatacept at 6, 12 and 24 months. The mean improvement from

baseline to 6 months for the abatacept treatment group (n=26) was 10.23 for the PCS (baseline 39.50) and 2.54 for the MCS (baseline 47.69). Mean changes in the PCS (change of 1.95 from a baseline of 41.10) and MCS (change of -0.30 from a baseline of 48.79) were small for the placebo group (n=20). At 12 and 24 months, the mean changes for both the PCS and MCS were higher but clinically insignificant in those who had received abatacept (mean change in PCS of 3.83 at 12 months [n=20] and 2.46 at 24 months [n=7]; mean change in MCS of 2.50 at 12 months and 3.75 at 24 months) compared with patients who received placebo (mean change in PCS of -0.81 at 12 months [n=14] and -2.17 at 24 months [n=5]; mean change in MCS of -2.89 at 12 months and -3.30 at 24 months).

Supporting or Exploratory Endpoints

Subjects in both groups had minimal bone erosion and JSN at baseline. At the 6 month radiographic assessment, both treatment groups had little mean change from baseline for all three x-ray scores (mTSS, erosion score and JSN score): change of 0-0.13 for all three endpoints for the abatacept group (n=22) and 0.01-0.47 for the placebo group (n=21). There was a trend in favour of previous abatacept treatment at 12 months but the number of evaluable subjects remaining at 24 months of follow-up (n=7 for abatacept and n=3 for placebo) makes it difficult to make any meaningful conclusions from the available data. The 12 month data for the abatacept group (n=17) showed a mean change of 0.02 for erosion score (baseline 3.40), 0 for JSN score (baseline 0.03) and 0.02 for the total mTSS score (baseline 3.43). Hence, the absence of erosive damage 6 months after abatacept therapy was evident but this was not seen in the control group. At 12 months, the placebo group (n=11) had a mean change of 0.85 for erosion score (baseline 3.04), 0.26 for JSN score (baseline 0.00) and 1.11 for the total mTSS score (baseline 3.04).

Patients in the abatacept group showed mean percent improvements in the individual ACR components by the end of the active study treatment period as evidenced at 6 months by a mean percent improvement from baseline in the tender joint count, swollen joint count and subject-rated pain of 65%, 57% and 70% respectively. However, these improvements were not maintained once abatacept was discontinued because the 12 and 24 month assessments in tender and swollen joint counts, as well as subject-rated pain, subsequently deteriorated. In comparison, the control group showed a worsening in ACR core components from the outset with the 6 month mean percent changes in the tender and swollen count and subject-rated pain being -63%, -10.5% and -83% respectively.

Study Conclusion

> Study IM101-046 was an exploratory trial whereby patients with undifferentiated inflammatory arthritis had a tendency towards less progression to definite RA (primary efficacy result) after receiving 6 months of monotherapy with abatacept 10 mg/kg compared to placebo. In addition, several secondary endpoints (physical function, radiographic and health-related quality of life) showed improvements with abatacept over no specific anti-rheumatic treatment. In general, the improvements in outcomes diminished with time (up to 18 months post-treatment) once abatacept was ceased. Further studies are required to delineate the optimal duration of treatment in this patient group.

Study IM101-071

Study IM101-071 was a multicentre, placebo-controlled, randomized (1:1:1) study of 2 doses of abatacept (weight tiered at 2 or 10 mg/kg) or placebo infusions on a background of continued MTX in adult Japanese patients with active RA. The study was of 6 months duration and had a similar design to another Phase II study (IM101-100). This trial aimed to reproduce the results in Japanese subjects. Abatacept was given IV on study Days 1, 15, 29 and thereafter every 28 days until Day 141. Subjects were assessed up until Day 169 (6

months). Subjects were required to be receiving MTX (6-8 mg/week) for at least for 12 weeks prior to inclusion, with a stable dose of MTX in the immediately preceding 28 days.

Study Population Characteristics

Study IM101-071 was conducted in Japan between June 2005 and November 2007. Subjects were required to be >20 years of age and have at least 10 swollen joints, 12 or more painful joints and CRP > 10 mg/L. Significant patient exclusion characteristics were similar to previous RA studies.

The studied population was clearly delineated and the three treatment groups were well matched with respect to demographic and baseline disease characteristics. Subjects had a mean age of 52.5-53.4 (range: 22-79) years and were predominantly female (~80%) with a relatively low body weight (mean of 56 kg). Patients involved in Study IM101-071 had a mean duration of RA of 7.3-8.5 years. Baseline disease parameters reflect active inflammatory joint disease – mean tender joint count of 21, mean swollen joint count of 17, mean HAQ-DI score of 1.24-1.50 and CRP values were elevated (mean 33 mg/L). The mean weekly dose of MTX at baseline and throughout the study was 7.1 mg, which is substantially lower than doses used in all other parts of the world.

Efficacy Endpoints

The proportion of subjects in each of treatment group at 6 months achieving:

- ACR20, 50 or 70 response,
- Improvements from baseline in DAS28-CRP score of at least 1.2 and those who achieved DAS remission (score <2.6),
- Improvement in the HAQ-DI of at least 0.30 units and
- The mean change from baseline in the SF-36 PCS and MCS.

Statistical Considerations

Descriptive statistics were provided for all clinical variables in each of the 3 treatment groups. The primary efficacy analysis was to test a non-zero slope of the dose-response using the Cochran-Armitage Chi square trend test for proportions. If the slope was statistically significant at the 5% level, a sequential testing procedure was used to preserve the overall alpha at 5%. First, a Chi square test was used to compare the abatacept 10 mg/kg dose group on day 169 with the placebo group and if this was significant then the abatacept 2 mg/kg data was compared to placebo.

The power calculation was based on the ACR20 response rates observed in Study IM101-100. It was estimated that 57 subjects per treatment group would be required to provide 80% power in detecting a linear trend in the dose-response curve at the 5% level (2-sided). The sample size was then adjusted for a 5% drop-out rate (n=3 for each group) between screening and first treatment. Hence, it was calculated that 60 subjects per treatment group were required.

Patient Disposition and Completion Status

Of the 195 patients enrolled into Study IM101-071, 194 received study drug treatment (n= 61 for abatacept 10 mg/kg, n=67 for abatacept 2 mg/kg and n=66 for placebo). One patient randomized to abatacept 10 mg/kg withdrew before any study drug was given. Most patients in each treatment group completed 6 months of follow-up: 100% (61/61) for abatacept 10 mg/kg, 98.5% (66/67) for abatacept 2 mg/kg and 86.4% (57/66) for placebo. The most common reasons for premature withdrawal in the placebo group were lack of efficacy (n=3) and patient request for discontinuation (n=3).

Results for efficacy variables

The proportion of subjects who achieved an ACR20 response at 6 months was 77.0% (47/61) for abatacept 10 mg/kg, 62.7% (42/67) for abatacept 2 mg/kg and 21.2% (14/66) for placebo. The estimated treatment difference between the high dose abatacept group and placebo was 55.8% (95% CI 41.4, 70.3) and the estimated treatment difference between the low dose abatacept group and placebo was 41.5% (95% CI 26.3, 56.7). Both of these pairwise comparisons between abatacept and placebo were statistically significant ($p<0.001$) and suggested a dose-response relationship. The data for the 6 month rates of ACR50 and ACR70 response showed a similar trend. The ACR50 response rates at day 169 were 45.9% (28/61) for abatacept 10 mg/kg, 37.3% (25/67) for abatacept 2 mg/kg and 6.1% (4/66) for placebo. The treatment differences between abatacept and placebo were 39.8% (95% CI 26.1, 53.6) for high dose abatacept and 31.3% (95% CI 18.3, 44.2) for low dose abatacept. Both pairwise analyses were statistically significant ($p<0.001$). The rates of ACR70 response at 6 months were 21.3% (13/61) for abatacept 10 mg/kg, 16.4% (11/67) for abatacept 2 mg/kg and 0 for placebo. Again, the treatment differences between either dose of abatacept and placebo were statistically significant ($p<0.001$) at 21.3% (95% CI 11.0, 31.6) for high dose abatacept and 16.4% (95% CI 7.5, 25.3) for low dose abatacept.

At 6 months, a higher proportion of patients treated with abatacept (86.9% [53/61] for high dose and 65.7% [44/67] for low dose) showed improvements in their DAS28 of at least 1.2 compared those who received placebo (28.8%, 19/66). The rates of DAS remission were 37.7% (23/61) for abatacept 10 mg/kg, 25.4% (17/67) for abatacept 2 mg/kg and 7.6% (5/67) for placebo.

The proportion of patients in each of the treatment groups who achieved an improvement from baseline of at least 0.30 units at 6 months baseline in the HAQ-DI was greater for the abatacept treatment groups than for the placebo arm: 60.7% (37/61) for abatacept 10 mg/kg, 49.3% (33/67) for abatacept 2 mg/kg and 24.2% (16/66) in the control group.

Larger mean improvements from baseline to 6 months were seen for all 8 items of the SF-36 for those who received abatacept 10 mg/kg. The mean improvement from baseline to 6 months for the abatacept 2 mg/kg treatment group were also significant for 7 of the 8 items comprising the SF-36 (changes in bodily function was not significant).

Study Conclusion

> Study IM101-071 confirmed the results of another dose finding trial (Study IM101-100) whereby patients with RA who received 6 months of abatacept 10 mg/kg + low dose MTX demonstrated significant improvements in disease activity compared to placebo. Patients who received the lower dose of abatacept (2 mg/kg) also showed improvements in the signs and symptoms of RA, physical function and health-related quality of life but the magnitude of these improvements was less than the higher dose of abatacept (10 mg/kg).

Safety

Introduction

The safety analysis included all patients who received at least part of 1 dose of study medication during the clinical trial program. Up to the cut-off date for this submission (31 October 2008), 4632 patients comprised the all exposure population (that is, received at least 1 dose of abatacept, either in a controlled or open-label setting) for the assessment of safety. In total, 1030 of these patients have received treatment with abatacept for at least 5 years. The all exposure population experience provides a total of 12,375 patient years (PY) of observation following treatment with abatacept. The mean exposure to abatacept

for the integrated safety population is 34.2 months (median 30.0 months) with an average of 35.5 infusions being given.

In this report, the safety data will be presented as follows. Firstly, the new pivotal study (IM101-023) in MTX naïve adult subjects will be discussed by 2 separate observation periods (the first 12 months of controlled observation, then OLE to 2 years). The cumulative experience of 483 subjects up to 2 years provides 717 PY of exposure. Secondly, the significant supporting study (IM101-043) will be presented by 2 observation periods – initial controlled 12 months and second year of OLE. Thirdly, the OLE Study IM101-064 will be evaluated. Fourthly, the integrated OLE experience of the 5 core Phase III licensing studies will be considered together (Studies IM101-100 and IM101-102 for the MTX-IR population; Study IM101-029 for TNF-IR population; and Studies IM101-031 and IM101-101 for other background treatment exposure). Thereafter, 3 other supporting studies will be presented individually – Studies IM101-046, IM101-034 and IM101-129.

Study IM101-023 (1 year status)

The safety population consisted of all randomized patients who received at least 1 dose of study medication. Two subjects were randomized but never received any study medication and thus were excluded from the safety analysis. Safety information was recorded on Days 1, 15 and 28 and then every 4 weeks thereafter until Week 52. Adverse Events (AE) were classified using the Medical Dictionary for Regulatory Activities (MedDRA, version 10.1) into preferred terms by System Organ Class (SOC). 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 majority of patients in both treatment groups received 14 infusions of study medication – 76.2% (195/256) for abatacept + MTX and 74.3% (188/253) for placebo + MTX. Most other patients (18.4% [47/256] for abatacept + MTX and 18.6% (47/253) for placebo + MTX) received between 8-13 infusions during the first 12 months.

Twelve subjects (5 [2.0%] on abatacept + MTX and 7 [2.8%] receiving placebo + MTX had their MTX discontinued during the trial; 112 subjects (53 [20.7%] on abatacept + MTX and 59 [22.3%] on placebo + MTX) had their MTX therapy interrupted; and 125 patients (57 [22.3%] on abatacept + MTX and 68 [26.9%] on placebo + MTX) had the MTX dose reduced, mainly because of experiencing AEs.

Protocol Rules for Dose Modification

The following rules applied to dose modifications or changes in dose administration during the double-blind phase of the study. If subjects experienced an increase in serum transaminases (alanine transaminase [ALT] or aspartate transaminase [AST]) of at least 3 x ULN (Upper Limit of Normal) then 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. The presence of any signs suggestive of infection required with-holding of treatment and study medication was to recommence after resolution of the infection. Patients with an absolute neutrophil count of < $1000/mm^3$ were to interrupt study treatment or discontinue therapy if the neutrophil count was < $500/mm^3$.

Overview of Adverse Events

During the first 52 weeks of treatment, the incidence and profile of AEs, serious adverse events (SAEs) and AEs leading to withdrawal or dose interruption were similar for patients who received abatacept compared to placebo + MTX subjects. The overall

percentages of patients who experienced any AE were 84.8% (217/256) for patients who received abatacept + MTX compared to 83.4% (211/253) for placebo + MTX subjects. The proportion of subjects with treatment related AEs was lower in the abatacept + MTX group (38.3%, 98/256) compared to the placebo + MTX arm (45.1%, 114/253). The only type of AE that occurred at a higher incidence in those who were given abatacept was acute infusional reactions (6.3% [16/256] for abatacept + MTX versus 2.0% [5/253] for placebo infusions + MTX) and peri-infusional AEs (12.5% [32/256] for abatacept + MTX versus 9.9% [25/253] for placebo infusions + MTX).

Adverse events leading to withdrawal

A similar proportion of subjects treated with abatacept + MTX (3.1%, 8/256) and placebo + MTX (4.3%, 11/253) withdrew from the study due to AEs. In addition, the type of AEs resulting in withdrawal was similar, apart from 1 patient treated with abatacept who withdrew due to an infusion reaction. The subject developed pruritus and urticaria on study Day 35 during the third infusion of abatacept despite prophylactic antihistamine and corticosteroid. The patient reported pruritis during her first infusion of abatacept. Two patients (1 in each treatment group) discontinued from the study because they developed systemic lupus erythematosus (SLE). Two patients (1 in each treatment group) withdrew because of elevated serum transaminases. One patient discontinued from the trial because of malignancy (pancreatic carcinoma in a patient treated with abatacept + MTX). Two patients (1 from each group) withdrew because of interstitial lung disease and a further 2 patients (1 in each arm) other respiratory related problems (a case of pneumonia in a subject treated with placebo infusions + MTX and a case of cryptogenic organizing pneumonia in a patient in the abatacept + MTX group). The other AEs leading to withdrawal were experienced by individual patients, apart from the 2 cases of gastrointestinal disorders (nausea and/or vomiting) in patients who received placebo + MTX.

In addition to AEs resulting in patient withdrawal, a significant number of subjects had their study medication interrupted for safety reasons. This occurred at a similar frequency in patients who received abatacept – 20.7% (53/256) for abatacept + MTX and 23.3% (59/253) for placebo + MTX. The most common reasons for medication interruptions were infections of minor severity (mainly, upper respiratory tract infections) and gastrointestinal disorders.

Most Frequent Adverse Events (Event rate of > 5%)

The most common AE was nausea which occurred at a higher frequency in patients treated with placebo + MTX (16.2%, 41/253) compared to abatacept + MTX (10.2%, 26/256). The other most common AEs (event frequency > 5%) with a similar incidence across the 2 treatment groups were headache (9.1-11.7%), upper respiratory tract infection (10.2-10.3%) and nasopharyngitis (8.2-10.3%). Other noteworthy common events occurring at a similar event frequency in both groups were urinary tract infection (6.6-8.7%), hypertension (5.5-6.6%), gastroenteritis (3.1-5.1%) and increased serum transaminases (5.1-6.3%).

Infusion Related Reactions

Infusion related reactions were divided into 2 overlapping, time-defined categories. Adverse events occurring during or within 1 hour of each infusion were defined as “acute infusion AEs” and may be linked to cytokine release. Symptoms or signs suggesting an acute infusion reaction include pruritus, fever, urticaria/rash, pyrexia, chills, rigors, angioedema, throat irritation, cough, bronchospasm, with or without associated hypotension or hypertension. “Peri-infusional AEs” were defined as those occurring

during the first 24 hours after the commencement of a study drug infusion. A similar approach was taken in all the trials.

Patients receiving abatacept (6.3%, 16/256) experienced acute infusion AEs at a higher event rate compared to subjects who were given placebo infusions (2.0%, 5/253). All but 1 of the acute infusion AEs was of mild or moderate severity. The patient who experienced a severe infusion reaction has been previously detailed in the study treatment withdrawal section.

Patients who received abatacept + MTX (12.5%, 32/256) also had a higher incidence of peri-infusional AEs than subjects who received placebo + MTX (9.9%, 25/253). In general, the pattern of AEs was similar between the placebo and abatacept treatment groups with the most common AEs being nervous system disorders (dizziness and headache), gastrointestinal (mainly nausea [3.1-3.2%]) and hypertension (1.6-2.4%). However, 2 types of AE occurred at a higher incidence in the abatacept + MTX group compared to placebo + MTX and these include dizziness (3.1% [9/256] versus 1.6% [4/253]) and headache (3.1% versus 1.6%). The majority of peri-infusional AEs were mild to moderate in severity; however, 2 patients (both on abatacept) experienced severe reactions. One of the severe acute infusion reactions consisted of urticaria that led to the patient withdrawing from the study, while the other severe infusion-related AE was a case of severe headache that resolved without specific treatment within 24 hours.

Serious Adverse Events (SAEs)

The incidence of SAEs up until 12 months was comparable between 2 treatment groups: - 7.8% (20/256) for patients in the abatacept + MTX group and 7.9% (20/253) for subjects in the placebo + MTX arm. The most common types of SAE were infections, respiratory conditions and gastrointestinal disorders. Infectious SAEs were observed in 5 patients (2.0%) from each of the treatment groups. Two patients in the abatacept group and 3 subjects in the placebo + MTX group had severe pneumonia, while severe soft tissue infections were recorded in 3 patients treated with abatacept + MTX and 2 subjects receiving placebo + MTX. Three patients in each treatment group had SAEs affecting the respiratory system, including 1 case of cryptogenic organizing pneumonia in a patient treated with abatacept + MTX. Overall, gastrointestinal disorders occurred in 3 patients treated with abatacept + MTX compared with 1 placebo + MTX treated patients. All other types of SAEs (for example, skin and cardiac disorders) occurred in such small patient numbers that conclusions about comparative incidence between the treatment groups cannot be drawn.

Infectious Adverse Events

(a) Overall

Up to Week 52, the overall infection rate was similar in subjects treated with abatacept + MTX (mild 29.7% [76/256] and moderate 20.3% [52/256]) to those who received placebo + MTX (mild 26.5% [67/253] and moderate 26.1% [66/253]). The most frequently recorded types of infection (occurring in >2.5% of subjects in either treatment group) were upper respiratory tract infections (URTIs) (12.1% [31/256] for abatacept vs 10.3% [26/253] for placebo + MTX), nasopharyngitis (8.2% [21/256] for abatacept vs 10.3% [26/253] for placebo + MTX), urinary tract infection (UTI) (6.6% [17/256] for abatacept vs 8.7% [23/253] for placebo + MTX) and gastroenteritis (4.3% [11/256] for abatacept vs 6.3% [16/253] for placebo + MTX). In addition, other noteworthy infections which occurred at slightly higher frequency in subjects treated with abatacept + MTX included oral herpes (3.5% [9/256] for abatacept vs 2.8% [7/253] for placebo + MTX) and Herpes zoster (2.7% [7/256] for abatacept vs 1.6% [4/253] for placebo + MTX). One patient in each treatment group also experienced genital herpes. Only 1 subject (treated with

placebo infusions + MTX) withdrew from the study during the first 12 months because of an infection.

(b) Serious infectious AEs

Five subjects in each group (2.0%) were observed to have experienced serious infections (defined as those reported as SAEs and/or treated with IV antibiotics) up until Day 365 of follow-up. The most frequently reported types of serious infection were pneumonia (5 cases – 3 for placebo + MTX and 2 for abatacept + MTX) and soft tissue infections (5 cases – 3 for abatacept + MTX and 2 for placebo + MTX). There were no reports of opportunistic infection such as tuberculosis or unusual fungal infections during the first year of the trial. Furthermore, no deaths were attributed to infection.

Autoimmune Disorders

Analysis of autoimmune (AI) disorders was undertaken because AI is an AE of special interest. Overall, 11 patients experienced AI related conditions in Study IM101-023, 6 of whom received abatacept + MTX and 5 received placebo + MTX. Two of the events (1 patient in each group) related to new cases of SLE, considered to be of moderate severity and resulting in the subjects withdrawing from the study. In addition, there were 2 cases of Sjogren's Syndrome (1 in each treatment group; both of mild severity and probably unrelated to study medication), 2 new cases of skin psoriasis (1 case from each arm; mild severity and possibly related to treatment), 2 cases of dry eyes/sicca syndrome (1 in each group and unrelated to study medication), 2 cases of atrophic gastritis (1 in each group; unrelated to DMARD therapy) and a single case of erythema nodosum in a subject who received abatacept (possibly treatment related).

The proportion of patients who converted from a negative Anti-nuclear Antibody (ANA) status at baseline to positive at Day 365 was similar for both treatment groups (9.3% [10/107] for subjects receiving abatacept + MTX and 10.4% [12/115] for patients in the placebo + MTX arm). Furthermore, the percentage of subjects who converted from a negative Anti-double stranded DNA at baseline to a positive result at 1 year was similar between the groups (0.5% [1/200] for subjects receiving abatacept + MTX and 1.5% [3/206] for patients in the placebo + MTX arm).

Malignancy

Only 1 patient developed a malignant neoplasm in the first 12 months of treatment. The subject (a 67 year old Asian male with a history of smoking) received 12 infusions of abatacept (750 mg) + MTX and discontinued study treatment on Day 288 because of a pancreatic carcinoma. The event is considered to be of an unlikely relationship to study treatment.

Deaths

Six patients (2 in the abatacept + MTX group and 4 in the placebo + MTX group) died during the first 12 months of the study. A 69 year old male who received a total of 12 abatacept (500 mg) infusions + MTX died on Day 324 (43 days after last abatacept infusion) of hypovolaemic shock secondary to upper gastrointestinal bleeding. At the time of his death, the patient was still recovering from pneumonia treated with levofloxacin that had onset 12 days earlier. Another subject, a 46 year old female, unexpectedly died on Day 317 of an acute myocardial infarction 3 days after receiving her 13th dose of abatacept (750 mg) + MTX. The submission did not contain narratives for the deceased patients who received placebo infusions + MTX.

Use in Pregnancy

The effect of study medication on pregnancy and lactation was not specifically examined in Study IM101-023. Female subjects were to have a negative pregnancy test at screening and patients of either gender were requested to use a reliable method on contraception (barrier and/or hormonal) during the study. However, 2 female patients (both treated with abatacept + MTX) became pregnant during the study. One subject was identified on study Day 1 as being pregnant but because of a delay in returning the test results subsequently received a single infusion of abatacept 750 mg plus commenced oral MTX. This patient was presumed to have had a spontaneous abortion as follow-up testing and specialist review on Day 36 confirmed that she was no longer pregnant. The other subject was a 32 year old female who was identified on study Day 262 as being pregnant and elected to have an abortion.

Laboratory Test Evaluations

The proportion of subjects who experienced marked changes from baseline in laboratory parameters was low for both treatment groups and no new safety issues were identified.

Haematology

No significant differences between the 2 treatment groups were observed for the mean changes in red blood cell count, haematocrit fraction, white cell count or platelet count up to 52 weeks. Furthermore, the proportion of patients who had a recorded AE because of a marked haematological laboratory abnormality was similar between the treatment groups. The most common haematological abnormality was lymphopenia which was recorded in 5.1% (13/254) of subjects treated with abatacept + MTX and 11.5% (29/252) of those in the placebo + MTX treatment group. Neutropenia was observed in 0.8% (2/254) treated with abatacept + MTX and 2.0% (5/252) given placebo + MTX. One subject treated with placebo infusions + MTX developed Grade 1 thrombocytopenia (platelet count 140 x 10^9/L from a baseline value of 450 x 10^9/L).

Liver and Kidney Function Abnormalities

The mean values and mean changes from baseline for blood chemistry parameters were similar for both treatment groups at 12 months. Patients treated with abatacept + MTX had a smaller incidence of elevations in hepatic transaminases (ALT or AST) or serum bilirubin than subjects who received placebo infusions + MTX. At Day 365, the percentage of patients treated with abatacept + MTX who had ALT results >ULN (from normal at baseline) at any time point was 5.9% (15/254) compared with 8.3% (21/253) for placebo + MTX. A similar observation was recorded for the proportion of subjects who had AST values >ULN – 2.8% (7/254) for abatacept + MTX versus 5.5% (14/253) for placebo + MTX. Moreover, 2 patients who received treatment with placebo + MTX had transient minor elevations in their serum bilirubin during the first year of the study.

The proportion of subjects up to Week 52 who recorded a significant increase from baseline in serum creatinine was similar between the treatment groups (13.0% [33/254] for abatacept + MTX compared to 12.7% [32/251] for the placebo + MTX arm).

Vital Signs

No treatment-based trend of change in vital signs (blood pressure, heart rate, respiratory rate and temperature) was observed during the 12 month study. Vital signs were only taken immediately before dosing and 60 minutes after the start of infusion of study medication. Hypertension was recorded within 60 minutes of infusion commencement in 2 patients treated with abatacept compared to 1 subject who was given placebo infusions.

Another patient while receiving their infusion of abatacept developed hypotension. All of these events were considered to be of either mild or moderate severity.

Safety conclusions

In Study IM101-023, abatacept (10 mg/kg) in combination with MTX was generally well tolerated in MTX naïve patients with recent onset, moderately-severely active RA. In particular, the proportion of patients who experienced AEs (including SAEs) and discontinuations due to AEs was comparable to those who received placebo infusions + MTX. Specific events of interest (such as infection, neoplasm and autoimmune disorders) with the use of an immunomodulator molecule like abatacept were reported at a low and similar frequency for both treatment groups. However, the overall patient numbers and relatively short duration of follow-up (12 months) in the study limits the validity of such an assessment. Some adverse events (namely, infusion related events) occurred at an expectedly higher incidence in those who received abatacept therapy although the absolute incidence and severity of AEs was acceptable in this treatment population.

Study IM101-023 (2 year status)

The safety population for the OLE phase consisted of all patients who received at least 1 dose of abatacept in Year 2 and the results were presented as a single pooled group rather than by their original randomized treatment group. Safety information was recorded every 4 weeks during the second year of the trial with routine laboratory testing taken immediately prior to abatacept infusion administration.

Drug Treatment Exposure

All 459 subjects (232 on abatacept + MTX and 227 on placebo + MTX in year 1) who completed the double-blind treatment period received at least 1 dose of abatacept in the OLE. Most (94.3%, 433/459) completed the second year of treatment and follow-up. Fifteen subjects (3.3% of 459) discontinued during the OLE period because of safety related reasons: 2 deaths, 11 patients due to adverse events and 2 subjects became pregnant.

During the combined 2 year treatment period for Study IM101-023, the mean exposure to abatacept was 18.7 months (median 17.1; range 1.9 – 25.7 months). On average, patients received 19.4 infusions (range: 1-27) over the 2 year study period. The proportion of patients who had at least 24 months of follow-up was 48.6% (223/459) while another 44.4% (204/459) completed 12-18 months of observation. A total of 20 (4.4% of 459) patients missed 2 infusions during the OLE and 2 patients missed 3 non-consecutive infusions.

Overview of Adverse Events and Most Frequent Adverse Events (Event rate of > 5%)

During the OLE phase of treatment (Year 2), AEs were recorded in 75.2% (345/459) of subjects. The pattern of AEs, SAEs and AEs leading to withdrawal or dose interruption in either treatment period (DB or OLE) were similar for patients who received abatacept + MTX. The proportion of subjects considered to have experienced treatment related AEs was lower in the OLE (27.9%, 128/459) compared with the DB phase (38.3%, 98/256). The most common AEs reported in the OLE phase of the study were URTI (9.4%), nasopharyngitis (8.7%), influenza (7.4%), UTI (5.7%) and hypertension (5.0%).

Adverse events leading to withdrawal

In the OLE period, 11 subjects (2.4% of 459) withdrew from the study due to AEs, 4 of which were considered serious and a total of 5 were considered to be treatment related. There was no particular pattern to the type of AEs resulting in withdrawal as all events

were singular in occurrence. However, 1 patient withdrew due to a serious infusion reaction (anaphylaxis).

Serious Adverse Events (SAEs)

A total of 29 subjects (6.3% of 459) experienced SAEs during the 12 month OLE phase, of which 10 (2.2% of 459) were considered to be treatment related. Ten recorded infections in 8 subjects (1.7% of 459) was the most common type of SAE: 4 cases of pneumonia (2 of which were fatal; 1 of which had associated septic shock) and singular cases of appendiceal abscess, subcutaneous abscess, folliculitis affecting the face and UTI. Interestingly, one of the subjects who developed severe pneumonia also experienced a moderate severity herpes zoster infection in the fortnight preceding the lung infection. Other common types of SAEs included 4 cases of gastrointestinal disorders (including 1 case of large and small bowel obstruction), 3 subjects with cholelithiasis, 4 subjects with neurological conditions (including 2 cases of convulsion), 5 subjects with cardiovascular disorders (including 2 patients developing significant arrhythmias and 1 case each of acute myocardial infarction and infusion-related anaphylactic shock). The 2 patients who reported generalized convulsions are also noteworthy. One of the subjects had a known history of epilepsy controlled on carbamazepine and lamotrigine and experienced an increase in seizure frequency. However, the other subject (a 53 year old female) with no known history of seizures, experienced new onset hypertension in the setting of severe hyponatraemia (serum sodium nadir of 116 μmol/L) and grand mal convulsions. The SAE onset was 13 days after her tenth infusion of abatacept and resulted in the patient withdrawing from the study. The hypertension and hyponatraemia resolved within 12 days of onset and no further seizures were documented.

The incidence rates of overall SAEs and infectious SAEs were assessed between the double-blind and OLE phase for subjects who received abatacept + MTX. When differences in drug exposure were taken into consideration, the rate of SAEs (overall and infectious) did not significantly differ between the 2 treatment periods. For overall SAEs, the incidence rate was 8.35 per 100 PY (Poisson 95% CI 5.10, 12.90; 20 events for 239.54 PY exposure) for the DB phase compared with 6.42 per 100 PY (Poisson 95% CI 4.30, 9.22; 29 events for 451.70 PY exposure) for the OLE period. For infectious SAEs, the incidence rate was 2.04 per 100 PY (Poisson 95% CI 0.66, 4.77; 5 events for 244.85 PY exposure) for the DB phase versus 1.73 per 100 PY (Poisson 95% CI 0.75, 3.42; 8 events for 461.57 PY exposure) for the OLE period.

Infusion Related Reactions

Acute infusion AEs were reported for 12 (2.6% of 459) subjects during Year 2 of the study. These events included 5 cases of hypertension and 1 patient suffered a severe infusion reaction. This subject (68 year old female) who received placebo infusions + MTX in Year 1, developed anaphylaxis (characterized by nausea, vomiting, tachycardia, hypotension and clamminess) during her first infusion of abatacept 750 mg on Day 1 of the OLE phase. She was admitted overnight to hospital after receiving emergency treatment with corticosteroid, antihistamine and intravenous fluid resuscitation. The patient withdrew from the study as a result of the AE that occurred during her first infusion of abatacept.

In the OLE, a total of 29 patients (6.3% of 459) experienced peri-infusional AEs. Most of these AEs were either of mild or moderate severity. However, in addition to the case of anaphylaxis already described, another patient developed severe hypertension within 24 hours of abatacept infusion.

Infectious Adverse Events

(a) Overall

During the OLE, infections were reported in 218 subjects (47.5% of 459) treated with abatacept + MTX. The most frequently recorded types of infection were respiratory tract (URTI 9.4% [43/459], nasopharyngitis 8.7% [40/459], influenza 7.4% [34/459], bronchitis 4.8% [22/459] pharyngitis 4.1% [19/459] and sinusitis 3.3% [15/459]), UTI (5.7%, [26/459] and gastroenteritis (4.4%, [20/459]). Other noteworthy infections occurring at lower frequency included oral herpes (2.4% [11/459]) and herpes zoster (1.7% [8/459]); as well as 2 cases each of genital herpes, varicella and herpes dermatitis. The overall rate of experiencing infection in the OLE was 66.68 per 100 PY (Poisson 95% CI 58.12, 76.14; 218 events for 326.95 PY exposure) which is comparable to that observed in the controlled phase for those who received abatacept + MTX (78.37 per 100 PY; Poisson 95% CI 65.57, 92.93; 132 events for 168.44 PY exposure).

(b) Severe or Opportunistic infectious AEs

Six subjects developed severe infections during the OLE period: 2 cases of pneumonia (both of which were fatal) and singular cases of UTI, gastroenteritis, erysipelas and cervicitis. There were no reports of tuberculosis but 2 potential opportunistic infections were reported. One of the fatal pneumonia cases was considered to be due to *Pneumocystis* infection but this was not conclusively proven. In addition, another subject (56 year old female) withdrew from the study after experiencing dengue fever (graded as moderate severity).

Autoimmune Disorders

In the OLE period, 6 patients experienced autoimmune conditions, consisting of 2 new cases of skin psoriasis (mild to moderate in severity; possibly related to therapy), 2 cases of Sjogren's Syndrome (unrelated to treatment), 1 case of atrophic gastritis (unrelated to treatment) and 1 new case of vasculitis, considered to be of moderate severity and possibly related to study medication.

The proportion of patients who converted from a negative ANA status at baseline to positive at 24 months (10.1% [17/168]) was similar to the rate observed at 12 months (9.3% [10/107] for subjects receiving abatacept + MTX and 10.4% [12/115] for patients in the placebo + MTX arm). Furthermore, the percentage of subjects (~1%) who converted from a negative Anti-double stranded DNA at baseline to a positive result at 2 years (3/304) was similar to that observed at 12 months (4/406).

Malignancy

No patients developed a malignant neoplasm in the OLE period of the trial. Five subjects reported benign lesions (such as skin papilloma) which are unrelated to study medication.

Deaths

Two patients (1 from each of the original treatment groups) died during the OLE period. Both deaths were due to pneumonia, 1 of which with associated septic shock. A 57 year old female who received a total of 16 abatacept infusions + MTX died on Day 465 (23 days after her last abatacept infusion) of presumed *Pneumocystis* pneumonia despite ventilatory support. Another subject, a 72 year old female, died on Day 701 of severe pneumonia 3 days after receiving her 12th dose of abatacept (+ MTX) in the OLE phase. Both events would appear to be associated with study medication.

Use in Pregnancy

The effect of study medication on pregnancy and lactation was not specifically examined in Study IM101-023. However, 2 female patients became pregnant during the OLE phase of the study. One subject who received a total of 23 infusions of abatacept had a spontaneous abortion on day 623. She was 35 years of age and had 4 previous successful pregnancies without complications. The other subject was a 20 year old female who was identified on study Day 620 (soon after her 9th infusion of abatacept) as being pregnant and subsequently delivered a healthy infant without any difficulties during the pregnancy.

Laboratory Test Evaluations

Haematology

Consistent with improvement in inflammatory disease status, the mean changes from baseline in haemoglobin level (mean improvement of 0.70 g/dL), white cell count (mean decrease of 1.88 x 10^9/L) and platelet count (mean decrease of 90 x 10^9/L) up to 24 months were within expectations. In addition, the proportion of patients who met the criteria for a markedly abnormal haematological laboratory abnormality was similar between the OLE and DB treatment phases. The most common haematological abnormality was lymphopenia which was recorded in 5.1% (13/254) of subjects treated with abatacept + MTX in the DB period and 8.5% (39/459) of those in the OLE phase. Neutropenia was observed in 0.8% (2/254) treated with abatacept + MTX in the DB study and 3.1% (14/458) in the OLE phase. Most of patients that developed markedly abnormal haematological parameters had transient abnormalities without clinical consequences. However, of note, 1 subject developed Grade 1 pancytopenia during the OLE period which resolved without treatment and did not lead to discontinuation from the trial. Another subject had extended periods of markedly low lymphocytes without any associated AEs (including infection).

Blood Chemistry Abnormalities

The mean values and mean changes from baseline for blood chemistry parameters (namely, serum transaminases [ALT or AST] and creatinine) were similar for both treatment periods (the initial and subsequent 12 months). Patients treated with abatacept + MTX in Year 2 of the study [5.2% (24/459)] had a similar incidence of elevations in hepatic transaminases (from normal at baseline to any level > ULN) compared with subjects who received the same treatment in Year 1 [5.9% (15/254)]. Most patients who recorded elevations in their serum transaminases had minor degrees of elevation (< x 2 ULN) and were transient in nature.

The most common laboratory abnormality in the OLE part of the study was the proportion of subjects who recorded a significant increase from baseline in serum creatinine (17.7% [81/459]). This result was slightly higher than that observed in the DB treatment phase (13.0% [33/254]).

Safety conclusions

In Year 2 of Study IM101-023 (the open-label extension phase), abatacept (10 mg/kg) in combination with MTX was continued to be well tolerated in most adult patients with RA. In particular, the incidence rate of SAEs (including infection related SAEs) was comparable between the open-label and double-blind treatment phases. However, 2 patients died of pulmonary infection related to their treatment and acute infusion reactions (including 1 case of anaphylaxis) were reported for 12 subjects (2.6%). No new safety signals emerged from the trial's open-label extension period.

Study IM101-043 (1 year status)

Study IM101-043 was a controlled study of 1 year duration with 2 treatment periods (Period 1 [Days 1-197] and Period 2 [Days 198-365]) whereby adult subjects with active RA who were inadequate responders to MTX were randomized 3:3:2 into 1 of 3 possible treatment groups for the initial 6 months: abatacept infusions (10 mg/kg) + MTX, infliximab infusions (3 mg/kg) + MTX or placebo infusions + MTX. All patients treated with placebo infusions + MTX in period 1 were re-allocated to receive abatacept + MTX in Period 2, whereas patients in either of the bDMARD groups continued their same treatment in Period 2.

The safety population consisted of all randomized patients who received at least 1 dose of study medication. Safety information was recorded on Days 1, 15 and 28 and then every 4 weeks thereafter until Week 52. The study report classified patients into 3 distinct treatment categories: Days 1-197 for all 3 of the original groups, Days 1-365 for abatacept and infliximab arms and Days 198-365 for the patients who switched from placebo infusions to abatacept.

Drug Treatment Exposure

The mean duration of exposure to study drug for the first 6 months for all 3 treatment groups was close to the planned duration of 197 days (193.8 days for abatacept + MTX, 191.7 days for infliximab + MTX and 194.4 days for the placebo + MTX group). Mean exposure across the entire 12 month DB period was 352.7 days for abatacept + MTX and 347.4 days for infliximab + MTX. The median number of infusions was 15 for patients in both bDMARD groups and more than 90% of subjects in both groups received treatment for greater than 10 months. Eleven subjects (3 [1.9% of 156] on abatacept + MTX and 8 [4.8% of 165] receiving infliximab + MTX) discontinued during Days 1-197 of the trial because of adverse events. A further 7 subjects (2 on abatacept + MTX and 5 on infliximab + MTX) discontinued in Period 2 of the study because of adverse events.

Overview of Adverse Events

During Days 1-197, the incidence and profile of overall AEs, treatment related AEs and AEs leading to discontinuation were similar for patients who received abatacept + MTX compared to placebo + MTX subjects (Table 11). The only difference between the 2 treatment groups was a lower rate of SAE in patients who received abatacept + MTX (5.1%, 8/156) compared to 11.8% (13/110) for placebo + MTX subjects. By comparison, during the first 6 months of DB follow-up, a higher proportion of subjects treated with infliximab + MTX compared to placebo + MTX reported treatment related SAEs (4.8% [8/165] vs 2.7% [3/110]) and discontinued because of AEs (4.8% [8/165] vs 0.9% [1/110]). However, the frequencies of overall AEs, treatment related AEs and SAEs were similar between the infliximab and placebo infusion groups.

During the entire 12 month DB period, the percentages of subjects reporting SAEs, treatment related SAEs and discontinuations due to AEs were approximately two fold higher in those who were given infliximab compared with the abatacept group (Table 12). In addition, the frequency of treatment related AEs was higher for infliximab + MTX (58.2%, 96/165) versus abatacept + MTX (46.2%, 72/156).

Table 11: Summary of subjects with AEs reported during Days 1-197 of the DB period

	Number (%) of Subjects							
	ABA (N=156)		INF (N=165)		PLA (N=110)		TOTAL (N=431)	
Deaths	1	(0.6)	1	(0.6)	0		2	(0.5)
SAEs	8	(5.1)	19	(11.5)	13	(11.8)	40	(9.3)
Related SAEs	3	(1.9)	8	(4.8)	3	(2.7)	14	(3.2)
Discontinued due to SAEs	2	(1.3)	4	(2.4)	0		6	(1.4)
AEs	129	(82.7)	140	(84.8)	92	(83.6)	361	(83.8)
Related AEs	64	(41.0)	74	(44.8)	46	(41.8)	184	(42.7)
Discontinued due to AEs	3	(1.9)	8	(4.8)	1	(0.9)	12	(2.8)

Table 12: Summary of subjects with AEs reported during Days 1-365 of the DB period

	Number (%) of Subjects					
	ABA (N=156)		INF (N=165)		TOTAL (N=321)	
Deaths	1	(0.6)	2	(1.2)	3	(0.9)
SAEs	15	(9.6)	30	(18.2)	45	(14.0)
Related SAEs	5	(3.2)	14	(8.5)	19	(5.9)
Discontinued due to SAEs	4	(2.6)	6	(3.6)	10	(3.1)
AEs	139	(89.1)	154	(93.3)	293	(91.3)
Related AEs	72	(46.2)	96	(58.2)	168	(52.3)
Discontinued due to AEs	5	(3.2)	12	(7.3)	17	(5.3)

During the second 6 months of the DB period (Days 198-365), the frequency of overall AEs (64.5%, 71/110) and treatment related AEs (23.6%, 26/110) was lower during the abatacept treatment phase for subjects in the placebo to abatacept treatment switch group compared to the first 6 months of treatment with abatacept in the abatacept group (82.7% [129/156] and 41.0% [64/156], respectively). No subjects in the treatment switch group discontinued due to an AE between study Days 198-365. However, the overall rate of SAEs in this group (10.9%, 12/110) was higher compared to the original abatacept arm (5.1%, 8/156) but similar to the Period 1 rates for the infliximab (11.5%, 19/165) and placebo infusion groups (11.8%, 13/110).

Adverse events leading to withdrawal

During the first 6 months (Days 1-197), a higher proportion of subjects treated with infliximab + MTX (4.8%, 8/165) withdrew from the study due to AEs compared to those who received abatacept + MTX (1.9%, 3/156) and placebo infusions + MTX (0.9%, 1/110). Three patients in the infliximab group withdrew due to infection (including 2 who experienced pneumonia). No subject in other 2 treatment groups withdrew because of infection and all other AEs resulting in withdrawal from the study were singular events of unclear relationship to study medications. One patient in the placebo infusion + MTX group discontinued because of raised serum transaminases.

Across the entire 12 month DB period, discontinuations due to AEs were more common in the infliximab group (7.3%, 12/165) than the abatacept arm (3.2%, 5/156). Three patients in the infliximab group withdrew because of pneumonia and another 3 subjects in the same treatment group developed infections (herpes encephalitis, UTI and erysipelas). No subjects in the abatacept group withdrew because of infections. A further 2 patients in the infliximab group discontinued from the study because they developed skin rashes and another 2 patients in the same treatment group withdrew because of gastrointestinal problems. One patient in the abatacept arm discontinued from the trial because of hypertensive crisis. No subject in the treatment switch group withdrew because of an AE.

Most Frequent Adverse Events

A similar percentage of patients in each of the 3 treatment groups reported an AE during Days 1-197: abatacept (82.7%, 129/156), infliximab (84.8%, 140/165) and placebo (83.6%, 92/110). Infections was the most common AE reported in each of the treatment groups and occurred at a similar frequency in all treatment groups: 48.1% (75/156) for abatacept + MTX, 52.1% (86/165) for infliximab + MTX and 51.8% (57/110) for placebo + MTX (Table 13). Nasopharyngitis, URTI and UTI appeared to occur at a lower incidence in those who received abatacept compared to the other 2 groups. The only common types of AE reported at a higher incidence in the abatacept treatment group were dyspepsia (10.9% [17/156] vs 2.7% [3/110] and 7.3% [12/165] for placebo and infliximab, respectively) and diarrhoea (9.6% [15/156] vs 5.5% [6/110] and 7.3% [12/165] for placebo and infliximab, respectively).

Table 13: Subjects with most frequently reported AEs during Days 1-197 of the DB period

SYSTEM ORGAN CLASS (SOC) (%) PREFERRED TERM (PT) (%)	ABA N = 156	INF N = 165	PLA N = 110
TOTAL SUBJECTS WITH AE	129 (82.7)	140 (84.8)	92 (83.6)
INFECTIONS AND INFESTATIONS	75 (48.1)	86 (52.1)	57 (51.8)
NASOPHARYNGITIS	10 (6.4)	17 (10.3)	8 (7.3)
INFLUENZA	8 (5.1)	8 (4.8)	6 (5.5)
PHARYNGITIS	8 (5.1)	6 (3.6)	6 (5.5)
UPPER RESPIRATORY TRACT INFECTION	7 (4.5)	16 (9.7)	14 (12.7)
URINARY TRACT INFECTION	4 (2.6)	7 (4.2)	10 (9.1)
GASTROINTESTINAL DISORDERS	56 (35.9)	65 (39.4)	31 (28.2)
DYSPEPSIA	17 (10.9)	12 (7.3)	3 (2.7)
DIARRHOEA	15 (9.6)	12 (7.3)	6 (5.5)
NAUSEA	14 (9.0)	15 (9.1)	8 (7.3)
NERVOUS SYSTEM DISORDERS	32 (20.5)	41 (24.8)	28 (25.5)
HEADACHE	16 (10.3)	25 (15.2)	18 (16.4)
DIZZINESS	9 (5.8)	8 (4.8)	6 (5.5)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	24 (15.4)	31 (18.8)	19 (17.3)
BACK PAIN	10 (6.4)	8 (4.8)	5 (4.5)
VASCULAR DISORDERS	16 (10.3)	30 (18.2)	12 (10.9)
HYPERTENSION	8 (5.1)	10 (6.1)	10 (9.1)

ABA = Abatacept, INF = Infliximab, and PLA = Placebo.
Population: All Treated Subjects.

Many of the most frequently reported AEs during Days 1-365 were reported at a higher rate in those who received infliximab compared with the abatacept group (Table 14). In particular, several types of AEs were recorded approximately twice or more as frequently in the infliximab group as the abatacept arm: - UTI (10.9% [18/165] for infliximab vs 5.1% [8/156] for abatacept), herpes simplex infection (6.1% [10/165] for infliximab vs 3.8% [6/156] for abatacept), gastroenteritis (7.9% [13/165] for infliximab vs 2.6% [4/156] for abatacept), hypotension (5.5% [9/165] for infliximab vs 0.6% [1/156] for abatacept), insomnia (7.3% [12/165] for infliximab vs 3.2% [5/156] for abatacept) and various types of skin and subcutaneous tissue disorders (30.3% [50/165] for infliximab vs 17.9% [28/156] for abatacept).

Table 14: Subjects with most frequently reported AEs during Days 1-365 of the DB period

SYSTEM ORGAN CLASS (SOC) (%) PREFERRED TERM (PT) (%)	ABA N = 156	INF N = 165
TOTAL SUBJECTS WITH AE	139 (89.1)	154 (93.3)
INFECTIONS AND INFESTATIONS	93 (59.6)	113 (68.5)
NASOPHARYNGITIS	20 (12.8)	26 (15.8)
INFLUENZA	13 (8.3)	11 (6.7)
PHARYNGITIS	12 (7.7)	17 (10.3)
UPPER RESPIRATORY TRACT INFECTION	11 (7.1)	19 (11.5)
SINUSITIS	10 (6.4)	7 (4.2)
URINARY TRACT INFECTION	8 (5.1)	18 (10.9)
HERPES SIMPLEX	6 (3.8)	10 (6.1)
GASTROENTERITIS	4 (2.6)	13 (7.9)
GASTROINTESTINAL DISORDERS	64 (41.0)	85 (51.5)
DIARRHOEA	21 (13.5)	21 (12.7)
DYSPEPSIA	19 (12.2)	17 (10.3)
NAUSEA	16 (10.3)	20 (12.1)
GASTRITIS	6 (3.8)	9 (5.5)
NERVOUS SYSTEM DISORDERS	46 (29.5)	54 (32.7)
HEADACHE	23 (14.7)	32 (19.4)
DIZZINESS	12 (7.7)	13 (7.9)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	36 (23.1)	42 (25.5)
BACK PAIN	12 (7.7)	10 (6.1)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	28 (17.9)	50 (30.3)
PRURITUS	5 (3.2)	10 (6.1)
URTICARIA	3 (1.9)	11 (6.7)
RASH	1 (0.6)	9 (5.5)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	25 (16.0)	36 (21.8)
OEDEMA PERIPHERAL	8 (5.1)	6 (3.6)
VASCULAR DISORDERS	23 (14.7)	37 (22.4)
HYPERTENSION	13 (8.3)	12 (7.3)
HYPOTENSION	1 (0.6)	9 (5.5)
PSYCHIATRIC DISORDERS	19 (12.2)	23 (13.9)
INSOMNIA	5 (3.2)	12 (7.3)

For Days 198-365, the treatment switch group (placebo → abatacept) had a lower rate of overall AEs compared with subjects who received abatacept during Days 1-197. This difference was mainly due to a lower rate of overall infections (31.8% [35/110] for the switch group versus 48.1% [75/156] for abatacept in Period 1) and overall gastrointestinal disorders (14.5% [16/110] for the switch group versus 35.9% [56/156] for abatacept in Period 1).

Infusion Related Reactions

Acute Infusion AEs

During Days 1-197, patients receiving infliximab (18.2%, 30/165) experienced acute infusion AEs at a higher event rate compared to subjects who were given abatacept (5.1%, 8/156) and placebo infusions (10.0%, 11/110). No anaphylaxis occurred during the first 6 months of the study, however, in the infliximab group 7 patients experienced hypotension and flushing compared to only a single subject in the abatacept treatment arm that reported flushing only. The majority of acute infusion AEs were of mild or moderate severity but 5 patients (4 in the infliximab and 1 in the abatacept group) experienced severe infusion related events. In the abatacept group, a 60 year old female developed severe bronchospasm during her second infusion that resolved after treatment with beta-agonists, Phenergan and hydrocortisone. No pre-medication was given prior to dosing although the patient experienced moderate bronchospasm during her first infusion of abatacept. The patient withdrew from the study as a result of the AE. The 4 subjects who had severe acute infusion AEs with infliximab all continued in the study and the events

included 2 cases of urticaria (immediately after the 7th and 8th infusion), 1 case of nausea (at the end of 3rd infusion) and 1 case of flushing with dyspnoea (soon after commencement of 8th infusion).

Over the 12 month DB period, acute infusion AEs were recorded in greater proportion of patients in the infliximab group (24.8%, 41/165) than the abatacept group (7.1%, 11/156). The majority of these AEs occurred during the first 6 months of the study – 8 of 11 events for abatacept and 30 of 41 for infliximab. Anaphylaxis was not observed in any patient treated with bDMARD in the first 12 months. The pattern of acute infusion AEs seen over Days 198-365 remained unchanged compared to the first 6 months. The only new severe AE reported after Day 197 was an infusion related reaction characterized by chest pain, nausea, headache, dizziness and diaphoresis in a 37 year old female 5 minutes after she received her 14th dose of infliximab. This resolved with treatment and she continued in the study. She had a history of urticaria after the 8th infliximab infusion which was severe (already outlined above).

For the placebo → abatacept treatment switch group, 4.5% (5/110) reported acute infusion AEs during Days 198-365. None of these events were severe and the types of AEs were similar to those reported with abatacept treatment during Days 1-197.

Peri-infusional AEs

Patients who received infliximab + MTX (28.5%, 47/165) also had a higher incidence of peri-infusional AEs than subjects who received abatacept + MTX (14.7%, 23/156) and placebo + MTX (17.3%, 19/110). The types of AEs experienced between the 3 treatment groups was similar with the most common AEs being nausea which occurred at a similar frequency (3.2-4.8%) and headache which was more common reported in the infliximab group (9.7%) compared to abatacept (5.1%) and placebo (4.5%). Peri-infusional hypotension was only observed in the infliximab group (4.2%). Flushing was also more common in the infliximab group (2.4%) versus abatacept (0.6%) and placebo (0) as were peri-infusional skin/subcutaneous disorders (infliximab 6.7% versus abatacept 0.6% and placebo 1.8%). The majority of peri-infusional AEs were mild to moderate in severity; however, 8 patients (3 receiving abatacept and 5 given infliximab) experienced severe reactions. The abatacept related events included severe headache, bronchospasm and urticaria. The infliximab peri-infusional AEs were 2 reports of headache and 1 case each of nausea, flushing with dyspnoea and urticaria.

Across Days 1-365, acute peri-infusional AEs were reported in a higher frequency for patients treated with infliximab (33.3%, 55/165) compared to those who were given abatacept (18.6%, 29/156). Similar to the observation seen for Days 1-197, this treatment difference was mainly due to higher reported rates of headache, vascular disorders and skin/subcutaneous AEs with infliximab (10.3%, 9.1% and 9.7% respectively) compared to abatacept treatment (5.8%, 3.8% and 0.6% respectively). No additional severe peri-infusional AEs were seen in either treatment group after Day 197.

In the treatment switch group, peri-infusional AEs were reported for 5.5% (6/110) of subjects while receiving abatacept during Days 198-365. All of these AEs were considered to be of either mild or moderate severity. The types and relative frequencies of AEs in the treatment switch group were similar to that observed in the original abatacept treatment group during Days 1-197.

Serious Adverse Events (SAEs)

The incidence of SAEs up until Day 197 was lower in the abatacept group (5.1%, 8/156) compared to the other 2 treatment groups: - 11.5% (13/165) for patients in the infliximab + MTX group and 11.8% (13/110) for subjects in the placebo + MTX arm. The most

common type of SAE in all 3 treatment groups was infections which were observed in 7 (4.2%) patients treated with infliximab, 3 (2.7%) subjects in the placebo + MTX group and 2 (1.3%) patients in the abatacept group. Two subjects in the abatacept group and 4 patients in the infliximab arm had severe pneumonia, while severe soft tissue infections were recorded in 3 patients treated with placebo + MTX and 1 subject receiving infliximab + MTX. Serious gastrointestinal disorders occurred in more patients treated with placebo + MTX (4 subjects, 3.6%) compared with 2 infliximab + MTX treated patients and no abatacept treated individuals. All other types of SAEs occurred in such small patient numbers that conclusions about comparative incidence between the treatment groups cannot be drawn.

Over the 12 month study period, SAEs were recorded in a higher proportion of subjects in the infliximab group (18.2%, 30/165) than the abatacept arm (9.6%, 15/156) but the rates of discontinuation from the trial because of SAEs were similar between the 2 bDMARD groups (3.6% [6/165] for infliximab and 2.6% [4/156] for abatacept). Like the first 6 months of the study, infections was the most common type of SAE affecting 8.5% (14/165) of patients in the infliximab + MTX group and 1.9% (3/156) subjects in the abatacept + MTX arm. More details about the serious infections will be discussed later. One patient in each of the bDMARD groups developed angina pectoris, vasculitis and significant hypertension (including 1 subject treated with abatacept who was recorded as experiencing hypertensive crisis resulting in study discontinuation). More patients in the infliximab group (5 versus 1 for abatacept) reported an exacerbation of RA as a serious AE. Only patients in the infliximab group recorded serious gastrointestinal (3 cases – acute pancreatitis, perforated appendicitis and gastritis) and hepatobiliary problems (2 cases – biliary colic and cholelithiasis). One patient who received treatment with abatacept + MTX developed severe thrombocytopenia and withdrew from the study.

For the treatment switch group, the frequency of SAEs reported during treatment with abatacept between Days 198-365 was higher (10.9%, 12/110) than that observed for the abatacept group between Days 1-197 (5.1%, 8/156). Three of the SAEs in this group were considered to be treatment related: - markedly elevated serum transaminases, vertigo and pneumonia with sepsis resulting in death.

Pre-Specified Infectious Adverse Events

Pre-specified infections were defined as *Mycobacterium*, *Herpes* virus family, invasive fungal and opportunistic infections. Up to Day 197, the frequency of pre-specified infections was similar in subjects treated with abatacept + MTX (7.7%, 12/156) and placebo + MTX (7.3%, 8/110) but higher in those who received infliximab + MTX (10.9%, 18/165). Serious pre-specified infections were also seen at a higher incidence in the infliximab group (3.0% [5/165] compared to 1.3% [2/156] for abatacept and 1.8% [2/110] for placebo + MTX). Herpes related infections were more frequently in the bDMARD groups (5.4% [9/165] for infliximab and 4.5% [7/156] for abatacept) compared to the placebo + MTX arm (0.9%, 1/110). One of the patients (58 year old female) treated with infliximab developed a serious case of Herpes zoster on Day 135 and this resulted in a treatment interruption. Pneumonia was the second most frequently recorded type of pre-specified infection during Days 1-197 at a similar rate in all 3 treatment groups (1.9% [3/156] for abatacept, 3.0% [5/165] for infliximab and 1.8% [2/110] for placebo + MTX). Three of the cases of pneumonia were graded as severe (2 subjects in the abatacept group and 1 patient in the infliximab group). The latter case involved a 64 year old male treated with infliximab + MTX who developed *Pneumocystis jiroveci* pneumonia on Day 63. While this infection resolved on anti-microbial treatment (and withdrawal from study medication), he developed a further episode of culture negative pneumonia with respiratory failure on Day 88, which subsequently resolved 29 days later.

Over the 12 month DB period, subjects treated with infliximab + MTX had a higher frequency of both overall (18.2%, 30/165) and serious (6.1%, 10/165) pre-specified infections compared to patients who received abatacept (10.3% [16/156] and 1.3% [2/156] respectively). Herpes virus infections were the most common type of pre-specified infection affecting 12 (7.3%) of patients in the infliximab group and 9 (5.7%) of subjects in the abatacept group. Two of those herpes infections were serious (both involving infliximab treated subjects) – Herpes encephalitis and Herpes zoster. The case of Herpes encephalitis affected a 61 year old female who had received 12 infusions of infliximab + MTX. This patient was hospitalized on Day 276 (23 days after her last infusion) with delirium and somnolence that progressed over the next 3 days. Investigations revealed an abnormal EEG consistent with temporal lobe slow wave activity, raised protein and cells (lymphomononuclear) on cerebrospinal fluid (CSF) analysis but negative polymerase chain reaction (PCR) for herpes virus and positive peripheral blood serology (IgM) for herpes. The subject had a history of herpes zoster 8 months prior to study entry. She gradually recovered over the next month after receiving acyclovir and discontinued form the study as a result of the SAE. Pneumonia and cellulitis were also more common types of infections in the infliximab group (4.8% [8/165] for pneumonia and 3.0% [5/165] for cellulitis) than the abatacept group (1.9% [3/156] for pneumonia and 0.6% [1/156] for cellulitis). However, tooth abscesses were reported in a similar frequency (1.3% [2/156] for abatacept and 1.8% [3/165] for infliximab). One patient with a history of typhoid-related gastrointestinal disease who received treatment with abatacept + MTX developed a non-serious relapse of the infection on Day 241 (16 days after 11th infusion). The infection resolved after a course of oral ciprofloxacin and did not require hospitalization. Another subject who received abatacept developed oral candidiasis which was the only recorded “invasive” fungal infection. However, 2 additional serious opportunistic infections were reported in the infliximab treatment group. A 26 year old female developed pulmonary tuberculosis on Day 303, 21 days after receiving her 13th infusion of infliximab + MTX. The patient had a negative purified protein derivative (PPD) test and normal chest x-ray at screening. Another subject developed probable peritoneal tuberculosis on Day 288 (8 days after the 12th infliximab infusion) which subsequently progressed. The patient died of septic shock after a complicated surgical course.

While receiving treatment with abatacept during Days 198-365, 3 (2.7% of 110) patients in the treatment switch group developed pre-specified infections: - 1 case each of herpes virus infection, oesophageal candidiasis and pneumonia with sepsis. The latter 2 cases were serious and the patient with pneumonia and sepsis subsequently died as a result of the SAE.

Autoimmune Disorders

In the first 6 months of Study IM101-043, 3 subjects (1 from each treatment group) recorded autoimmune events. One patient each in the abatacept and placebo group experienced peripheral vasculitis, while the subject treated with infliximab was recorded to have sicca syndrome. Over 12 months of follow-up, 2 additional autoimmune events were reported which involved another case of cutaneous vasculitis in a subject who received abatacept and a report of sicca symptoms in a patient in the placebo → abatacept treatment switch group.

A higher proportion of patients (24.7%, 38/154) who received infliximab + MTX converted from a negative ANA status (titre < 1:160) at baseline to positive at Day 197 compared to subjects who received abatacept + MTX (1.4%, 2/147) and placebo + MTX arm (3.8%, 4/105). At the end of the 12 month period, the rate of negative to positive ANA

seroconversion was higher in both bDMARD groups (35.9% [51/142] for infliximab and 5.1% [7/137] for abatacept) but particularly so for patients treated with infliximab + MTX.

Furthermore, the percentage of subjects who converted from a negative anti-double stranded DNA (titre < 5.4 IU/mL for the Farr method) at baseline to a positive result at Day 197 was higher for subjects receiving infliximab + MTX (34.9%, 51/146) than for patients who received abatacept + MTX (0.7%, 1/138) or placebo + MTX (3.9%, 4/102). At Day 365, this observation was maintained with 43.0% (61/142) patients treated with infliximab + MTX converting from a negative to positive anti-double stranded DNA compared to 2.2% (3/135) of subjects treated with abatacept + MTX for the entire 12 months and 3.0% (3/101) of patients in the treatment switch group.

Malignancy

Four patients developed a malignant neoplasm in the first 12 months of the study (1 in the abatacept + MTX group, 2 in the infliximab + MTX arm and 1 in the placebo + MTX group). All of the malignant cancers were detected in the first 6 months and were considered to be of an unlikely relationship to study treatment. The subject who received abatacept developed a Grade II transitional cell carcinoma of the bladder. The two patients in the infliximab group had malignant anorectal neoplasm and fibrosarcoma respectively. All three of these subjects withdrew from the trial. One patient in the placebo + MTX group had a basal cell carcinoma and remained in the study.

Deaths

Four patients died during the first 12 months of the study (1 in the abatacept + MTX group, 2 in the infliximab + MTX arm and 1 in the placebo → abatacept treatment switch group). A 66 year old male who received a total of 5 abatacept (750 mg) infusions + MTX died on Day 80 (27 days after last abatacept infusion) of a stroke. However, at the time of his death the patient was still recovering from pneumonia that had onset 23 days earlier. Another subject, a 66 year old female, died on Day 271 of pneumonia and sepsis a few days after receiving her second dose of abatacept (750 mg) + MTX in the treatment switch period. One of the patients treated with infliximab + MTX died of a malignant fibrosarcoma which is probably unrelated to study medication. The other patient (61 year old male) who died received a total of 12 infliximab infusions + MTX. The patient died on Day 288 of septic shock and probably had underlying peritoneal tuberculosis as granulomas with acid fast bacilli were identified on histopathology of a surgical specimen obtained by exploratory laparotomy.

Use in Pregnancy

Two patients (1 from both bDMARD groups) became pregnant during the study. One subject was identified as being pregnant 4.5 months into the study and discontinued. The outcome of the pregnancy is unknown. The other subject treated with infliximab + MTX was identified on study Day 15 as being pregnant (that is, a single dose of infliximab + had taken continuous MTX for several years prior), discontinued from the trial and had a spontaneous abortion.

Laboratory Test Evaluations

The clinical laboratory data was unremarkable for all treatment groups and no new safety issues were identified for either of the bDMARDs. No unexpected significant differences between the treatment groups were observed for the mean changes in red blood cell count, haematocrit fraction, white cell count or platelet count up to 52 weeks. Furthermore, the proportion of patients who developed a marked haematological laboratory abnormality was very low. Of note, 3 subjects (1 treated with abatacept + MTX and 2 with infliximab + MTX) developed marked thrombocytopenia, all of which were

transient, not associated with a significant AE and returned to normal values during continued treatment.

The mean values and mean changes from baseline for blood chemistry parameters (serum transaminases and creatinine) were small and comparable for all treatment groups at 6 and 12 months. Between Days 1-197, patients in all 3 treatment groups had a similar incidence of significant elevations in hepatic transaminases (defined as > x 3 ULN for ALT and/or AST): - 1.9% (3/156) for abatacept + MTX, 3.0% (5/165) for infliximab + MTX and 2.8% (3/110) for placebo infusion + MTX. For but 3 patients, the raised serum transaminases was a temporary abnormality (that is, evident at 1 or 2 visits only). At Day 365, the percentage of patients treated with abatacept + MTX who had ALT and/or AST results > x 3 ULN (from normal at baseline) at any time point was 2.6% (4/156) compared with 5.5% (9/165) for infliximab + MTX. In addition, 2 subjects treated with infliximab + MTX recorded a significant increase (> x 1.5 change from baseline value) in serum creatinine which was reported as an AE.

Vital Signs

No treatment-based trend of change in vital signs (blood pressure, heart rate, respiratory rate and temperature) was observed during the 12 month study.

Safety conclusions

In Study IM101-043, the 6 month safety profile of abatacept (10 mg/kg) in combination with MTX was similar to infliximab (3 mg/kg) + MTX and placebo infusions + MTX for overall adverse events. However, abatacept treatment was associated with a lower incidence of serious adverse events, discontinuations due to adverse events, pre-specified infections and infusion related reactions compared to infliximab. The 12 month comparative safety data for the 2 bDMARDs showed the same trend with respect to the relative frequencies and types of adverse events observed in the first 6 months. The incidence of malignancy and pre-specified autoimmune events was low in both treatment groups although a higher proportion of subjects who received infliximab demonstrated seroconversion for autoantibodies. The clinical laboratory data was unrevealing of any new safety concerns.

Study IM101-043 (OLE Period)

Study IM101-043 had an OLE phase in which all subjects who completed until Day 365 received monthly abatacept 10 mg/kg for an average of 18 months following an initial 12 month DB treatment period with background MTX and either abatacept, infliximab or placebo. The safety population for the OLE phase consisted of all patients who received at least 1 dose of abatacept after Day 365 and the results were presented as a single pooled group rather than by their original randomized treatment group. Safety information was recorded every 4 weeks during the OLE with routine laboratory testing taken immediately prior to abatacept infusion administration. Safety data was also collected for up to 56 days following the last dose of abatacept in the OLE.

Drug Treatment Exposure

Of the 384 subjects (139 on abatacept + MTX, 141 on infliximab + MTX and 104 in the treatment switch group in year 1) who completed the DB treatment period, 372 (96.9%) received at least 1 dose of abatacept in the OLE. During the combined DB and OLE treatment periods for Study IM101-043, the mean exposure to abatacept was 30.5 months (median 32.3; range 1.9 – 44.1 months). On average, patients received 32.2 infusions (range: 1-50) over the entire study period. The proportion of patients who received at least 24 months of abatacept was 77.2% (287/372) while a total of 94.9% (353/372)

completed 12 of abatacept in the OLE. Thirteen subjects (3.5% of 372) discontinued during the OLE period because of safety related reasons: 3 deaths, 9 patients due to adverse events and 1 subject became pregnant.

Overview of Adverse Events and Most Frequent Adverse Events (Event rate of > 5%)

Overall, AEs were recorded in 93.5% (348/372) of subjects during the OLE. The most common categories of AEs during the OLE were infections (73.1%, 272/372), gastrointestinal disorders (46.0%, 171/372) and musculoskeletal conditions (36.8%, 137/372). The majority of AEs were mild (n=84, 22.6%) or moderate (n=194, 52.2%) in intensity. The proportion of patients considered to have treatment related AEs (as assessed by the investigator) was similar in the OLE (43.8%, 163/372) compared with the DB phase (46.2%, 72/156). In addition, the pattern of AEs, SAEs and AEs leading to withdrawal were similar for patients in both treatment periods (DB or OLE). Furthermore, the potential effect of increasing duration of exposure to abatacept and the risk of SAEs, infection related AEs and SAEs and other AEs of special interest such as malignant neoplasms and autoimmune disorders was assessed by comparing incidence rates for the OLE to that observed during the DB period (Table 15). None of these AE types had an increased incidence during the OLE compared to the DB trial phase.

Table 15: Incidence rates of AEs

	Double-blind Period		Open-label Period	
	Abatacept (n = 384)		Abatacept (n = 372)	
	Subjects with event (Exposure: person -years)	Incidence / 100-Person years (95% CI)	Subjects with event (Exposure: person -years)	Incidence / 100-Person years (95% CI)
Serious Adverse Events	30 (189.76)	15.81 (10.67, 22.57)	82 (663.93)	12.35 (9.82, 15.33)
Infections and Infestations SOC SAEs	4 (198.12)	2.02 (0.55, 5.17)	14 (741.51)	1.89 (1.03, 3.17)
Adverse Events				
Infections and Infestations SOC AEs	127 (132.92)	95.55 (79.65, 113.68)	272 (354.23)	76.79 (67.93, 86.47)
Malignant Neoplasm	1 (199.20)	0.50 (0.01, 2.80)	2 (751.50)	0.27 (0.03, 0.96)
Autoimmune Disorders	3 (198.22)	1.51 (0.31, 4.42)	12 (742.39)	1.62 (0.84, 2.82)

CI = confidence interval

The most frequently reported individual types of AEs reported in the OLE phase of the study were nasopharyngitis (18.5%, 69/372), UTI (17.7%, 66/372), diarrhoea (15.1%, 56/372), headache (14.5%, 54/372), URTI (13.2%, 49/372), influenza (12.1%, 45/372) and hypertension (11.3%, 42/372).

Adverse events leading to withdrawal

In the OLE period, 9 subjects (2.4% of 372) withdrew from the study due to AEs, 4 of which were considered serious. There was no particular pattern to the type of AEs resulting in withdrawal as all events were singular in occurrence.

Serious Adverse Events (SAEs)

A total of 82 subjects (22.0% of 372) experienced SAEs during the OLE, of which 11 (3.0% of 372) were considered to be treatment related. The most common individual types of SAEs were worsening of RA (18 patients, 4.8%), UTI (5 subjects, 1.3%), osteoarthritis (4 cases, 1.1%) and a non-specific terminology of "arthritis" (4 patients, 1.1%). In total, 14 subjects (3.8%) had serious infections which included 5 cases of UTI, 5 reports of various types of soft tissue infection, 2 cases of appendicitis and 1 case of osteomyelitis. One patient developed severe bronchitis but there were no reports of serious lower respiratory tract infection or pneumonia. Seven subjects experienced serious cardiovascular disorders including 5 patients suffering myocardial infarction, 1 subject developing a significant arrhythmia and 1 patient having cardiac failure. Twelve patients (3.2% of 372) experienced fractures but a relationship for this type of SAE to abatacept treatment is unlikely.

The incidence rates of overall SAEs and infectious SAEs were assessed between the DB and OLE phase for subjects who received abatacept + MTX. When differences in drug exposure were taken into consideration, the rate of SAEs (overall and infectious) did not significantly differ between the 2 treatment periods. For overall SAEs, the incidence rate was 15.81 per 100 PY (Poisson 95% CI 10.67, 22.57; 30 events for 189.76 PY exposure) for the DB phase compared with 12.35 per 100 PY (Poisson 95% CI 9.82, 15.33; 82 events for 663.93 PY exposure) for the OLE period. For infectious SAEs, the incidence rate was 2.02 per 100 PY (Poisson 95% CI 0.55, 5.17; 4 events for 198.12 PY exposure) for the DB phase versus 1.89 per 100 PY (Poisson 95% CI 1.03, 3.17; 14 events for 741.51 PY exposure) for the OLE period.

Infusion Related Reactions

Acute infusion AEs were reported for 28 (7.5% of 372) subjects treated with abatacept during the OLE. These events included 5 cases of hypertension, 5 cases of dizziness and 4 patients suffered infusion site extravasation. Three subjects reported these AEs during their first infusion of abatacept. Two of these patients (rash and headache) had received infliximab infusions in Year 1 and 1 subject who developed severe hypertension was from the original abatacept treatment group. No patient withdrew from the OLE as a result of an acute infusion AE.

Fifty patients (13.4% of 372) experienced peri-infusional AEs in the OLE. Most of these AEs were either of mild or moderate severity and none resulted in treatment withdrawal. Six subjects reported peri-infusional AEs during the initial month of treatment in the OLE, 4 of whom had previously received infliximab and 2 had been given abatacept in the DB phase. All of these events resolved within 1-4 days and were considered mild or moderate in severity. However, 2 patients experienced severe peri-infusional AEs (arrhythmia and arthralgia), neither of which were considered by the investigator to be related to abatacept. There were no reports of anaphylaxis or hypersensitivity occurring within 24 hours of abatacept infusion during the OLE.

Infectious Adverse Events

(a) Overall

During the OLE, infections were reported in 272 subjects (73.1 % of 372) treated with abatacept + MTX. The most frequently recorded types of infection were respiratory tract in location (nasopharyngitis 18.5% [69/372], URTI 13.2% [49/372], influenza 12.1% [45/372], bronchitis 10.8% [40/372] pharyngitis 10.5% [39/372] and sinusitis 7.8% [29/372]), UTI (17.7%, [66/372]) and gastroenteritis (5.9%, [22/372]). Other noteworthy infections occurring at lower frequency included oral herpes (4.6% [17/372]) and herpes zoster (2.7% [10/372]); as well as 10 cases (2.7%) of bronchopneumonia or lower respiratory tract infection, none of which were considered severe. For infectious AEs overall, the incidence rate was 95.55 per 100 PY (Poisson 95% CI 79.65, 113.68; 127 events for 132.92 PY exposure) for the DB phase versus 76.79 per 100 PY (Poisson 95% CI 67.93, 86.47; 272 events for 354.23 PY exposure) for the OLE.

(b) Severe or Opportunistic infectious AEs

Fourteen subjects developed severe infections during the OLE period: - 5 cases of UTI, 5 reports of various types of soft tissue infection, 2 cases of appendicitis, 1 case of osteomyelitis and 1 report of severe bronchitis. Most of the infections resolved with antibiotic treatment and 2 cases (cellulitis and soft tissue infection) resulted in discontinuation from abatacept.

One patient developed latent pulmonary tuberculosis on Day 523 (~6 months into the OLE) which was reported as severe but the subject continued on with abatacept. This patient received infliximab in the DB period and had a normal chest x-ray and negative PPD at study entry. There was a single report of protozoan infection (*Cyclosporidium* infection) and 6 cases of parasitic infection (2 reports of parasitic gastroenteritis, 2 cases of acarodermatitis, 1 report of acariasis and 1 case of *Blastocystitis* infection), all of which occurred in subjects enrolled at sites in South America and none were regarded as severe. No invasive fungal infections were recorded but 11 patients (3.0%) developed onchomycosis, 9 subjects (2.4%) had oral candidiasis, 11 patients (3.0%) experienced various cutaneous fungal infections and 6 subjects (1.6%) had vulvovaginal fungal infections.

Autoimmune Disorders

Twelve patients (3.2% of 372) reported autoimmune conditions in the OLE period including of 7 new cases (1.9% of 372) of skin psoriasis, all of which were mild to moderate in severity except for 1 case rated as severe. In addition, there were 2 cases of Sjogren's Syndrome and 1 case each of leucocytoclastic vasculitis, RA vasculitis and erythema nodusum, all of which were considered to be unrelated to study medication. None of the events resulted in discontinuation from the study. There were no reports of demyelinating diseases.

The proportion of patients who converted from a negative ANA status at baseline to a positive status increased during the OLE period relative to the DB phase for the original abatacept group but remained stable for the original placebo group. At 2 years the proportion of subjects in the original abatacept group who ANA seroconverted was 14.6% (14/96) compared with 6.1% (6/98) at Day 365. However, for the original placebo arm the rates of seroconversion seen at 12 months (7.8%, 6/77) remained relatively stable during the OLE (5.3% [4/75] at Day 729). For subjects who initially received infliximab + MTX and then changed to abatacept after 12 months, the rate of ANA seroconversion decreased from 48.5% (48/99) at Day 365 to 22.4% (22/98) at Day 729. Furthermore, the percentage of subjects who converted from a negative anti-dsDNA at baseline to a positive

result at 2 years was low for both the original abatacept (2.6%, 3/114) and placebo groups (1.1%, 1/98). A similar low rate of seroconversion for anti-dsDNA was seen for both of these groups at Day 365 (2.5% [3/119] for abatacept and 3.4% [3/99] for placebo). In contrast, for patients in the infliximab arm, the rate of anti-dsDNA seroconversion at Day 365 was 48.3% (57/118) but this declined to 13.3% (15/113) at Day 729 after subjects in this group switched to abatacept in the OLE.

Malignancy

Two patients developed a malignant neoplasm (basal cell carcinoma of the skin) in the OLE period, both of which resolved with treatment. A further 19 benign lesions (such as skin papilloma and benign thyroid nodules) which are unrelated to study medication were recorded in 17 subjects.

Deaths

Three patients, all of whom received abatacept in the DB treatment period, died during the OLE period. The deaths were considered by the investigator to be not related to study medication. The cause of death included 1 case each of myocardial infarction (Day 1136 in a 60 year old female), respiratory failure (Day 673 in a 53 year old female) and accident (Day 641 in a 52 year old female).

Use in Pregnancy

One patient became pregnant during the OLE phase of the study. A 26 year old subject who received a total of 26 abatacept infusions discontinued from the study due to the identification of pregnancy on Day 679. She delivered a healthy female infant after 40 weeks of gestation.

Laboratory Test Evaluations

Haematology

Consistent with improvement in inflammatory disease status, the mean changes from baseline in platelet count (mean decrease of 66 x 10^9/L) and white cell count (mean decrease of 1.05 x 10^9/L) up to 24 months were within expectations. The mean changes from baseline to Day 729 in haemoglobin and haematocrit level were small and not clinically significant. Furthermore, patients who met the criteria for markedly abnormal haematological laboratory abnormalities were uncommon in the OLE treatment phases. The most common haematological abnormality was transient lymphopenia which was recorded in 3.0% (11/372) of subjects in the OLE phase. There was a single case of transient neutropenia observed in the OLE and no patients were recorded to have thrombocytopenia. 0.8% (2/254) treated with abatacept + MTX in the DB study and 3.1% (14/458) in the OLE phase.

Blood Chemistry Abnormalities

The mean changes from baseline up until Day 1121 (Month 25 of OLE) for blood chemistry parameters (namely, serum transaminases [ALT or AST] and creatinine) were small and of no clinical significance. Patients treated with abatacept + MTX in the OLE period of Study 101043 had a low incidence of elevations in hepatic transaminases (from normal at baseline to any level > ULN) – 3.0% (11/372) for raised ALT and 1.1% (4/372) for elevated AST. All but 1 patient who recorded elevations in their serum transaminases had minor degrees of elevation (< x 2 ULN) that were transient in nature and did not result in treatment withdrawal.

The most common laboratory abnormality in the OLE phase was the proportion of subjects who recorded a significant increase from baseline in serum creatinine (11.1% [41/372]). For the majority of subjects, the abnormal creatinine values were a minor

transient change without clinical consequences. However, for 3 subjects the elevation in serum creatinine was marked but did not result in treatment cessation as it resolved.

Safety conclusions

In the open-label extension period of Study IM101-043, abatacept (10 mg/kg) in combination with MTX continued to be well tolerated in most adult patients with RA for an median exposure of 20 months, following 12 months of prior treatment with either infliximab, abatacept or placebo + MTX. In particular, the incidence rate of SAEs (including infection related SAEs), malignancy and autoimmune disorders observed during the open-label period was comparable to that seen in double-blind treatment phase. Infections were the most commonly observed adverse event in the open-label treatment period but most of these were of either mild or moderate severity and resolved with antibiotic treatment. Study drug administration was generally well tolerated during the open-label phase with a relatively low incidence of acute infusion reactions, most of which were mild or moderate in severity and did result in drug discontinuation. No new safety signals emerged from the open-label extension period of the study.

Study IM101-064

Study IM101-064 was an open-label trial in which adult subjects with active RA (TNF-IR) received abatacept 10 mg/kg in combination with non-bDMARD therapy. The safety results were presented in 2 reports, a short-term (6 month) analysis and an extended experience (up to ~2.5 years of follow-up). The safety population for this study consisted of all patients who received at least 1 dose of abatacept. Safety information was recorded every 4 weeks with routine laboratory testing taken immediately prior to abatacept infusion administration.

Drug Treatment Exposure

A total of 1046 subjects received at least 1 dose of abatacept in the trial and most (82.2%, 860/1046) completed the initial 6 months of follow-up. Of these, 530 (50.7%) patients entered into the long-term phase and 25 (4.7% of 530) were still on-going at the data cut-off date of October 31, 2008. During the combined short-term and extended treatment periods for Study IM101-064, the mean exposure to abatacept was 13.7 (range 7.3 – 34.5) months.

Overview of Adverse Events and Most Frequent Adverse Events (Event rate of > 2%)

Overall, AEs were recorded in 78.7% (823/1046) of subjects during the initial 6 month study period. The most common categories of AEs during this short-term phase were infections (38.9%, 407/1046), gastrointestinal disorders (24.8%, 259/1046) and CNS conditions (18.5%, 194/1046), which was principally explained by the most common individual type of AE being headache (9.9%, 104/1046). The other most frequently reported individual types of AEs up to Day 169 of the study were nausea (5.3%, 55/1046), URTI (4.4%, 46/1046), sinusitis (2.7%, 28/1046), diarrhoea (2.6%, 27/1046), bronchitis (2.5%, 26/1046), UTI (2.1%, 22/1046) and dizziness (2.1%, 22/1046).

In the long-term treatment period, AEs were reported for 61.7% (327/530) of patients. The most frequently reported individual types of AEs in the extension phase were nasopharyngitis (6.2%, 33/530), bronchitis (5.3%, 28/530) and back pain (5.1%, 27/530).

Adverse events leading to withdrawal

In the short-term period, 39 subjects (3.7% of 1046) withdrew from the study due to AEs. Seventeen of these AEs which prompted withdrawal were serious. The most common reasons for discontinuation were infections (8 subjects, 0.8%), gastrointestinal complaints

(6 subjects, 0.6%) and CNS disorders (5 subjects, 0.5%), which were mainly headache and dizziness. The infections resulting in withdrawal from the study before Day 169 were 2 cases of pneumonia and all of the other AEs were singular in occurrence (intestinal abscess, diverticulitis, herpes infection, bacterial arthritis, urosepsis and sinusitis). Gastrointestinal related discontinuations included 3 cases of nausea; and 1 case each of ischaemic colitis, aphthous stomatitis and diarrhoea.

Another 15 subjects (2.8% of 530) withdrew from the extended follow-up period because of AEs, 6 of which were serious (2 cases each of pneumonia, skin erythema and pulmonary embolism).

Serious Adverse Events (SAEs)

A total of 109 subjects (10.4% of 1046) experienced SAEs during the OLE, of which 26 (2.5% of 1046) were considered to be treatment related. The most frequent individual type of SAE was worsening of RA (17 patients, 1.6%). Serious infections were reported for 25 subjects (2.4% of 1046) consisting of 7 cases of pneumonia, 5 reports of various types of URTI, 3 cases of various types of gastrointestinal infection, 3 reports of UTI and 2 cases of infective arthritis. Two patients developed severe immunological conditions (anaphylaxis and angioneurotic oedema) unrelated to infusion administration, which resulted in discontinuation. Seventeen subjects (1.6% of 1046) experienced serious cardiovascular disorders including 3 patients suffering myocardial infarction, another 3 subjects reporting various types of coronary artery disease, 3 patients with significant arrhythmia and 1 patient having cardiac failure.

During the extended treatment phase, 89 SAEs were reported in 60 subjects (11.3% of 530). Musculoskeletal conditions (4.5%, 24/530) were the most common category of SAE, mainly explained by the number of subjects reporting a disease flare (2.8%, 15/530). Serious infections were reported for 13 subjects (2.5% of 530) consisting of 3 cases of gastroenteritis, 2 cases of pneumonia, 2 reports of UTI and various singular type infections (bacteraemia, herpes zoster and staphylococcal infection). Six serious cardiac AEs (including 3 cases of acute coronary syndrome) were also observed in the extended follow-up phase.

Infusion Related Reactions

Fifty-seven subjects (5.4% of 1046) experienced acute infusion AEs up to Day 169. All of these events were mild or moderate in severity. The most common AEs were dizziness (12 subjects, 1.1%) and headache (12 patients, 1.1%). Other noteworthy acute infusion AEs included 12 patients suffering various types of infusion site reactions (pain, rash or swelling), 10 cases of hypertension (and another 2 with hypotension), 5 patients with pruritus, 4 subjects with flushing and 2 with rash. Three patients withdrew from the short-term treatment period as a result of an acute infusion AE. Up to 6 months, 156 patients (14.9% of 1046) experienced peri-infusional AEs (those occurring during the first 24 hours after infusion). Most of these AEs were either mild or moderate in severity; however, 10 of these AEs were rated serious and 4 resulted in treatment withdrawal. The most frequently reported peri-infusional AEs during the initial 6 months were headache (63 subjects, 6.0%) and nausea (43 subjects, 4.1%).

In the extended treatment phase of Study IM101-064, 13 patients (2.5% of 530) had acute infusion AEs. All but 2 of these events (1 case each of bradycardia and headache) were considered to be of mild or moderate severity and none resulted in treatment discontinuation. Forty-one patients (7.7% of 530) experienced peri-infusional AEs, of which 4 were considered to be severe (the 2 acute events outlined above, plus 2 cases of nausea). There were no reports of anaphylaxis or hypersensitivity occurring within 24 hours of abatacept infusion during Study IM101-064.

Pre-Specified Infectious Adverse Events

During the first 6 months of the study, pre-specified infections were reported in 64 subjects (6.1 % of 1046). The most frequently recorded types of pre-specified infections were herpes simplex (13 subjects, 1.2%), pneumonia (11 patients, 1.1%), herpes zoster infection (10 subjects, 1.0%), cellulitis (7 patients, 0.7%) and tooth abscess (7 subjects, 0.7%). Another 3 subjects experienced other types of infection and 1 patient developed varicella. Twelve of the pre-specified infections were severe occurring at a similar rate regardless of whether the subjects were current (6 cases, 1.0%) or previous users of anti-TNF drugs (6 cases, 1.3%). Four of the severe infections were pneumonia and 1 patient experienced septic shock.

During the extended treatment phase, infectious AEs were reported for 32.8% (174/530) of patients. The most frequently reported infections were nasopharyngitis (6.2%, 33/530) and bronchitis (5.3%, 28/530). Serious infections were reported for 13 subjects (2.5% of 530) in OLE consisting of 3 cases of gastroenteritis, 2 cases of pneumonia, 2 reports of UTI and other singular types of infection (such as bacteraemia, herpes zoster, staphylococcal infection, appendicitis and viral infection). No patients developed TB or other opportunistic infections during the both periods of Study IM101-064.

Autoimmune Disorders

Thirteen patients (1.2% of 1046) reported autoimmune conditions in the initial 6 month follow-up period including of 4 cases of skin psoriasis (1 of which had a past history of psoriasis); 2 cases each of Sjogren's Syndrome, erythema nodosum, autoimmune thyroiditis and sicca syndrome; and 1 case of keratoconjunctivitis. The relationship of these AEs to abatacept therapy is unclear. None of the events resulted in patient's discontinuing from the study.

In the extended treatment period, another 8 subjects (1.5% of 530) reported a pre-specified autoimmune disorder, none of which were serious. The events included 2 cases of new onset of skin psoriasis, 3 subjects with cutaneous vasculitis and 1 case each of SLE, cutaneous lupus, sicca syndrome and erythema nodosum. There were no reports of demyelinating disease developing in patients during both periods of Study IM101-064.

Malignancy

Six patients (0.6% of 1046) developed malignant neoplasms in the initial 6 months: - 2 with basal cell carcinoma of the skin, 2 with breast cancer (both withdrew), 1 with lung adenocarcinoma and 1 with uterine cancer (discontinued). Another 4 (0.7% of 530) malignancies were identified in 3 subjects during the extended phase: - another subject with breast cancer identified on day 977 (who also had basal cell skin cancer on Day 523), 1 who developed diffuse B-cell lymphoma (Grade 4 – identified on Day 201) and another patient with recurrent bladder carcinoma (onset from Day 189).

Deaths

Two patients died during the initial 6 month treatment period and another patient died in the extended follow-up phase. All of the deaths were considered to be unrelated to abatacept. The causes of death included 1 case each of congestive heart failure in a 54 year old female (28 days after 5th infusion), sudden cardiac death in a 67 year old female with a history of hypertension (2 days after 5th infusion) and acute respiratory failure (Day 232) in a 64 year old female with known COPD.

Use in Pregnancy

One patient became pregnant during the long-term study phase. A 34 year old subject who received a total of 24 abatacept infusions discontinued from the study due to the

identification of pregnancy on Day 533. She had an uncomplicated delivery of a healthy male infant who at 6 months of age had no medical problems.

Laboratory Test Evaluations

The laboratory data was unremarkable and no new safety issues were identified. Over the entire study observation period (from Day 1 to withdrawal), patients who met the criteria for a markedly abnormal laboratory result were uncommon. The most common haematological abnormality was transient lymphopenia which was recorded in 34 subjects (3.3% of 1046). There was a single case of mild thrombocytopenia in a patient in the extended treatment phase (identified on Day 198) that resulted in the subject discontinuing from abatacept. Patients had a low incidence of elevations in hepatic transaminases in Study IM101-064 – 5 developed raised ALT and 1 had an elevated AST value. All of those who recorded elevations in their serum transaminases had minor degrees of elevation (< x 2 ULN) that were transient in nature and did not result in treatment withdrawal.

Safety conclusions

> In the open-label Study IM101-064, abatacept (10 mg/kg) in conjunction with non-bDMARD therapy was well tolerated with an acceptable safety profile in the majority of adult patients with active RA and a history of exposure to anti-TNF medications. In particular, the incidence rate of SAEs (including infection related SAEs), infusion related reactions, malignancy and autoimmune disorders were within expectations. Infections were the most commonly observed adverse event and most of these were of either mild or moderate severity and resolved with antibiotic treatment. Study drug administration was generally well tolerated with a relatively low incidence of acute infusion reactions. No new safety issues were identified in Study IM101-064.

Extended safety follow-up analysis

This application was further supported by the cumulative safety data obtained from the OLE phases of the 5 key studies (IM101-100, -102, -029, -031 and -101) that were submitted with the original licensing application for abatacept in Australia. Subjects who completed the core study periods (12 months, except 6 months for Study IM101-029) of the above trials were eligible to continue receiving abatacept 10 mg/kg until commercial availability in their country of residence. The number of patients entering into each of the OLE periods was 219 for Study IM101-100, 539 for Study IM101-102, 317 for Study IM101-029, 1184 for Study IM101-031 and 80 for Study IM101-101.

The analysis of safety was presented by 2 population experiences: - an “integrated population” which included patients from the entire 5 core studies, as well as long-term safety data from Studies IM101-043, -064 and -015; and a “prior therapy population” (MTX-naïve, MTX-IR and TNF-IR). The data cut-off date for the OLE dataset was 31 October 2008. The integrated population contained a total of 4149 patients representing a total drug exposure of 11,658 patient-years. The cumulative mean exposure to abatacept was 34.2 months (median 30.0 months; range 1.9 - 94.0 months) with an average of 35.5 infusions. Of these, 1030 patients received abatacept for at least 5 years.

Safety data were also presented for both populations to display the effect of abatacept on specific AEs of interest such as infection, infusion reactions, malignancy and autoimmune disorders. Safety parameters were assessed every 28 days in the OLE phases of the studies. Incidence rates per 100 PY and associated 95% Poisson confidence intervals were calculated overall for a specified treatment period and by annual intervals.

Common Adverse Events

The incidence rate of AEs reported for the integrated population in the OLE (228.23 per 100 PY [95% CI 220.03, 236.66) did not increase relative to the overall rate of AEs observed during the short term treatment periods with either abatacept (386.70 per 100 PY [95% CI 372.31, 401.51) or those who received control therapy (361.42 per 100 PY [95% CI 338.62, 385.35]). The most frequently reported types of AEs in the integrated OLE population were infections (72.48 per 100 PY [95% CI 69.59, 75.46]), gastrointestinal disorders (28.77 per 100 PY [95% CI 27.37, 30.22]) and musculoskeletal conditions (26.88 per 100 PY [95% CI 25.54, 28.77]). No particular category of AEs occurred at a higher incidence in the long-term integrated population compared with the short-term treatment groups.

Clinically Significant Infusion Reactions

Expectedly, the incidence rate of infusion related events decreased in the OLE (2.26 per 100 PY) compared to the short-term treatment period (11.6 per 100 PY). Two patients suffered serious reactions (anaphylaxis and chest pain) related to abatacept infusion in the integrated OLE population. The presence of anti-drug antibodies was not correlated with the occurrence of significant infusion reactions.

Adverse Events leading to Discontinuations

In the long-term dataset, the incidence of AEs resulting in withdrawal from treatment was lower (2.90 per 100 PY [95% CI 2.56, 3.27]) than that seen in the short-term abatacept exposure cohort (6.93 per 100 PY [95% CI 5.90, 8.09]) and control treatment groups (4.72 per 100 PY [95% CI 3.37, 6.42]). The most frequently reported AEs leading to treatment discontinuation in the long-term integrated population were malignancy (69 cases at an incidence of 0.74 per 100 PY; particularly breast cancer [7 cases at rate of 0.08 per 100 PY]), infections (55 cases at an incidence of 0.59 per 100 PY; especially pneumonia [10 cases at rate of 0.11 per 100 PY]) and cardiac disorders (23 cases at an incidence of 0.25 per 100 PY; consisting of 6 cases of acute myocardial infarction and 5 with cardiac arrest). In the short-term abatacept dataset, the most frequent reasons for treatment cessation were somewhat different – mainly, infections (32 events at a rate of 1.37 per 100 PY; 5 of which were pneumonia) and various skin conditions such as rash (15 AEs at a rate of 0.64 per 100 PY).

Serious Adverse Events (SAEs)

The overall rate of SAEs in the long-term integrated population (14.52 per 100 PY [95% CI 13.66, 15.43) was similar to that recorded for the short-term treatment periods (abatacept 18.15 per 100 PY [95% CI 16.41, 20.02] and control therapy 16.89 per 100 PY [95% CI 14.17, 19.98]). Furthermore, the annual incidence rates of SAEs did not increase with increasing duration of exposure to abatacept (up to 5 years). Excluding worsening of RA and other musculoskeletal conditions, the most frequently reported types of SAEs in the long-term integrated population were infections (2.79 per 100 PY [95% CI 2.45, 3.16]) and malignancy (1.59 per 100 PY [95% CI 1.34, 1.88]). However, the rate of infections observed in the long-term integrated cohort was similar when compared with the short-term abatacept data (3.68 per 100 PY).

Infectious Adverse Events

For the long-term integrated population, the overall rate of infections was 72.48 per 100 PY (95% CI 69.59, 75.46) which is stable compared to the data for the short-term abatacept (98.0 per 100 PY [95% CI 93.20, 102.99]) and control treatment groups (92.65 per 100 PY [95% CI 84.98, 100.82]). URTIs (10.01 per 100 PY), nasopharyngitis (8.52 per 100 PY), bronchitis (6.40 per 100 PY), UTI (6.42 per 100 PY), sinusitis (5.40 per 100 PY)

and influenza (3.81 per 100 PY) were most commonly reported types of infections in the long-term treatment population.

The annual incidence rate of infections overall was highest in the first year of treatment and decreased thereafter with continued abatacept treatment (up to 5 years). The overall rate of infections (per 100 PY) were 95.10 in Year 1, 59.19 in Year 2, 43.37 in Year 3, 30.56 in Year 4 and 28.83 in Year 5. The profile of infections did not change over the ensuing years with various types of URTI and UTI being most commonly reported.

Serious Infections

The incidence of serious infections was 2.79 per 100 PY (95% CI 2.45, 3.16) for the long-term integrated abatacept treatment group, 3.68 per 100 PY (95% CI 2.94, 3.16) for the short-term abatacept and 2.60 (95% CI 1.63, 3.94) per 100 PY for the control group. The most commonly reported serious infections were pneumonia, cellulitis, UTI and gastroenteritis. The overall rate of serious infections showed the same trend as overall infections with the highest incidence in the first 12 months (3.73 per 100 PY) and decreasing thereafter in occurrence (2.85 in Year 2, 2.40 in Year 3, 2.46 in Year 4 and 1.82 in Year 5).

Opportunistic Infections

A total of 42 opportunistic infections have been reported in the long-term integrated population at an event rate of 0.41 per 100 PY (95% CI 0.23, 0.83). This includes 7 cases of tuberculosis (4 pulmonary, 1 latent and 2 extra-pulmonary). All but 1 subject (except the patient with latent tuberculosis) withdrew from abatacept and no deaths occurred as a consequence of opportunistic infection.

Malignancy

The incidence rate of malignancy is 1.44 per 100 PY (95% CI 1.21, 1.71) for the long-term integrated population. A total of 135 malignancies were observed in 132 patients, sub-divided into solid organ cancers (55 cases), non-melanoma skin cancers (67 cases – 43 basal cell carcinomas of the skin and 24 squamous cell cancers) and haematological malignancies (13 cases). The most frequent solid cancers were lung neoplasms (14), breast cancer (9), gastrointestinal cancers (7), prostate cancer (5), cervical cancer (4) and endometrial cancer (3). In the haematological cancer category, there were 6 cases of B-cell lymphoma. The overall and individual types of malignancy had an incidence comparison using Standardized Incidence Ratios (SIR) for the USA general population. All malignancies for abatacept treated subjects had an incidence within the SIR range. When the rate of new cases of malignancy was assessed in 12 monthly periods up to 5 years, the overall incidence of malignancy and that of the individual types was stable over the entire time frame.

Deaths

A total of 57 deaths have been recorded in the long-term integrated population. The principal causes of death were cardiac events (19 cases) and serious infections (10 cases; including 5 with septic shock and 4 due to pneumonia). The overall rate of death was 0.61 per 100 PY (95% CI 0.47, 0.80), which is consistent with the peer reported rate of mortality. The overall rate of death due to infection was 0.11 per 100 PY of exposure (95% CI 0.05, 0.20), which is also consistent with the rate reported in several patient cohorts with severe RA requiring aggressive therapy.

Autoimmune Disorders

Because of its mechanism of action, abatacept has the potential to aggravate or precipitate AI disorders. The incidence of AI conditions during the long-term treatment period (143

events at an incidence of 1.63 per 100 PY [95% CI 1.38, 1.92]) is similar compared to the short-term abatacept data (2.07 per 100 PY [95% CI 1.53, 2.75]). The most common types of AI events in the long-term dataset were psoriasis (n=68), cutaneous vasculitis (n=17), Sjogren's syndrome (n=16) and erythema nodosum (n=13). Other significant AI conditions reported in the long-term integrated population were cutaneous lupus (n=5), SLE (n=4), autoimmune thyroiditis (n=3), autoimmune hepatitis (n=2) and 1 case each of optic neuritis and ulnar nerve demyelination. No correlation between the development of anti-abatacept antibodies and AI disorders was seen.

Cardiovascular (CV) Events

Patients with long-standing active RA have an increased risk of CV morbidity and mortality. The overall rate of cardiac disorders in the long-term integrated population was 3.87 per 100 PY (95% CI 3.47, 4.31) compared with 7.08 per 100 PY (6.03, 8.26) for the short-term abatacept group. The rate of cardiac events was within expectations for the treatment population and was stable over 5 years of follow-up. The most frequent cardiac AEs were various types of arrhythmias, ischaemic events (n=72) and ventricular dysfunction (n=26).

Laboratory Parameters

Individual cases of markedly abnormal laboratory parameters were rare (incidence < 0.05 per 100 PY) in the extended treatment dataset. There were 4 reports of pancytopenia which were confounded by alternative explanations. In the long-term integrated population, 19 cases of significant hepatitis have been received (including 2 with hepatic failure) but their relationship to abatacept treatment is unclear as most were receiving background MTX and had other risk factors for hepatitis such as excessive alcohol intake.

Analysis by Prior Therapy

In this analysis the cumulative safety experience across 3 subgroups defined by their prior treatment (MTX-naïve, MTX-IR and TNF-IR) was considered. In addition, to background anti-rheumatic treatment, the 3 groups are different with respect to duration and severity of RA. The mean duration of RA is 6.5 months for the MTX-naïve group, ~8 years for the MTX-IR group and ~12 years for TNF-IR group. This reflects the more refractory nature of the TNF-IR cohort who have cycled through more therapies than the MTX-IR population. Table 16 summarizes the incidence rates of AEs by prior anti-rheumatic treatment. Although the incidence of overall AEs is similar between the 3 patient populations, the incidence of SAEs, infections and infusion related reactions are higher in the TNF-IR group than the MTX-IR cohort. Malignancies also appeared to occur at a higher rate in the TNF-IR population.

Table 16: Incidence rates of AEs by prior therapy population

	MTX-naïve n=483	MTX-IR n=1280	TNF-IR N =1419
Mean (SD) exposure to abatacept (months)	18.1 (6.8)	42.5 (24.1)	17.0 (17.7)
	Incidence rate per 100 person-years (95% Poisson CI)		
Overall AEs	184.37 (166.78, 203.30)	260.28 (246.00, 275.17)	359.05 (339.18, 379.78)
Deaths	0.56 (0.15, 1.43)	0.65 (0.44, 0.93)	0.45 (0.21, 0.86)
SAE	6.54 (4.77, 8.76)	14.62 (13.37, 15.97)	20.52 (18.33, 22.90)
SAE SOC of Infection and Infestation	1.83 (0.97, 3.12)	2.75 (2.28, 3.30)	3.90 (3.06, 4.89)
Infection	65.24 (57.80,73.38)	72.03 (67.70, 76.58)	92.69 (86.33,99.40)
Bacterial	34.25 (29.50, 39.56)	39.69 (37.07, 42.44)	49.16 (45.24, 53.32)
Viral	35.12 (30.22, 40.57)	29.20 (27.08, 31.43)	34.74 (31.59, 38.13)
Fungal	4.47 (3.04, 6.35)	5.03 (4.36, 5.78)	5.82 (4.77, 7.03)
Parasitic	0.70 (0.23, 1.64)	0.52 (0.33, 0.78)	0.10 (0.01, 0.36)
Opportunistic	0.28 (0.03, 1.01)	0.22 (0.11, 0.41)	0.36 (0.14, 0.73)
Hospitalized infections	1.55 (0.77, 2.76)	2.63 (2.17, 3.16)	3.51 (2.72, 4.45)
Serious pneumonia	0.84 (0.31, 1.82)	0.59 (0.38, 0.86)	1.43 (0.95, 2.07)
Hospitalized pneumonia	0.70 (0.23, 1.63)	0.54 (0.35, 0.81)	1.33 (0.87, 1.95)
Malignancy	0.28 (0.03, 1.01)	1.30 (0.98, 1.68)	1.84 (1.29, 2.55)
Autoimmune disorders	1.70 (0.88, 2.97)	1.78 (1.41, 2.23)	1.85 (1.29, 2.56)
Acute-infusional events	3.77 (2.47, 5.53)	3.65 (3.00, 4.40)*	5.07 (4.10, 6.20)
Peri-infusional events	8.27 (6.22, 10.80)	9.41 (8.42, 10.48)	17.51 (15.53, 19.68)

*N = 993 since acute-infusional events were not captured in IM101100

Conclusions for Extended Exposure Populations

The extended duration safety data obtained from the open-label extension periods of the core Phase II/III studies suggest that the incidence and types of adverse events occurring in patients receiving abatacept for up to 5 years is similar to the experience known from the controlled trials. Some adverse events related to abatacept therapy such as infections (including serious infections) and infusion related reactions persist but do not increase in incidence with prolonged duration of treatment.

Study IM101-046

Study IM101-046 was an exploratory trial undertaken in subjects with undifferentiated arthritis. It consisted of an initial 6 month treatment period in which subjects were randomized to either abatacept 10 mg/kg monotherapy or placebo infusions for 6 months

followed by an 18 month follow-up observation period. The safety population for the study consisted of all patients who received at least 1 dose of study medication in the DB treatment phase (n=28 for both treatment groups). Safety information was recorded every 4 weeks during the active treatment period with routine laboratory testing taken immediately prior to infusion administration. Safety data was also collected for up to 28 days following the last dose of study medication in those who prematurely withdrew.

Drug Treatment Exposure

Of the 56 subjects randomized and who received at least 1 dose of study medication in the study, the 6 month completion rate was 78.6% (22/28) for abatacept and 60.7% (17/28) for placebo. The mean exposure to abatacept was 7.1 months - 1 patient received a single infusion; 2 received 4 infusions and 25 subjects were given 6-8 of the scheduled 8 infusions.

Overview of Adverse Events and Most Frequent Adverse Events (Event rate of > 10%)

Overall, AEs were recorded in 64.3% (18/28) of subjects treated with abatacept and 71.4% (20/28) of patients receiving placebo during the 6 month drug treatment period and for up to 56 days following the last infusion. However, AEs judged to be treatment related were numerically higher in the abatacept group (50% [14/28] versus 35.7% [10/28] for placebo). The most common types of AEs were infections (35.7% [10/28] for abatacept and 39.3% [11/28] for placebo), gastrointestinal disorders (21.4% [6/28] for abatacept and 25% [7/28] for placebo) and respiratory conditions (17.9% [5/28] for abatacept and 21.4% [6/28] for placebo). Three patients in the placebo had AEs of severe intensity (single events of sciatica, viral infection and pharyngeal oedema). No patients in the abatacept treatment group had AEs of severe intensity. No autoimmune disorders were observed.

The most frequently reported individual types of AEs reported at similar frequencies in both treatment groups were diarrhoea (14.3% abatacept; 10.7% placebo), headache (10.7% abatacept; 7.1% placebo), nasopharyngitis (10.7% abatacept; 7.1% placebo), UTI (7.1% abatacept; 10.7% placebo) and gastroenteritis (0 for abatacept; 10.7% placebo).

Adverse events leading to withdrawal

Two subjects (1 from each group) withdrew from the study due to an AE. Dyspnoea as a consequence of an infusion related event led to the withdrawal of the abatacept treated patient. One patient in the placebo group developed thrombocytopenia.

Serious Adverse Events (SAEs)

During the study drug treatment period, 2 patients (1 from each treatment group; 3.6% of 28) experienced SAEs. A 74 year old male treated with abatacept was diagnosed with basal cell carcinoma on Day 158, which was considered unrelated to treatment and of mild severity. The placebo group patient (52 year old female) was hospitalized for sciatica on Day 128. During the 18 month follow-up phase, SAEs were reported for another 2 subjects (1 from each group). The placebo subjects was identified as having a goitre on Day 422 while the abatacept treated patient was reported as having irritable bowel syndrome on Day 285 (4 months after last dose of abatacept) which is unrelated to therapy.

Infusion Related Reactions

One subject in each group was reported to have experienced an acute infusion AE. A 40 year old female receiving treatment with her first dose of abatacept on day 1 developed dyspnoea of moderate severity which resolved on ceasing the infusion and giving anti-histamines. The investigator rated the AE as being treatment related and as such the

patient withdrew from the study. One patient receiving placebo infusion reported headache.

During the first 6 months, 2 patients receiving abatacept (7.1% of 28) and 3 subjects in the placebo group (10.7% of 28) experienced peri-infusional AEs. Headache was the most common of these AEs reported by 3 patients (1 for abatacept and 2 for placebo). No reports of anaphylaxis or hypersensitivity occurring within 24 hours of abatacept infusion were seen during this study.

Infectious Adverse Events

During the study drug treatment period, infections were reported in 10 subjects (35.7% of 28) treated with abatacept and 11 patients (39.3% of 28) in the control group. The most frequently reported infections were nasopharyngitis (n=3 for abatacept [10.7%] and n=2 for placebo [7.1%]) and UTI (n=2 for abatacept [7.1%] and n=3 for placebo [10.7%]). Only 1 infection was recorded as being severe (viral infection in a placebo treated patient).

Malignancy

One patient treated with abatacept was reported to have a malignant neoplasm (basal cell carcinoma of the skin) in the 24 month study.

Deaths

No deaths were recorded during the study.

Use in Pregnancy

One patient became pregnant during the study. A 23 year old who received abatacept for 6 months became pregnant at 12 months (that is, 6 months after the last dose of abatacept) and delivered a healthy infant at term. The pregnancy and delivery were uncomplicated.

Laboratory Test Evaluations

No new safety issues emerged from the laboratory data. The mean changes from baseline in haematology and blood chemistry parameters (ALT, AST and creatinine) were small, showed considerable variation with no consistent pattern and were of no clinical significance. Three patients developed significantly abnormal laboratory abnormalities. One patient treated with abatacept developed mild transient neutropenia without clinical sequelae. Another subject receiving abatacept developed increased serum transaminases on Day 141 which persisted for 120 days (but never > x 3 ULN) before resolving. One patient who received placebo infusions had progressive severe thrombocytopenia. At baseline, the platelet count was 284 x 10^9/L and this declined steadily throughout the study (86 x 10^9/L at Day 169; and 22 x 10^9/L at Day 319, which is the last recorded value). This patient was discontinued from the study.

Safety conclusions

> In this exploratory study (IM101-046) involving patients with undifferentiated inflammatory arthritis, abatacept (10 mg/kg) given for 6 months was well tolerated in adult patients with early stage disease. During the initial 6 month active treatment period with either abatacept or placebo infusions, AEs were reported at similar rates for both groups and the incidence of SAEs and discontinuation due to AEs were low and comparable. One subject treated with abatacept experienced a significant acute infusion reaction but no new safety issues were identified.

Study IM101-034

Study IM101-034 was a Phase I open-label trial of escalating doses (2, 8 and 16 mg/kg) of abatacept given as either single or multiple administrations in combination with

background DMARD. It was conducted in several sites in Japan between February 2004 and December 2005 and recruited adult subjects with active RA. Subjects were between the ages of 20 and 65 years and were required to have RA for at least 6 months. Other inclusion criterion were background DMARD (usually MTX in low dose, that is, 6-8 mg/week), at least 6 tender joints and 3 swollen joints and ESR > 28 mm/hr or CRP >10 mg/L. Nineteen subjects (n=6 for 2 and 16 mg/kg and n=7 for 8 mg/kg) were treated in the single dose phase and followed for 57 days. Eighteen patients (n=6 for all 3 dose groups) received multiple doses of abatacept (days 1, 15, 29 and 57) and were observed until day 127.

No AEs lead to discontinuation from the study or death. Only 1 SAE was recorded – subcutaneous haematoma in a patient who received multiple doses of abatacept 2 mg/kg. Adverse events were observed in 89.5% (17/19) of subjects in the single dose groups and all patients in the multiple dose groups. There were no clear differences between the 2 dose groups (single or multiple drug administrations) with respect to AEs. In addition, no dose dependent relationship with AEs was observed in either dosing group apart from a higher observed incidence of increased blood cholesterol with abatacept 16 mg/kg in the multiple dose groups.

The most common AEs reported in at least 2 subjects in any of the single dose administration groups were increased blood pressure (42.1%, 8/19), nasopharyngitis (21.1%, 4/19) and tachycardia (10.5%, 2/19). For AEs relating to abnormal laboratory results – 7/19 (36.8%) had elevated white blood cell counts, 6/19 (31.6%) had decreased lymphocyte counts, 6/19 (31.6%) had positive white blood cells in the urine detected, 5/19 (26.3%) had increased serum cholesterol and 2/19 (10.5%) had microproteinuria recorded. For subjects in the multiple dose groups, the most common AEs were increased blood pressure (38.9%, 7/18), nasopharyngitis (16.7%, 3/18) and stomatitis (16.7%, 3/18). For AEs relating to abnormal laboratory results in the multiple dose group –6/18 (33.3%) had increased serum cholesterol, 6/18 (33.3%) had positive white cells in the urine and 3/18 (16.7%) had positive red blood cells in the urine. Of the 6 subjects with increased blood cholesterol in the multiple dose group, 3 (50% of 6) received abatacept 16 mg/kg, 2 (33.3% of 6) were given 2 mg/kg and 1 (16.7% of 6) received 8 mg/kg.

None of the patients in the multiple dose group developed anti-drug antibodies. However, 7 subjects in the single dose group (4 of 8 subjects given abatacept 2 mg/kg; 2 of 7 patients given 8 mg/kg; and 1 of 6 subjects given 16 mg/kg) recorded positive anti-CTLA4 antibodies. All patients developed the antibodies between days 80 and 123 after receiving abatacept and no effect upon safety or PK parameters was observed.

Conclusion

> Good short-term tolerability and safety was seen in adult Japanese patients with active RA who received either single or multiple doses of abatacept 2, 8 or 16 mg/kg in this Phase I study.

Study IM101-129

Study IM101-129 was an open-label Phase III trial evaluating the longer-term safety (at least 6 months drug exposure, or those with early withdrawal [before Week 24]) of abatacept in Japanese subjects who participated in either the Phase I Study IM101-034 (n=10) or Phase II Study IM101-071 (n=78). A further 26 new adult subjects with a history of prior MTX intolerance were also recruited into this OLE assessment, resulting in a total of 114 patients being evaluated in Study IM101-129. Subjects were given a fixed dose of abatacept 10 mg/kg at week 1, 2, 4 and every 4 weeks thereafter. Background MTX (up to 8 mg/week; mean 7.15 mg/week) was given to the patients recruited from the preceding Phase I and II studies. However, the newly included subjects were not permitted to have

combination DMARD therapy for the initial 12 weeks of observation. Background NSAID and low dose corticosteroid were allowed. The study was conducted in 40 investigator sites in Japan between December 2006 and December 2007 (the data cut-off date). Subjects were required to be greater than 20 years of age with RA for at least 6 months duration. Other inclusion criteria were at least 8 tender and 6 swollen joints at baseline. Subjects had a mean age of 53.8 years (range: 23-75 years) and 79.8% (91/114) were female. The mean duration of RA at baseline was 9.8 years. Patients had moderate-severe disease activity at enrolment with the mean baseline tender joint being 16.8, mean swollen joint count of 12.8, mean HAQ-DI score of 1.29 and mean baseline CRP 28.9 mg/L.

All 10 patients from Study IM101-034 completed at least 6 months of follow-up. Two subjects (of 78) from Study IM101-071 discontinued between 3-6 months (both withdrew consent) and the rest completed at least 6 months of observation. For the 26 newly recruited patients, 3 (11.5%) withdrew before 3 months, another 13 (50%) discontinued between months 3-6 and only 10 (38.5%) completed at least 6 months of follow-up. Hence, for the new subjects, the mean exposure to abatacept treatment was only 4.5 months (median 3.8 months; range 1.0-6.6 months) compared to the 2 other recruitment groups whereby the mean (and median) drug exposure was > 6 months.

One patient withdrew from the study because of an AE (at ~2.5 months). This involved a newly enrolled subject who developed severe inflammatory bowel disease at Week 3 after receiving their initial dose of abatacept. The AE was regarded as possibly related to abatacept. No deaths were observed. No malignant neoplasms were reported for the interim report period; however, 2 subjects were subsequently identified as having cancers (lymphoma and gastric cancer) in the period between the data cut-off date and 30 April 2008. No patients experienced drug related autoimmune disorders.

Nine SAEs were recorded involving 1 patient (10% of 10) from the Phase I study, 4 subjects (5.1% of 78) from the Phase II study and 4 patients (15.4% of 26) who were newly recruited. The types of SAEs were gastroenteritis (1 patient each from the Phase I and new subject groups), thoracolumbar spinal compression fracture (2 patients from the Phase II study and 1 subject from the new enrolment group), meniscal injury and knee arthroplasty (both patients from the Phase II trial) and singular events affecting 2 newly recruited subjects (severe inflammatory bowel disease in a single individual, who also developed a gastric ulcer at 5 weeks; and worsening of pre-existing interstitial lung disease).

Overall, AEs were observed in 75.4% (86/114) of subjects with no discernible difference between the 3 enrolment groups with respect to the incidence and type of AEs. The most common AEs (incidence > 5%) were nasopharyngitis (16.7%, 19/114), increased blood pressure (9.6%, 11/114), stomatitis (7.9%, 9/114), constipation (7.0%, 8/114) and URTI (7.0%, 8/114). Infections was the common category of AEs affecting 33.3% (38/114) of patients with an unequal representation depending on the background enrolment group – 20% (2/10) for subjects from the Phase I trial, 32.1% (24/78) for patients from the Phase II study and 42.3% (11/26) for newly recruited subjects. The most commonly reported infections were nasopharyngitis (16.7%, 19/114), gastroenteritis (3.5%, 4/114) and sinusitis (2.6%, 3/114).

Infusion related AEs occurred in 21.9% (25/114) of patients with the only events affecting more than a single person being raised blood pressure (7.9%, 9 subjects) and bradycardia (1.8%, 2 subjects). No patients experienced anaphylaxis or serious infusion related reactions. However, infusion AEs were more commonly observed in the newly recruited subjects (34.6%, 9/26) compared to those involved in the forerunner trials (20% [2/10] for Study IM101-034 and 17.9% [14/78] for Study IM101-071).

Significant abnormal laboratory results were seen in 39.5% (45/114) of patients with no between enrolment group differences being recognized. The most common significant laboratory abnormalities were elevated white blood cell counts (9.6%, 11/114); decreased white blood cell counts (8.8%, 10/114) which was mainly marked lymphopenia (8 cases); and raised GGT (11.4%, 13/114). One patient, originally from the Phase II study (and also receiving concurrent low dose MTX) developed a mild transient increase in AST during the 6 month OLE period.

Seven of 101 (6.9%) patients tested for anti-drug antibodies were positive, all of which were anti-CTLA4. Six of the 7 subjects were involved in the Phase II Study IM101-071 (3 of which had antibodies with neutralizing activity) and 1 was a newly enrolled patient. No association between the development of anti-CTLA4 antibodies and AEs was observed in Study IM101-129.

Conclusion

Study IM101-129 which recruited adult Japanese patients with active RA and prior MTX intolerance or inadequate response showed an acceptable safety and tolerability profile for up to 6 months of abatacept therapy. No new safety concerns emerged in this population.

Post-Marketing

A brief post-marketing report for abatacept use in adult subjects RA was provided with this application. However, the sponsor submitted a comprehensive Risk Management Plan (RMP, version 8, developed for the EU and dated 19 November 2009) which included the post-marketing experience. The data cut-off date for the EU-RMP was 22 June 22 2008. The RMP proposed by the sponsor outlines the current and planned safety risk management activities for abatacept in patients with RA. Clinical aspects of the RMP are discussed in *Section V*.

Clinical Summary and Conclusions

The clinical efficacy data for the extension of indication in RA is supported by a single new pivotal Phase III trial (IM101-023) of 2 years duration which involved a total 509 adult patients with moderately to severely active RA who were MTX-naïve with recent onset disease (< 2 years duration). Study IM101-023 was designed as a 1 year double-blind controlled study followed by a second year of open-label treatment with abatacept 10 mg/kg + MTX. This design allowed for an assessment of the efficacy of abatacept (versus an active comparator) regarding improvement in the clinical features and the progression of joint damage of RA at Year 1 and then an assessment of the maintenance of the efficacy with continued abatacept treatment at 2 years. Supportive data was supplied from another controlled Phase III trial (Study IM101-043) in which there was a biological DMARD comparator and the open-label extension periods (up to 5 years duration) from several studies (including IM101-064 and the 5 core licensing trials involved in the original licensing application). Collectively, the open-label extension trials involved 4632 patients who had received the recommended dose of abatacept (10 mg/kg) for an average of 2.5 years.

The rationale for this submission is to extend the treatment indication in adult patients with RA to include patients who are MTX-naïve with relatively recent onset disease who are at high risk of progression. The efficacy of abatacept in the newly presented pivotal study (IM101-023), as well as the previous Phase II-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 was 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 adult patients that were heterogeneous with respect to prior treatment and had 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 key efficacy findings included in this submission demonstrate that: -

- Treatment with abatacept 10 mg/kg + MTX resulted in a significant improvement in the symptoms and signs of RA (as indicated by the rates of categorical DAS28 response), as well as less progression of joint damage (as indicated by the mean change in total Sharp-Genant score from baseline to Week 52) compared with placebo infusions + MTX (Study IM101-023);
- A variety of secondary efficacy outcome measures measured at 52 weeks in Study IM101-023 examining the clinical (ACR response) and radiographic benefits (erosion score changes) with abatacept + MTX confirmed the primary outcome findings as being valid;
- Patients treated with abatacept 10 mg/kg + MTX had a significant improvement in physical function (as indicated by changes in HAQ-DI) and health related quality of life at Week 52 compared with those who received placebo + MTX and these improvements were maintained to 2 years of follow-up (Study IM101-023);
- The treatment effect of abatacept 10 mg/kg + MTX on improving many disease aspects of RA at year 1 were maintained or showed further improvement at the end of Year 2, with increasing proportions of patients achieving clinically relevant endpoints such as a major clinical response, Disease Activity Score (DAS28) remission, lack of radiographic progression and EULAR response (OLE of Study IM101-023);
- Treatment with either abatacept 10 mg/kg or infliximab 3 mg/kg (+ MTX) resulted in a similar level of improvement in RA disease activity at 12 months as assessed by various outcome measures and both bDMARD therapies were significantly better than placebo + MTX at 6 months (Study IM101-043);
- Overall response rates to therapy with abatacept 10 mg/kg were maintained or continued to improve with prolonged durations of treatment, as evidenced by significant numbers of patients achieving high rates of response (ACR50, ACR70 and DAS28 remission) over extended follow-up periods (up to 5 years).

The safety of abatacept use in RA was assessed by reviewing the safety data collected from the 4632 patients who received at least part of 1 infusion of abatacept in the clinical development program (controlled or open-label setting). This represents a total drug exposure to abatacept for adult RA patients that approximates 12,375 patient-years (as of the data cut-off date of 31 October 2008). In general, abatacept was well tolerated in patients concurrently receiving MTX or other conventional DMARDs. Individual follow-up time ranges from 16 weeks to more than 5 years with the majority of safety data collected from patients involved in the 8 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 reveal two particular safety risks requiring on-going vigilance: - risk of infection (particularly, serious infection) and acute infusion reactions during or within 24 hours of infusion of abatacept which are uncommon but a significant safety concern. Infectious risk is of particular interest because of the mode of action of abatacept and patients with advanced RA are at a higher risk of infection than the general population. In the long-term integrated abatacept treatment population, the rate of serious infection was 2.79 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 42 patients developed opportunistic infections in the long-term abatacept database with 7 of these events being tuberculosis.

The incidence of overall adverse events, deaths, malignancy and other adverse events of special interest (namely, autoimmune disease) was consistent with the expected incidence in RA populations from epidemiological studies. The safety profile of abatacept was consistent across the patient subgroups with the exception of a higher rate of certain adverse events such as serious infections and infusion related reactions in patients who had previously received anti-TNF medications.

Conclusion/Recommendation

In conclusion, the data included with this submission show a favourable benefit to risk ratio for the use of abatacept in MTX naïve adult patients with severely active, erosive RA that is at high risk of progression. Hence, the evaluator recommended acceptance of the sponsor's application for the extension of indications in the treatment of RA to include:

Orencia in combination with methotrexate is also indicated in the treatment of severe, active and progressive rheumatoid arthritis in adult patients not previously treated with methotrexate".

The submitted dataset from the pivotal study (IM101-023) shows a consistent effect for abatacept when added to MTX in reducing the signs and symptoms of RA. Radiographic progression was also significantly less in patients treated with abatacept + MTX (compared to placebo + MTX) as evidenced by lower comparative mean changes in the mTSS and its components over 1 year of observation, as well as the proportion of patients without radiographic evidence of erosive progression.

The sponsor has also provided additional long-term safety and efficacy data for the use of abatacept in the treatment of adult patients with RA. In general, these data have been appropriately included in an updated product information summary for abatacept.

No specific conditions of registration are indicated beyond the sponsor's outlined pharmacovigilance strategy and risk minimization plan.

V. Pharmacovigilance Findings

Risk Management Plan

Safety Specification

The summary of the Ongoing Safety Concerns as specified by the sponsor is as follows:

Important Identified Risks	• Infections with special reference to TB and COPD • Infusion-related reactions
Important Potential Risks	• Malignancies, with special reference to lymphoma, non-melanomatous skin cancer, lung cancer and breast cancer • Autoimmune symptoms and disorders • Immunogenicity • Pregnancy • Progressive multifocal leukoencephalopathy
Important Missing Information	• Vaccination • Hepatic and Renal Impairment • Combination therapy including biologic therapy • Elderly subjects

The clinical evaluator noted that the safety specification was comprehensive and no deficiencies or omissions were present in the document. The last potential risk, PML (Progressive Multifocal Leucoencephalopathy), has only been added since the last RMP update (version 7; dated 5 February 5 2009) as a suspected case of PML in an adult patient with RA receiving abatacept has been reported. This patient had a past history of PML diagnosed by brain biopsy histology 10 years ago while taking MTX between 1996 and 1998. The patient also had received several other DMARDs in recent years including 2 anti-TNF agents (adalimumab and infliximab). After receiving 5-6 infusions of abatacept the patient presented with status epilepticus and was thought to have a recurrence of PML. However, CSF analysis was negative for JC virus. Abatacept was discontinued and the patient improved. The sponsor in collaboration with external experts considered the case inconclusive for PML as there was a lack of laboratory confirmation, a non-progressive clinical course and atypical brain MRI findings.

Of the two important identified risks, reactivation of tuberculosis (TB) is a major concern in patients with RA receiving treatment with immunosuppressive therapies. Treatment with anti-TNF drugs is estimated to increase the relative risk of TB reactivation 5-fold. Since activated T-cells are an important host defence against TB, abatacept may plausibly increase the risk of TB reactivation. However, the data so far suggests that abatacept may be associated with a lower risk of TB reactivation than anti-TNF medications. In Study IM101-043 whereby adult patients with active RA were eligible to receive either abatacept or infliximab, 2 cases of TB were reported for infliximab within 12 months of follow-up and no patients treated with abatacept developed TB. During the DB periods of the 5 core RA studies, 1 case of TB was identified with both placebo + MTX treatment and abatacept + MTX therapy. A further 6 cases of TB have been identified in the OLE periods of abatacept treatment. The cumulative trial experience provides an estimated incidence rate of 0.06 per 100 patient-years. In addition, post-marketing surveillance (PMS) has identified another 2 potential cases of TB in association with abatacept. The first PMS report occurred in a 59 year old Caucasian female with a history of pulmonary TB while receiving anti-TNF treatment. She received no prophylactic anti-TB therapy upon commencement of abatacept and after receiving 5 months of therapy developed an enlarging pulmonary nodule on serial chest imaging that resulted in cessation of abatacept. She was also treated with triple anti-TB chemotherapy. The second PMS report involved a French patient (age and gender unknown) who developed pulmonary TB after receiving abatacept for 20 days (2 doses). This subject also had received treatment with

adalimumab up until the time of the symptom onset and hence both drugs were suspected in the causality.

The second identified risk of infusion related reactions is a concern for all bDMARDs. During the DB periods of the RA clinical studies, severe infusional AEs were rare with abatacept (1 case of anaphylaxis and 1 case of anaphylactoid reaction), particularly in comparison to infliximab (Study IM101-043). In PMS, 17 reports of anaphylaxis, 15 cases of serious hypersensitivity and 2 reports of anaphylactic shock have been reported.

The RMP also acknowledged 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=53; 2.7% overall) were involved in the clinical RA trials and patients aged > 65 years were also probably under-represented (n=323; 16.5% of the overall population). Subjects with active hepatitis B virus (HBV) infection (defined by the presence of HBsAg or HBcAb or detectable concentrations of HBV) or hepatitis C virus (HCV) infection (defined as the presence of HCV antibody or detectable concentrations of HCV) were also excluded from the clinical trials because all biological DMARDs are considered to have the potential to reactivate latent viral infections. Furthermore, in Study IM101-031, which was part of the original licensing application, the safety of abatacept in subjects with 4 specific co-morbid conditions: - asthma (n=83), chronic obstructive pulmonary disease (COPD) (n=54), congestive heart failure (n=18) and diabetes mellitus (n=96) was evaluated. However, the number of patients with these co-morbidities was relatively small and hence the results should be cautiously interpreted. Nonetheless, subjects with COPD had a higher incidence in the DB period of respiratory related AEs (43.2% [16/37] for abatacept + MTX versus 23.5% [4/17] for placebo infusion + MTX) and overall SAEs (27.0% [10/37] for abatacept + MTX versus 5.9% [1/17] for placebo infusion + MTX). No apparent increased risk of AEs was seen in patients with asthma, diabetes or heart failure.

Pharmacovigilance activities

The Office of Product Review (OPR) evaluator noted that the sponsor stated that routine pharmacovigilance activities are proposed to monitor all the specified ongoing safety concerns and that the following additional pharmacovigilance activities have also been proposed.[7]

- The continuation of the open-label periods of the 5 core RA studies. Subjects in these studies will be followed for up to 5 years. These activities would appear to apply to the important identified risks, the important potential risks: *Malignancies*, *Autoimmune symptoms and disorders* and *Pregnancy* and the important missing information *Elderly subjects*.
- Specialised case report forms (CRF) will be utilised for the important identified risks and the important potential risks: *Malignancies*, *Autoimmune symptoms and disorders* and *Progressive multifocal leukoencephalopathy*. The sponsor stated that these forms have been designed to collect targeted clinical information on events of special interest in adults with RA and children/adolescents with polyarticular JIA.

[7] 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.

- With approval of abatacept within each market, the post-marketing epidemiology studies will be initiated in the relevant markets. These studies include analyses of administrative data and observational cohort studies using data from biologic registries. For the pharmacoepidemiology studies, a listing and analysis of infections and malignancies occurring by treatment group will be provided annually and rates will be calculated after specific exposure milestones are reached. The sponsor reported that in the epidemiology program, a doubling of an underlying incidence of 1 in 1,000 can be detected after approximately 15,000 person-years abatacept exposure with adequate power and this could be achieved by 2011-2012.

  The abatacept post-marketing epidemiology program currently includes biologics registries and pharmacoepidemiology studies to assess the risks associated with the use of abatacept during the post-marketing period in geographically-diverse populations and subgroups. The primary objective of the overall abatacept post-marketing epidemiology program is to quantify the risk of pre-specified AEs in subjects treated with abatacept in clinical practice.

  The main objectives of the individual epidemiology studies include:

  - Estimation of the incidence rates and relative risks of the following events subjects treated with abatacept compared to those treated with DMARDs.
    - Overall hospitalized infections and tuberculosis
    - Malignancies, especially non-melanoma skin, lymphoma, lung and breast cancers
    - Specific autoimmune disorders
    - Mortality
  - Estimation of the incidence rates and relative risks of these events in subjects with RA treated with other biological therapies, excluding abatacept, compared to those receiving DMARDs.
  - Characterisation of these risks in subgroups such as children, the elderly and those receiving abatacept in combination with another biologic therapy.
  - Characterisation of pregnancy outcomes in women exposed to abatacept during pregnancy.
  - Characterisation of the risks of clinically important signals of AEs that may arise from clinical studies, spontaneous reports, or other sources during the post-marketing period.

- Although the nonclinical and limited clinical data do not suggest that abatacept interferes with embryonic development; controlled clinical studies in pregnant women have not been conducted. Consequently, *Pregnancy* has been identified as a potential safety risk in the RMP. Abatacept, which is an immune system co-stimulation modulator, could potentially affect the immune system of the foetus during development. The potential effects of abatacept on the developing foetus will be further evaluated by subject participation in pregnancy registries in the USA and EU. A pregnancy registry (IM101121) has been established in the USA to investigate the safety in both the mother and offspring up to 1 year following delivery.

In principle there was no objection by the OPR evaluator to the sponsor implementing the additional pharmacovigilance activities as proposed to further monitor all the specified ongoing safety concerns, except for the important missing information *Vaccinations* and *Hepatic and renal impairment*. However, the specified ongoing studies were not considered to be part of the planned clinical studies in the pharmacovigilance plan, therefore the related study protocols have not been reviewed. Nevertheless an update on

the progress/results/analysis of these studies as outlined in the RMP will be expected in future Periodic Safety Update Reports (PSURs).

Risk minimisation activities

The sponsor has concluded that routine risk minimisation activities are sufficient for all the specified ongoing safety concerns, except for the important identified risk of *Infections*.[8] The OPR evaluator concurred that the sponsor's conclusions appeared to be reasonable. Routine risk minimisation activities will include careful labelling and packaging, including suitable warnings in the product literature for all the specified ongoing safety concerns.

For the important identified risk of *Infections* a patient Alert Card will be used to inform subjects of the need for an adequate history and screening for infections, such as TB and hepatitis, prior to treatment with abatacept, as well as the need to seek immediate medical attention when signs and symptoms of infections occur during treatment.

The OPR evaluator made a number of recommendations concerning the proposed Australian PI but these are beyond the scope of this AusPAR.

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

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

Clinical

In the abatacept RA clinical trial program, a total of 4632 subjects representing 12,375 patient-years (PY) of exposure have received at least part of one infusion of abatacept in a controlled setting as of the data cut-off date.

Included in this total are data from the long-term (LT) extensions of the pivotal Phase II/III studies in the MTX-inadequate responder (MTX-IR), TNF-α-inadequate responder (TNF-IR) and other background treatment populations representing safety experience with 4,149 subjects for up to 8 years (11,658 PY of clinical study exposure). The approval of the original RA treatment indication in Australia was based on 5 Phase II/III studies which investigated the efficacy and safety of abatacept in adult patients with moderately to severely active RA over 6-12 months. In Figure 1 on the next page which is copied from the EMA Scientific Discussion for Orencia (EPAR), these five studies are shown shaded in grey.[9]

Also included were data from a new pivotal study, IM101023, conducted in 483 subjects with early RA (less than 2 years since disease onset), subjects who had severe disease the prognostic factors for which were indicative of progressive disease (erosion on X-ray and seropositive for RF or CCP) and who had not been previously treated with MTX. This

[8] 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.

[9] EMA. Scientific Discussion for Orencia (EPAR). Available at http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Scientific_Discussion_-_Variation/human/000701/WC500095025.pdf.

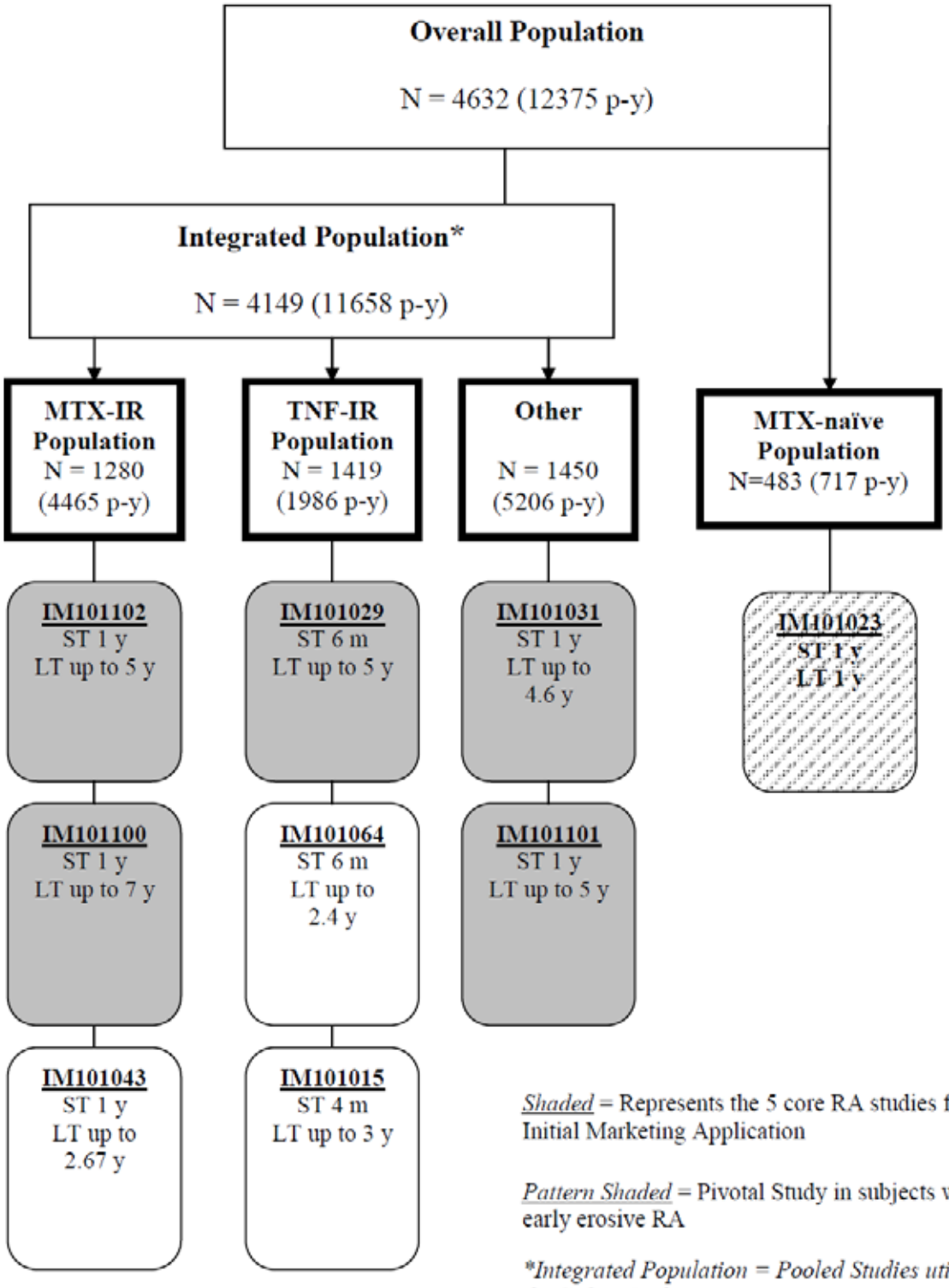
study is shown on the right hand side of Figure 1 by the area with the diagonal shading and is the principal study for this submission.

In the same Figure 1, there are 3 studies represented by unshaded areas, IM101064, IM101043 and IM101015. Two of them have been identified as being of significance to the amended PI and they are firstly Study IM101064, an uncontrolled open-label trial of up to 2.5 years duration of the efficacy and safety of abatacept in combination with non-biological DMARDs in adult patients who were inadequate responders to TNF-α inhibitors (TNF-IR) and who have limited future treatment options and secondly Study IM101043, a controlled study in adult patients with active RA, who were inadequate responders to MTX (MTX-IR), of infliximab versus abatacept for 12 months followed by an open-label extension period of up to 2.5 years.

There are a total of 9 studies shown in Figure 1 and a total of 16 studies identified for evaluation in the submission by the clinical evaluator. The 7 studies extra to those shown in Figure 1 are briefly outlined in the clinical evaluation as 8 "new" studies but the first of these, IM101015[10], is the third of the 3 studies shown as unshaded areas in Figure 1. These 7 studies are not of primary importance with regard to the extension of indications for which the sponsor is applying but they have been evaluated.

[10] Study IM101015 was an exploratory short-term study examining the changes in synovial immune response following abatacept in adult patients with active RA and prior anti-TNF failure.

Figure 1: Studies covered by the present submission



Pharmacodynamics

Two PD aspects were considered in the evaluation – the effect of abatacept on disease-related biomarkers and the development of immunogenicity. Additional data relating to changes in biomarkers were collected in the pivotal study, IM101023 and in the two studies, IM101043 and IM101015 (two of the three unshaded areas in Figure 1). For the review of immunogenicity, results from a number of studies were assessed, including IM101023 (the pivotal study in MTX-naive subjects), IM101043 (the comparator trial vs the bDMARD, infliximab), IM101013 and IM101063 (studies involving Orencia as an subcutaneous injection [SCI]) as well as the results of an integrated summary according to prior treatment characteristics.

Effects on biomarkers

Abatacept in a heterogeneous group of adult patients with RA produced desirable effects by reducing systemic levels of various disease-related biomarkers and synovial changes associated with the disease.

Immunogenicity

Abatacept is associated with a relatively low incidence of immunogenicity and the formation of anti-drug antibodies does not appear to be significantly associated with safety issues or loss of efficacy. Patients who have extended periods free from drug exposure may have a higher incidence of immunogenicity with re-challenge.

Pharmacokinetics

The pharmacokinetics of subcutaneously administered abatacept have been studied in both healthy individuals and in adult patients with RA. These data are not strictly relevant to the amendments applied for in this current submission. The sponsor is planning a separate submission to cover the SCI dosage form. C_{max} and AUC increased in a dose-proportional relationship over the tested range of 50-150 mg of SC abatacept and drug clearance appeared to be increased in those subjects who developed antibodies to abatacept. It was also shown that patients with a weight > 100 kg will require a weight-based dosage regimen as opposed to a fixed dose in order to control for inter-individual variability of exposure to abatacept.

Efficacy in Adult RA

Evaluable studies for efficacy were as follows:

- The pivotal Phase III study IM101023 in MTX-naive patients with active RA at high risk of disease progression with both 1-year (double-blind) and 2-year (open-label) outcome data for clinical, radiographic, physical functioning and QoL endpoints.
- Study IM101043 in adult patients with RA who were MTX-IR (in first 12 months, patients had 3 treatment options, 2 of which were bDMARDs, infliximab or abatacept).
- Long-term follow-up of efficacy from the OLE periods in 3 of the 5 studies in the original submission with the data presented in an integrated fashion depending on pre-treatment – MTX-IR population (Studies IM101102 and IM101100) and TNF-IR population (Study IM101029).
- Study IM101064, open-label trial in adult subjects with active RA who were TNF-IR.

- Study IM101046, an exploratory study in 56 adult patients with recent onset undifferentiated inflammatory arthritis.
- Study IM101071, a 6-month, placebo-controlled, Phase II, dose-response study in adult Japanese subjects with active RA who were MTX-IR.

Pivotal Study IM101023 (12-month status)

This was a prospective, multicentre, randomized, double-blind, placebo-controlled study of 1 year duration with 2 treatment groups: placebo infusions + MTX and abatacept infusions (10 mg/kg) + MTX. It was planned that 500 subjects with early onset, erosive RA would be randomly assigned in a ratio of 1:1 to each of the two treatment groups. Subjects enrolled in the study were required to be MTX-naive, or have very limited prior exposure to MTX. After 6 months, adjustments in MTX or corticosteroid therapy as well as the addition of 1 conventional DMARD were allowed.

The two co-primary endpoints were:

- Clinical – proportion of subjects in each treatment group who achieved DAS28-CRP remission (score < 2.6) at week 52,
- Radiographic – the mean change in the Genant-modified Total Sharp Score (mTSS) from screening to week 52 between the 2 treatment groups.

There were a number of secondary endpoints, including proportions of subjects with ACR50, ACR70 responses, radiographic (mean changes from baseline in Erosion and Joint Space Narrowing scores), proportion of patients with an improvement of at least 0.3 units in HAQ-DI and finally the mean change from baseline in SF-36 parameters.

The primary clinical endpoint of the percentage of subjects achieving remission (defined as DAS28-CRP, 2.6) at 12 months was significantly higher for patients in the abatacept + MTX treatment group (41.4% [106/256], 95% CI [35.4, 47.4]) compared with the placebo + MTX arm (23.3% [59/253], 95% CI [18.1, 28.5]). The estimated treatment difference was 18.1%, 95% CI [9.6, 26.6], $p < 0.001$. Treatment with abatacept + MTX resulted in a reduction in the rate of progressive joint damage compared with MTX monotherapy as evidenced by the mean change from baseline in the mTSS at Week 52. There was a mean change in mTSS of 0.63 (SD 1.74, baseline mean 7.50) for abatacept + MTX versus 1.06 (SD 2.45, baseline mean 6.67) for placebo + MTX, $p = 0.040$. These results plus those for the principal secondary endpoints are shown in Table 1.

The results for all secondary efficacy variables as well as for all supporting or exploratory endpoints were consistent with the primary efficacy results.

The sponsor was requested to explain in detail how the radiographic co-primary endpoint achieved was statistically significant. The sample size of the pivotal study allowed the detection, with 90% power, of a treatment difference of 1.6 units between the control and abatacept groups for the mean change in mTSS at 12 months. However, from Table 1, the mean changes from baseline in the radiographic total score were 0.63 for the abatacept + MTX group and 1.06 for the placebo + MTX group. This would imply a notional treatment difference of only 0.43 (1.06 – 0.63), a very small value. *How was the pivotal study sufficiently powered to detect a treatment difference down to this level which is almost four-fold lower than the value of 1.6, the latter being the smallest treatment difference the study was powered to detect? This issue must be comprehensively addressed in the pre-Advisory Committee on Prescription Medicines (ACPM) submission.*

Pivotal Study IM101023, open-label extension (2-year status)

Patients treated with either abatacept + MTX or placebo + MTX who completed the 12-month double-blind period were allowed to receive open-label treatment with abatacept (10 mg/kg) thereafter in conjunction with continued MTX (10-20 mg/week). All 459 subjects (232 on abatacept + MTX and 227 on placebo + MTX in year 1) who completed the double-blind treatment period received at least one dose of abatacept in the OLE. Most (94.3%, 433/459) completed the second year of treatment and follow-up.

At 24 months of treatment, the 2 original treatment groups were assessed for the following protocol-specified secondary outcomes:

- Proportion of patients achieving a clinically significant improvement in HAQ-DI, defined as a reduction of at least 0.30 units from baseline and
- Mean change from baseline in total mTSS, erosion score and JSN score.

There were also a number of tertiary defined objectives after 24 months of follow-up. No hypothesis testing or power calculation was done in the OLE of Study IM101023.

The proportion of patients originally treated with abatacept + MTX during year 1 who maintained clinically significant improvements in their HAQ-DI scores (a reduction of 0.30 units from baseline) during Year 2 was high at 94.7% (178/188) at 18 months and 94.1% (177/188) at 24 months. For patients treated with placebo + MTX during the first 12 months, the rate of categorical HAQ response achievement was maintained but not improved upon with the addition of abatacept to MTX in Year 2 of the study. The sustained HAQ response rate was 93.4% (156/167) at 18 months and 92.8% (155/167) at 24 months.

The results for the radiographic endpoints are shown in Table 4. Patients treated with abatacept + MTX for 2 years had a mean change from baseline of 0.84 units in mTSS at 24 months (baseline mean 7.73) compared with 1.75 units for subjects originally randomised to placebo + MTX (baseline mean 7.24). The result for mTSS reflecting a treatment difference between 1 and 2 years of abatacept + MTX was primarily accounted for by the difference in mean change for erosion score.

Study IM101043 (12-month status)

This was a prospective, multicentre, randomized, double-blind, active- and placebo-controlled study of 1 year duration with 2 treatment periods, Period 1 (Days 1-197) and Period 2 (Days 198-365). Adult subjects with active RA who were inadequate responders to MTX were randomized 3:3:2 into 1 of 3 possible treatment groups for the initial 6 months. These groups were, respectively, those treated with abatacept infusions (10 mg/kg) + MTX, infliximab infusions (3 mg/kg) + MTX or placebo infusions + MTX. Treatment with placebo infusions was limited to 6 months with these patients re-allocated to receive abatacept + MTX in Period 2. All other subjects, those treated with either abatacept or infliximab in Period 1, continued with the same treatment in Period 2.

The primary efficacy endpoint was the comparison in the mean change from baseline to Day 197 (6 months) in the DAS28 score between the abatacept + MTX treatment group and the placebo infusion + MTX group. There were a number of secondary and other endpoints.

The primary efficacy endpoint was reached with the mean reduction in DAS28 score at Day 197 being greater for patients in the abatacept + MTX treatment group (mean decrease of 2.53 from baseline of 6.86, n = 150) compared with the placebo + MTX arm (mean decrease of 1.48 from baseline of 6.79, n = 102), yielding an adjusted treatment difference of -1.04, 95% CI [-1.42, -0.67], $p < 0.001$. The results for the secondary and

supporting endpoints at Day 197 were consistent with the primary result. Similar Day 197 results were achieved with respect to infliximab. The 12-month data indicated that the efficacy of abatacept and that of infliximab were both largely maintained and comparable between the two bDMARDs for major efficacy variables such as ACR50 and major clinical response (ACR70).

Study IM101043 Open Label Extension (2-year status)

All patients who completed the 12-month double-blind period of Study IM101043 were allowed to receive open-label treatment with abatacept (10 mg/kg) thereafter in conjunction with continued MTX (15-25 mg/week). Of the 384 subjects (139 on abatacept + MTX, 141 on infliximab + MTX and 104 in the treatment switch group in Year 1) who completed the double-blind treatment period, 372 (96.9%) received at least one dose of abatacept in the OLE. Approximately 2/3 (68.0%, 253/372) completed the OLE at the time of data cut-off (31/10/2008), although 11.6% (43/372) prematurely discontinued before that date. The most common reasons for discontinuation from the OLE were withdrawal of consent (3.2%, 12/372), adverse events (2.7%, 10/372) and lack of efficacy (2.4%, 9/372). Continued treatment for up to 2 years with abatacept + MTX was shown to result in significant proportions of patients either maintaining or continuing to improve as measured by ACR and DAS responses with supporting improvements in health-related outcomes.

Long-term efficacy updates (Studies IM101102, IM101100 and IM101029)

The efficacy data from the open-label extensions of 3 of the core RA studies involving a mixture of adult patients (both MTX-IR and TNF-IR) demonstrated that treatment with abatacept (often in combination with MTX) resulted in significant proportions of patients maintaining a clinically significant response (ACR50 and 70 responses, DAS clinical remission or low disease activity) for up to 5 years of follow-up.

Study IM101064

Adult patients with active RA despite background non-biologic DMARD treatment were treated with open-label abatacept + continued non-biologic DMARD in this study. Both previous (off therapy for at least 2 months) and current users of anti-TNF medications were represented (each group had to contain at least 1/3 of all recruited subjects). The efficacy data from the short-term (6 months) and long-term OLE demonstrated that continued treatment for up to 2 years with abatacept resulted in significant proportions of patients maintaining clinically significant improvements in disease activity with supporting improvements in functional and health-related outcomes.

Study IM101046

This study was an exploratory trial in patients with undifferentiated inflammatory arthritis. There were 57 patients enrolled and randomized to double-blind treatment with either abatacept (n = 29) or placebo (n = 28). There was a tendency towards less progression to definite RA (primary efficacy result) after receiving 6 months of monotherapy with abatacept 10 mg/kg compared to placebo.

Study IM101071

This was a multicentre, placebo-controlled, randomized (1:1:1) study of 2 doses of abatacept (2 or 10 mg/kg) or placebo infusions on a background of continued MTX in adult Japanese patients with active RA. Of the 195 patients enrolled, 194 received study drug treatment (n = 61 for abatacept 10 mg/kg, n = 67 for abatacept 2 mg/kg and n= 66 for placebo). The study's results confirmed those of another dose-finding trial (IM101100) in that patients with RA who received 6 months of abatacept 10 mg/kg + low

dose MTX demonstrated significant improvements in disease activity compared to placebo. Patients who received the lower dose of abatacept (2 mg/kg) also showed improvements in the signs and symptoms of RA, physical function and health-related quality of life but the magnitude of these improvements was less than for the higher dose.

Safety

Up to the cut-off date of 31 October 2008, 4632 patients comprised the all-exposure population (received at least 1 dose of abatacept, either in a controlled or open-label setting) for the assessment of safety. In total, 1030 of these patients had received treatment with abatacept for at least 5 years. The all-exposure population experience yielded a total of 12,375 PY of observation following treatment with abatacept. The mean exposure to abatacept for the integrated safety population was 34.2 months (median 30.0 months) with an average of 35.5 infusions given.

Study IM101023 (1 year status)

The majority of patients in both treatment groups received 14 infusions of study medication; 76.2% (195/256) for abatacept + MTX and 74.3% (188/253) for placebo + MTX. The overall percentages of patients who experienced any AE were 84.8% (217/256) for patients who received abatacept + MTX compared to 83.4% (211/253) for placebo + MTX subjects. The proportion of subjects with treatment-related AEs was lower in the abatacept + MTX group (38.3%, 98/256) compared to the placebo + MTX arm (45.1%, 114/253). The only types of AE that occurred at a higher incidence in those who were given abatacept were acute infusional reactions (6.3%, 16/256 for abatacept + MTX vs 2.0%, 5/253 for placebo infusions + MTX) and peri-infusional AEs (12.5%, 32/256 for abatacept + MTX vs 9.9%, 25/253 for placebo infusions + MTX). A similar proportion of subjects treated with abatacept + MTX (3.1%, 8/256) and placebo + MTX (4.3%, 11/253) withdrew from the study because of an AE.

The most common AE was nausea which occurred at a higher frequency in patients treated with placebo + MTX (16.2%, 41/253) compared to abatacept + MTX (10.2%, 26/256). The other most common AEs (event frequency > 5%) with a similar incidence across the 2 treatment groups were headache, URTI and nasopharyngitis. Other noteworthy common events occurring at a similar frequency in each group were UTI, hypertension, gastroenteritis and increased serum transaminases.

The incidence of SAEs up to 12 months was comparable between the two treatment groups, 7.8% (20/256) for patients in the abatacept + MTX group and 7.9% (20/253) for subjects in the placebo + MTX arm. The most common types of SAE were infections, respiratory conditions and gastrointestinal disorders. Infectious SAEs were observed in 5 patients (2.0%) from each group. The most frequently reported types of serious infection were pneumonia (5 cases, 2 for abatacept + MTX and 3 for placebo + MTX) and soft tissue infections (5 cases, 3 for abatacept + MTX and 2 for placebo + MTX). There were no reports of opportunistic infections such as TB or unusual fungal infections during the first year of the trial. Furthermore, no deaths were attributed to infection.

Analysis of autoimmune disorders was an AE of special interest. Overall, 11 patients experienced autoimmune related conditions, 6 of whom received abatacept + MTX and 5 of whom received placebo + MTX. Two of the events (1 in each group) were new cases of SLE, each considered of moderate severity and resulting in subject withdrawal. In addition, there were 2 cases each of Sjögren's syndrome, cutaneous psoriasis, dry eyes/sicca syndrome and atrophic gastritis (1 in each group for all) and a single case of erythema nodosum (in abatacept + MTX group).

There was only one patient who developed a malignant neoplasm (pancreatic cancer) in the first 12 months of treatment. This was a patient in the abatacept + MTX group and he had received 12 infusions. The AE was thought to be of unlikely relationship to study treatment.

Six patients (2 in the abatacept + MTX group and 4 in the placebo + MTX group) died during the first 12 months of the study.

The proportions of subjects who experienced marked changes from baseline in laboratory parameters were low for both treatment groups and no new safety issues were identified.

Study IM101023 (2-year status)

In Year 2 of the study, the open-label extension phase, abatacept (10 mg/kg) in combination with MTX continued to be well tolerated in most adult patients with RA. The incidence rates of SAEs, including infection related SAEs, were comparable between the double-blind and open-label treatment phases (8.35 per 100 PY for the double-blind vs 6.42 per 100 PY for the open-label). Two patients died of pulmonary infection related to their treatment. Acute infusion reactions (including 1 case of anaphylaxis) were reported for 12 subjects (2.6%). No new safety signals emerged from the trial's OLE.

Study IM101043 (1 year status)

In this study, the 6 month safety profile of abatacept (10 mg/kg) in combination with MTX was similar to that of infliximab (3 mg/kg) + MTX and placebo infusions + MTX for overall AEs. Abatacept treatment, however, was associated with a lower incidence of SAEs, discontinuations due to AEs, pre-specified infections and infusion related reactions, compared to infliximab. The 12 month comparative safety data for the 2 bDMARDs showed the same trend with respect to the types of AEs and their relative frequencies observed in the first 6 months. The incidences of malignancy and of pre-specified autoimmune events were low in both treatment groups although a higher proportion of subjects who received infliximab demonstrated seroconversion. The clinical laboratory data did not reveal any new safety concerns.

Study IM101043 (OLE)

Study IM101043 had an OLE phase in which all subjects who completed Day 365, received monthly abatacept 10 mg/kg for an average 18 months (median 20 months) following an initial 12 month double-blind treatment period with one of abatacept, infliximab or placebo and background MTX. The incidence rates of SAEs (including infection related SAEs), malignancy and autoimmune disorders observed during the OLE were comparable with those observed in the double-blind phase. Infections were the most commonly occurring AE in the open-label treatment period and most of these were of either mild or moderate severity and resolved with antibiotic treatment. There was a relatively low incidence of acute infusion reactions.

Study IM101064

This was an open-label trial in which adult subjects with active RA (TNF-IR) received abatacept 10 mg/kg in combination with non-bDMARD therapy. The safety results were presented in 2 reports, a short-term (6 month) analysis and one based on extended experience of up to 2.5 years. The incidence rates of SAEs (including infection related SAEs), infusion related reactions, malignancy and autoimmune disorders were within expectations. Infections were the most commonly observed AE and most of these were of either mild or moderate severity and resolved with antibiotic treatment.

Extended safety follow-up analysis

Also presented were the cumulative safety data obtained from the OLE phases of the 5 studies (IM101-100, -102 -029, -031 and -101) that were submitted in the original application for registration of abatacept in Australia. The analysis of data was presented by 2 populations, an integrated population and a prior therapy population (MTX-naive, MTX-IR and TNF-IR). The types and incidences of AEs in patients receiving abatacept for up to 5 years were similar to those of AEs occurring in the controlled trials. With regard to the analysis by prior population, although the incidences of overall AEs were similar between the 3 groups, the incidences of SAEs, infections and infusion related reactions were higher in the TNF-IR group as opposed to the MTX-IR cohort. This is perhaps reflective of the more refractory nature of the disease in the TNF-IR cohort patients who, generally, have cycled through more therapies than the MTX-IR population. Malignancies also occurred at a higher rate in the TNF-IR population.

Other studies (Study IM101046, Study IM101034 and Study IM101129)

Abatacept demonstrated an acceptable safety and tolerability profile in these exploratory and/or short-term studies.

Post-marketing experience

The clinical evaluator noted the provision in the submission of a brief post-marketing report of abatacept use in adult subjects with RA. However, there does not appear to be any evaluation of these data in the clinical evaluation report. The Delegate noted that the Orencia EPAR mentions post-marketing experience of abatacept of some 32,187 PY, the majority of which was from regions where abatacept was approved for use without restriction to prior failure to other therapies. Elsewhere in the same document, there is a reference to a total exposure of approximately 73,882 PY, including some 60,225 PY of post-marketing pharmacovigilance. *The sponsor was asked to clarify these different figures.* It would appear that, world-wide for both the populations of MTX-inadequate responders and of MTX-naive patients, there are over 10,000 patients in total represented in the post-marketing exposure. *The sponsor, in its pre-ACPM response, was requested to give a short written summary of this latter experience in these 10,000 patients. The sponsor was also requested to give an estimate of the numbers of MTX-naive patients exposed in the post-marketing experience so far and, if possible, to give a summary of that experience.*

Risk Management Plan

The sponsor submitted a comprehensive Risk Management Plan (RMP, version 8, developed for the EU and dated 19 November 2009 with a data cut-off date of 22 June 2008).

The clinical evaluator assessed the safety specifications of the RMP. The sponsor has identified 2 important risks: infections (including TB/re-activation of TB and infections in patients with COPD) and infusion related reactions. In addition, 5 potential risks that require on-going surveillance or evaluation have been identified. These include the development of malignancy (including lymphoma, non-melanoma skin cancers, lung cancer and breast cancer), autoimmune disorders, immunogenicity, pregnancy and PML (progressive multifocal leucoencephaopathy). The potential risk of PML has been added since the last RMP update (version 7, dated 5 February 2009) with the report of a suspected case of PML in an adult patient with RA receiving abatacept. *The sponsor was asked to provide a report on this case in its pre-ACPM response as the Delegate found the time-line difficult to follow. It would appear that there have been no de novo reports of patients with PML on abatacept. The sponsor was requested to confirm this in its pre-ACPM response.*

The RMP was evaluated in full by the Office of Product Review and was found to be acceptable. The RMP evaluator has identified a number of deficiencies concerning the proposed PI. *The Delegate requested that the sponsor, as a matter of urgency, respond to the RMP evaluator in relation to the relevant issues raised and also give a summary of that response in its pre-ACPM response.*

There would appear to be a full planned analysis of the pharmacoepidemiological data across the various patient registries which have been established but this is not expected to start before 2011. *The sponsor was requested to provide an up-date on this in its pre-ACPM response.*

Risk-Benefit Analysis

Delegate Considerations

The pivotal study for this submission was IM101023. Treatment with abatacept 10 mg/kg + MTX resulted in a significant improvement in the symptoms and signs of RA as demonstrated by the proportions of subjects in each treatment group who achieved DAS28-CRP remission (score < 2.6) at week 52 [41.4% in abatacept + MTX vs 23.3% in placebo + MTX]. The co-primary endpoint was the mean change in the Genant-modified Total Sharp Score (mTSS) from screening to week 52, compared between the two groups [0.84 in the abatacept + MTX group vs 1.75 in placebo + MTX].

A variety of secondary efficacy outcome measures, clinical (ACR50 and ACR70), radiographic (mean changes from baseline in erosion score and JSN and proportions of subjects with no X-ray progression), functional (proportion of patients achieving an improvement of at least 0.30 units on HAQ-DI) and QoL (mean change from baseline in the physical and mental health components of the SF-36), all supported the primary outcomes.

Treatment effects maintained or improved at Year 2 endpoint in the pivotal study, for example in parameters such as major clinical response, DAS28 remission, lack of radiographic progression and EULAR response.

Other studies submitted were not strictly relevant to the MTX-naive population. There was reassuring evidence of continuing efficacy of abatacept in other populations of adults with RA over extended periods of follow-up (up to 5 years).

There is some concern over how optimal was the choice of MTX monotherapy for the control group as opposed to a possible choice of MTX + other non-biological DMARDs. Conventional, non-biological DMARDs were not permitted to be added to the MTX until after 6 months. How reflective of clinical practice this may be, is uncertain. However, the Delegate did not view this issue as one of great moment. *The sponsor was requested to make a comment on this matter.*

The magnitude of the radiological treatment effect for abatacept does appear small. While the result may be statistically significant, the result does not appear to be clinically significant. It is also difficult to compare the radiological result with those of other therapies, since this must necessarily be done across studies. There was no head to head comparison with a TNFα inhibitor in the population of MTX-naive subjects and so, not only for the radiological treatment effect but also for other treatment effects, such comparisons would be difficult. *The sponsor should also explain how the radiological primary result is of both statistical and clinical significance.*

The safety analyses from the RA clinical trial program reveal 2 particular risks requiring on-going vigilance: the risk of infection, particularly serious infection and acute infusion reactions within 24 hours of the infusion of abatacept which are uncommon but a significant safety concern. The pivotal study, IM101023 was only a small study but its

safety results were consistent with what is already known about the safety profile of abatacept. In all the clinical trials and safety databases reviewed by the clinical evaluator, the safety profile of abatacept was consistent across the patient sub-groups with the exception of a higher rate of certain AEs such as serious infections and infusion related reactions in patients who had previously received and not responded to anti-TNF medications.

The decision as to whether to recommend approval of the application for the requested extension of indications in MTX-naive patients essentially turns upon one small, relatively short-term controlled study, IM101023. There were some 500 patients with about 250 in each arm (abatacept + MTX and placebo + MTX). The volume of other data in the submission was reassuring in terms of the continuing safety and efficacy of abatacept in other patient populations but it did not inform the debate surrounding the use of abatacept as a first-line therapy. On the other hand, the pivotal study was well-designed and there was a definite positive efficacy benefit demonstrated from the first of the co-primary endpoints which was confirmed by various sub-group and sensitivity analyses, although the study was not necessarily powered for these. The Delegate reiterated concerns about the statistical and clinical significance of the radiological component of the co-primary endpoint. No new safety signals arose from the pivotal study.

The Delegate was inclined to recommend, albeit guardedly, approval of the submission. However, for the Delegate to have the confidence to implement such a recommendation, it will be necessary for the sponsor to provide firstly a clear explanation of the statistical and clinical significance of the radiological co-primary endpoint and secondly as much evidence as possible which supports the safety and efficacy of abatacept in the MTX-naive population and which is derived from the substantial body of data from post-marketing experience in that particular population.

The Delegate proposed to approve the submission for the extension of indications:

Orencia in combination with methotrexate is also indicated in the treatment of severe, active and progressive rheumatoid arthritis in adults not previously treated with methotrexate.

In addition to the questions directed to the sponsor, the following questions were directed to the ACPM

- Does the ACPM agree with the Delegate that there are sufficient data in the pivotal study IM101023 to support the proposed extension of indications as first-line in combination with methotrexate or do the committee members share the view of the EU scientific assessor that, at this stage, such approval is premature and that the indication should be restricted to second-line?
- Is the ACPM persuaded that the co-primary radiological endpoint in the pivotal study, namely that to do with the mean change from baseline in the mTSS, is of both statistical and clinical significance? Would members of the committee please note that the sponsor has been specifically asked to address this issue in the pre-ACPM response.
- Is the ACPM persuaded that the post-marketing experience in the patient population made up of those who are MTX-inadequate responders and those who are MTX-naive provides evidence of sufficient weight to support the proposed extension of indications in the MTX-naive population? Would the ACPM also note that the sponsor has been specifically requested to address this issue in the pre-ACPM response, particularly with regard to patients who are MTX-naive.

Response from Sponsor

The sponsor was requested to explain in detail how the radiographic co-primary endpoint achieved was statistically significant. The sponsor should also explain how the radiological primary result is of both statistical and clinical significance.

In the IM101023 study, the co-primary endpoints were DAS28-CRP remission at Month 12 and progression of structural damage defined as the change from baseline to Month 12 in the Genant modified Sharp total score. Based on the sample size estimates, the study had 90% power to detect a difference in the change in total score between abatacept and MTX and MTX if such a difference truly existed. In IM101023, subjects in the abatacept and MTX group had significantly less progression of structural damage compared with the MTX group as demonstrated by the mean change from baseline in total score at Month 12 (p = 0.040).

Progression of structural damage was further evaluated in a secondary endpoint evaluating the change from baseline to Month 12 in the Genant-modified Sharp erosion and joint space narrowing (JSN) scores. Subjects in the abatacept and MTX group [0.50 (1.39)] had significantly less progression of structural damage compared with the MTX group [0.89 (2.24)] as demonstrated by the mean change from baseline (SD) in the erosion score at Month 12 (p = 0.033). There was little progression of structural damage as demonstrated by the mean change from baseline (SD) in the JSN score in the abatacept and MTX group [0.13 (0.53)] and the MTX group [0.17 (0.54)] at Month 12; however, there was no statistically significant difference between the two treatment groups.

When the study was designed, it was estimated that the mean change from baseline in total score would be 1.0 for the abatacept and MTX group and 2.6 for the MTX group. It was estimated that a treatment effect of 1.6 (common SD of 5) would be observed between abatacept and MTX (abatacept and MTX) verses MTX alone. This assumed that both erosions and joint space narrowing would contribute to the treatment effect as was seen in the IM101102 study. In the IM101023 study, the mean change from baseline (SD) in total score was 0.63 (1.74) for the abatacept and MTX group and 1.06 (2.45) for the MTX group. The progression of structural damage with abatacept and MTX was lower than expected and also low in absolute terms.

What was not anticipated was that the progression of JSN on MTX was also low. The IM101023 study and the COMET study are similar in terms of patient population with both enrolling patients with much earlier disease (mean 6-8 months) than in studies such as AIM or TEMPO.[11,12]

In both these early RA studies, JSN at baseline was preserved and there was little progression of JSN with either MTX monotherapy or combination therapy (mean abatacept and MTX 0.13 and Etanercept and MTX 0.01).

In IM101023, the key differential effect between MTX monotherapy and combination therapy in the progression of structural damage is the development of new erosions. The mean change from baseline (SD) in erosion score was similar in IM101023 [0.50 (1.39) for the abatacept and MTX group and 0.89 (2.24) for the MTX group] and IM101102 [0.63 (1.77) for the abatacept and MTX group and 1.14 (2.81) for the placebo and MTX group].

[11] Emery P, Breedveld B, Hall S et al. Comparison of methotrexate monotherapy with a combination of methotrexate and etanercept in active, early, moderate to severe rheumatoid arthritis (COMET): A randomised, double-blind, parallel treatment trial. Lancet 2008; 372: 375-382.

[12] Klareskog L, van der Heijde D, Jager J, et al. Therapeutic effect of the combination of etanercept and methotrexate compared with each treatment alone in patients with rheumatoid arthritis: double-blind randomised controlled trial. Lancet 2004; 363: 675-681.

Developing new erosions will lead to irreversible joint damage and the IM101023 study showed that treatment with MTX monotherapy leads to statistically and clinically significant increase in progression of erosions when compared to MTX and abatacept. In IM101023, clinically and statistically significant benefit of abatacept and MTX over MTX monotherapy was observed in signs and symptoms as well as in physical function. Taken together, abatacept and MTX offers a new therapeutic option to decrease the disease activity, slow the joint damage and improve the physical function and quality of life in patients with early, erosive RA.

The sponsor was asked to clarify these different figures. The sponsor, in its pre-ACPM response, was requested to give a short written summary of this latter experience in these 10,000 patients. The sponsor was also requested to give an estimate of the numbers of MTX-naive patients exposed in the post-marketing experience so far and if possible, to give a summary of that experience.

The estimated sales and average dose and duration of treatment, based on the prescribing information, were used to calculate the approximate number of patients treated. However, the dose and duration of therapy depend on many factors including age (adult, paediatric), weight, renal function, specific treatment indication and the patient's therapeutic response. Nevertheless, by making the following assumptions regarding average dosage and duration of treatment, it is possible to arrive at an approximation of the number of patients treated with abatacept during the period:

• The patient was an adult who received 750 mg of abatacept for the treatment of rheumatoid arthritis.

• The patient received this dose for 1 year.

• The patient received a total dose of 10,500 mg.

The total number of mg sold divided by the number of mg each patient received gives the total number of patients exposed. The sponsor provided a table which summarised the patient exposure from each PSUR submitted since the drug was first authorised on 22 December 2005.

The cumulative postmarketing exposure does not differentiate the patient population from MTX-inadequate responders or MTX-naive. The approximate cumulative number exposure includes clinical trial exposure and postmarketing exposure yielding ~73,000 patient-years.

The sponsor was asked to provide a report on this case in its pre-ACPM response as the Delegate found the time-line difficult to follow.

The sponsor provided a detailed report on the case of PML. The case and follow up MRI scans were reviewed by 4 expert consultants, which resulted in an inconclusive diagnosis of PML. PML is caused by JC virus reactivation associated with immunosuppression, thus a causal role of immunosuppressive therapy including abatacept cannot be excluded.

To date there has been no reports of de novo PML.

The Delegate requested that the sponsor, as a matter of urgency, respond to the RMP evaluator in relation to the relevant issues raised and also give a summary of that response in its pre-ACPM response.

A response was sent to the OPR and a copy of the response was provided.

The first full analysis of the pharmacoepidemiological data will be conducted once there are a total of 5,000 person-years of abatacept exposure in the core studies: IM101045A (United Health Care), IM101045B (National Data Bank for Rheumatic Diseases), IM101125

(Anti-Rheumatic Therapy in Sweden), IM101127 (German biologics register), IM101212 (DREAM database in the Netherlands) and IM101213 (British Columbia RA Cohort). Based on the patient-year estimates obtained thus far, the sponsor anticipated that this milestone will be reached in mid-2011.

Relative risk estimates from each data source will be obtained in the second half of 2011. The sponsor indicated how these estimates will be calculated.

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 of the submission to register an extension of indications for the indication:

Orencia in combination with methotrexate is also indicated in the treatment of severe, active rheumatoid arthritis in adults not previously treated with methotrexate.

Although only one case of anaphylaxis was documented, the potential risk of this should be highlighted and a suitable protocol for diagnosis and management of any hypersensitivity reactions developed. The committee was particularly concerned with the limited access to medical assistance if required. It was considered important that post-market monitoring of such reactions be carried out systematically. All these issues should be addressed in both the PI and the RMP.

The ACPM advised the use of the term "progressive" was unhelpful and difficult to prove without patient deterioration. It was noted that the radiological changes demonstrated were limited, however, relatively early onset cases were studied where the likelihood of seeing substantial change was minimal.

The Committee also recommended a number of changes to the Product Information (PI) and Consumer Medicines Information (CMI) but these are beyond the scope of this AusPAR.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Orencia containing abatacept (rch) for the new indication:

Orencia in combination with methotrexate is also indicated in the treatment of severe, active and progressive rheumatoid arthritis in adults not previously treated with methotrexate.

Included among specific conditions of registration were the following:

- The implementation in Australia of the abatacept Risk Management Plan (RMP) Version 8, dated 19 November 2009 and any subsequent revisions, as agreed with the TGA and its Office of Product Review.
- The sponsor must, at all times, maintain protocols concerning the administration of Orencia to patients and concerning the appropriate monitoring and management of patients being given Orencia. These protocols must be, at all times, consistent with the currently approved Product Information and Risk Management Plan documents and with safe use of the product.
- The sponsor must, at all times, employ a combination of routine and enhanced pharmacovigilance measures, including its Medical Surveillance Team, to monitor and review all serious adverse events of special interest, including infusion-related reactions and anaphylaxis, at least on a monthly basis.

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.

PRODUCT INFORMATION

ORENCIA®
(abatacept)

(LYOPHILIZED POWDER FOR IV INFUSION))

NAME OF THE MEDICINE

ORENCIA® (abatacept (rch)). Abatacept is a costimulation modulator of the interaction of CD80 and CD86 on antigen presenting cells with CD28 on T-lymophocytes. Abatacept is a soluble fusion protein that consists of the extracellular domain of human cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) linked to the modified Fc (hinge, CH2, and CH3 domains) portion of human immunoglobulin G1. Abatacept is produced by recombinant DNA technology in Chinese hamster ovary cells. The apparent molecular weight of abatacept is 92 kilodaltons.

DESCRIPTION

ORENCIA® is supplied as a sterile, white, preservative-free, lyophilized powder for parenteral administration. Following reconstitution with 10 mL of sterile water for injection, the solution of ORENCIA® is clear, colorless to pale yellow, with a pH range of 7.2 to 7.8. Each single-use vial provides 250mg abatacept, 500mg maltose, 17.2mg sodium phosphate monobasic and 14.6mg of sodium chloride.

PHARMACOLOGY

General

Abatacept modulates a key costimulatory signal required for full activation of T lymphocytes expressing CD28. T lymphocytes are found in the synovium of patients with RA. Activated T lymphocytes contribute to the pathogenesis of RA and other autoimmune diseases. Full activation of T lymphocytes requires two signals provided by antigen presenting cells: recognition of a specific antigen by a T cell receptor (signal 1) and a second, costimulatory signal. A major costimulatory pathway involves the binding of CD80 and CD86 molecules on the surface of antigen presenting cells to the CD28 receptor on T lymphocytes (signal 2). Abatacept binds specifically to CD80 and CD86 inhibiting this costimulatory pathway. Studies indicate that abatacept affects both memory and naïve T lymphocyte responses.

Studies *in vitro* and in animal models demonstrate that abatacept attenuates T lymphocyte dependent antibody responses and inflammation. *In vitro*, abatacept attenuates T lymphocyte activation as measured by decreased proliferation and cytokine production in human lymphocytes. Abatacept decreases antigen specific TNFα, interferon-γ, and interleukin-2 production by T lymphocytes. In a rat collagen-induced arthritis model, abatacept suppresses inflammation, decreases anti-collagen antibody production and reduces antigen specific production of interferon-γ.

Pharmacodynamics

Dose finding studies were conducted with abatacept monotherapy (placebo, 0.5 mg/kg, 2 mg/kg, and 10 mg/kg) and in combination with MTX (placebo, 2 mg/kg, and 10 mg/kg). In both studies,

the American College of Rheumatology (ACR) 20 response rate increased with increasing doses at 2 mg/kg and 10 mg/kg. In clinical trials with ORENCIA® using doses approximating 10mg/kg, inhibition of T lymphocyte activation, decreases in products of macrophages, fibroblast-like synoviocytes, and B cells, and reductions in acute phase reactants of inflammation were observed. Decreases were seen in: serum levels of soluble interleukin-2 receptor, a marker of T lymphocyte activation; serum interleukin-6, a product of activated macrophages and fibroblast-like synoviocytes; rheumatoid factor, an autoantibody produced by plasma cells; and C-reactive protein, an acute phase reactant of inflammation. In addition, serum levels of matrix metalloproteinase-3, which produces cartilage destruction and tissue remodeling, were decreased. Reductions in serum TNFα were also observed. These changes are consistent with the mechanism of action of this selective costimulation modulator.

Pharmacokinetics

Healthy adults and adult RA

Absorption

Abatacept is administered intravenously.

Distribution

The pharmacokinetics of abatacept were studied in healthy adult subjects after a single 10 mg/kg intravenous infusion and in RA patients after multiple 10 mg/kg intravenous infusions (see Table 1).

Table 1: Pharmacokinetic Parameters (Mean, Range) in Healthy Subjects and RA Patients After 10 mg/kg Intravenous Infusion(s)

PK Parameter	Healthy Subjects (After 10 mg/kg Single Dose) n=13	RA Patients (After 10 mg/kg Multiple Doses[a]) n=14
Peak Concentration (C_{max}) [mcg/mL]	292 (175-427)	295 (171-398)
Terminal half-life ($t_{1/2}$) [days]	16.7 (12-23)	13.1 (8-25)
Systemic clearance (CL) [mL/h/kg]	0.23 (0.16-0.30)	0.22 (0.13-0.47)
Volume of distribution (Vss) [L/kg]	0.09 (0.06-0.13)	0.07 (0.02-0.13)

[a] Multiple intravenous infusions were administered at days 1, 15, 30, and monthly thereafter.

The pharmacokinetics of abatacept in RA patients and healthy subjects appeared to be comparable. In RA patients, after multiple intravenous infusions, the pharmacokinetics of abatacept showed proportional increases of C_{max} and AUC over the dose range of 2 mg/kg to 10 mg/kg. At 10 mg/kg, serum concentration appeared to reach a steady-state by day 60 with a mean (range) trough concentration of 24 (1-66) mcg/mL. No systemic accumulation of abatacept occurred upon continued repeated treatment with 10 mg/kg at monthly intervals in RA patients.

Population pharmacokinetic analyses in RA patients revealed that there was a trend toward higher clearance of abatacept with increasing body weight. Age and gender (when corrected for body weight) did not affect clearance. Concomitant MTX, NSAIDs, corticosteroids, and TNF blocking agents did not influence abatacept clearance.

Metabolism and elimination

Studies were not carried out to evaluate the metabolism or elimination of abatacept in humans. Owing to steric and hydrophilic considerations, abatacept would not be metabolized by liver

cytochrome P450 enzymes. Because of its large molecular weight abatacept is not expected to undergo renal elimination.

Special populations

Paediatric and Adolescent Patients. Population pharmacokinetic analysis of abatacept serum concentration data from patients with juvenile idiopathic arthritis (JIA) aged 6 to 17 years following administration of abatacept 10 mg/kg revealed that the estimated clearance of abatacept, when normalized for baseline body weight, was higher in JIA patients (0.44 ml/h/kg) versus adult RA tients. After accounting for the effect of body weight, the clearance of abatacept was not related to age or gender. Mean estimates for distribution volume and elimination half-life were 0.12 l/kg and 11.2 days, respectively. As a result of the higher body-weight normalized clearance in JIA patients, the predicted systemic exposure of abatacept was lower than that observed in adults, such that the observed mean (range) peak and trough concentrations were 217 (57 to 700) and 11.9 (0.15 to 44.6) mcg/mL, respectively. Administration of other concomitant medications such as methotrexate, corticosteroids, and NSAIDs did not influence the clearance of abatacept in JIA patients.

No formal studies were conducted to examine the effects of either renal or hepatic impairment on the pharmacokinetics of abatacept. Thus both the long-term safety and effectiveness of abatacept in children with renal or hepatic impairment are also unknown. The use of abatacept in this special population is not recommended.

CLINICAL TRIAL EFFICACY INFORMATION

Adult Rheumatoid Arthritis

Clinical trials

The efficacy and safety of ORENCIA® were assessed in six randomized, double-blind, placebo-controlled studies in patients ≥ age 18 with active RA diagnosed according to American College of Rheumatology (ACR) criteria. The trials are designated as follows: Study I (IM103002), Study II (IM101100), Study III (IM101102, AIM), Study IV (IM101029, ATTAIN), Study V (IM101031, ASSURE) and Study VI (IM101023, AGREE). Studies I, II, III, IV and VI required patients to have at least 12 tender and 10 swollen joints at randomization. Study V did not require any specific number of tender or swollen joints. ORENCIA® or placebo treatment was given intravenously at weeks 0, 2, and 4 and then every 4 weeks thereafter.

Study I, a supportive study, evaluated ORENCIA® as monotherapy in 122 patients with active RA who had failed at least one non-biologic DMARD or etanercept. In Study II and Study III, the efficacy and safety of ORENCIA® were assessed in patients with an inadequate response to MTX and who were continued on their stable dose of MTX. In Study IV, the efficacy and safety of ORENCIA® were assessed in patients with an inadequate response to a TNF blocking agent, with the TNF blocking agent discontinued prior to randomization; other DMARDs were permitted. Study V primarily assessed safety in patients with active RA requiring additional intervention in spite of current therapy with DMARDs; all DMARDs used at enrollment were continued. In Study VI, the efficacy and safety of ORENCIA® were assessed in MTX-naive patients with early, erosive RA (≤2 years disease duration). In Study VI, patients previously naive to MTX were randomized to receive ORENCIA® plus MTX or MTX plus placebo.

In Study VI, the efficacy and safety of abatacept were assessed in methotrexate-naive, Rheumatoid Factor (RF) and/or anti-Cyclic Citrullinated Peptide 2 (Anti-CCP2)-positive patients with early, erosive rheumatoid arthritis (≤ 2 years disease duration) who were randomized to receive abat acept plus methotrexate or methotrexate plus placebo. For all patients randomized and treated, the median age was 51 years, the median disease duration was 3 months and the median tender and swollen joint counts were 28 and 20, respectively. Patients were randomized to receive abatacept (10 mg/kg,

weight-tiered dose) plus MTX or MTX plus placebo for the first 12 months of treatment. In both groups, the MTX dose was titrated to at least 15 mg per week not to exceed 20 mg per week. The co-primary endpoints of this study were the proportion of subjects in abatacept+MTX group versus placebo+MTX who achieved DAS-28-CRP remission and to compare inhibition of joint damage progression measured by the Genant-modified Sharp total score at 12 months of treatment.

Study I patients were randomized to receive one of three doses of ORENCIA® (0.5, 2, or 10 mg/kg) or placebo ending at week 8. Study II patients were randomized to receive ORENCIA® 2 or 10 mg/kg or placebo for 12 months. For studies I and II, only results in the 10mg/kg group are discussed below. Study III, IV, V and VI patients were randomized to receive a fixed dose approximating 10 mg/kg of ORENCIA® or placebo for 12 months (Studies III, V and VI) or 6 months (Study IV). The dose of ORENCIA® was 500 mg for patients weighing less than 60 kg, 750 mg for patients weighing 60 to 100 kg, and 1 gram for patients weighing greater than 100 kg.

Clinical response

ACR response

The percent of ORENCIA®-treated patients achieving ACR 20, 50, and 70 responses and major clinical response (defined as achieving an ACR 70 response for a continuous 6-month period) in Studies III, IV and VI are shown in Table 2. Month 6 and 12 ACR response rates in Study II for the 10 mg/kg group were similar to the ORENCIA® group in Study III. ACR response rates at 3 months in Study I were supportive of these findings.

In Studies III and IV, improvement in the ACR 20 response rate versus placebo was observed after administration of the first dose, as measured at day 15, and was maintained through the double-blind study period. In Study VI, improvement in the ACR 20 response rate in ORENCIA®+MTX-treated patients versus MTX+placebo-treated patients was observed at 29 days, and was maintained through the double-blind study period. The ACR 50 response with ORENCIA® was significantly greater than placebo at months 2 and 3, respectively, for Studies III and IV, with continued improvement in the ACR50 response rate through the double-blind period (month 12 in Study III and month 6 in Study IV). In the placebo-controlled periods of Studies II, III and VI, ACR response rates were maintained to 12 months in ORENCIA®-treated patients. In the uncontrolled open-label long-term extension of Studies II, III, IV and VI, durable and sustained ACR 20, 50, and 70 responses have been observed through 7 years, 5 years, and 2 years, respectively, of ORENCIA® treatment based on as-observed analyses

In study II, ACR responses were assessed at 7 years with 31/43 (72%) ACR 20 responses, 25/43 (58%) ACR 50 responses, and 19/43 (44%) ACR 70 responses. In study III, ACR responses were assessed at 5 years with 224/268 (84%) ACR 20 responses, 165/270 (61%) ACR 50 responses, and 107/270 (40%) ACR 70 responses. In study IV, ACR responses were assessed at 5 years with 66/89 (74%) ACR 20 responses, 45/88 (51%) ACR 50 responses, and 21/ 91 (23%) ACR 70 responses. In study VI, ACR responses were assessed at 2 years with 196/219 (90%) ACR 20 responses, 169/217 (78%) ACR 50 responses, and 124/216 (57%) ACR 70 responses.

Greater improvement was seen in all ACR response criteria components in ORENCIA®-treated patients than in placebo-treated patients through 6 (Study IV) and 12 (Study II and III) months. In Study VI, greater improvement was seen in all ACR components at 12 months in ORENCIA®+MTX-treated patients than in MTX+placebo-treated patients. In the open-label extension of Studies II, III, and IV, improvements in the individual ACR components were maintained through 7, 5, and 5 years, respectively, of ORENCIA® treatment.

Table 2: Clinical Responses in Controlled Trials

	Percent of Patients					
	MTX-Naive		Inadequate Response to MTX		Inadequate Response to TNF Blocking Agent	
	Study VI		Study III		Study IV	
Response Rate	Abatacept[a] + MTX n=256	Placebo +MTX n=253	Abatacept[a] +MTX n=424	Placebo +MTX n=214	Abatacept[a] + DMARDs[b] n=256	Placebo + DMARDs[b] n= 133
ACR 20						
Month 3	64%*	53%	62%***	37%	46%***	18%
Month 6	75%**	62%	68%***	40%	50%***	20%
Month 12	76%***	62%	73%***	40%	NA	NA
ACR 50						
Month 3	40%***	23%	32%***	8%	18%**	6%
Month 6	53%***	38%	40%***	17%	20%***	4%
Month 12	57%***	42%	48%***	18%	NA	NA
ACR 70						
Month 3	19%**	10%	13%***	3%	6%*	1%
Month 6	32%**	20%	20%***	7%	10%**	2%
Month 12	43%***	27%	29%***	6%	NA	NA
Major Clinical Response[c]	27%***	12%	14%***	2%	NA	NA
DAS28-CRP Remission[d]						
Month 12	41%***	23%	NA	NA	NA	NA

* p<0.05, ORENCIA® vs placebo or ORENCIA®+MTX vs MTX+placebo (Study VI).

** p<0.01, ORENCIA® vs placebo.or ORENCIA®+MTX vs MTX+placebo (Study VI)

*** p<0.001, ORENCIA® vs placebor ORENCIA®+MTX vs MTX+placebo (Study VI).

a Fixed dose approximating 10 mg/kg.

b Concurrent DMARDs included one or more of the following: MTX, azathioprine, chloroquine/hydroxychloroquine, gold, leflunomide, sulfasalazine, and anakinra.

c Major clinical response is defined as achieving an ACR 70 response for a continuous 6-month period

d DAS28-CRP Remission is defined as a DAS28-CRP score <2.6

Among ORENCIA®-treated patients in Study III, 14% achieved a major clinical response, as compared with 2% in placebo patients. In addition, 6% of ORENCIA®-treated patients in this 12-month study achieved an extended major clinical response (continuous ACR 70 response over 9 months), as compared with 0.5% in placebo patients. In Study III, for patients treated with ORENCIA® over two years including double-blind and open-label periods, the percentage of subjects achieving a major clinical response and an extended major clinical response increased to 34.3% and 24.5%, respectively.

ORENCIA®-treated patients experienced greater improvement than placebo-treated patients in morning stiffness.

DAS28 remission

Disease activity was also assessed using the Disease Activity Score 28 (DAS28). In Studies III and IV, the baseline mean DAS28 was 6.8 and 6.9 units, respectively, representing a high degree of disease activity. In Study III, the mean improvement in DAS28 at 12 months in ORENCIA® -treated patients of 2.9 was significantly greater than the mean improvement of 1.5 observed in placebo-treated patients. DAS28 defined remission was achieved in 17% of ORENCIA® -treated patients compared to 2% of placebo-treated patients at 12 months.

In Study IV, at month 6, a significantly greater improvement in DAS28 was observed in the ORENCIA® -treated patients than in placebo-treated patients (reduction of 2.0 vs. 0.7 units respectively, DAS28-defined remission was achieved in 10% of ORENCIA® -treated patients compared to 1% of placebo-treated patients at 6 months.

In Study VI, patients treated with ORENCIA® plus MTX had a higher DAS28-CRP remission rate at 12 months than those treated with MTX plus placebo (Table 2). Of patients treated with ORENCIA® plus MTX who achieved DAS28-CRP remission, 54% had no active joints, 17% had one active joint, 7% had two active joints, and 22% had three or more active joints, where an active joint was a joint that was rated as tender or swollen or both.

Radiographic response

Structural joint damage was assessed radiographically over a two-year period in Study III in RA patients with inadequate response to MTX. The results were measured using the Genant-modified Total Sharp score (TSS) and its components, the erosion score and Joint Space Narrowing (JSN) score. The baseline median TSS was 31.7 in ORENCIA®-treated patients and 33.4 in placebo-treated patients. In the first year, patients received ORENCIA® or placebo in double-blind fashion. ORENCIA®/MTX inhibited the progression of structural damage compared to placebo/MTX after 12 months of treatment as shown in Table 3.

Inhibition of progression of structural damage with ORENCIA® was observed regardless of disease duration (less than 2 years, 2 to 5 years, 5 to 10 years, and greater than 10 years).

Table 3: Mean Radiographic Changes Over 12 Months in Study III

Parameter	ORENCIA®/MTX n=391	Placebo/MTX n=195	P-value[a]
Total Sharp score	1.21	2.32	0.012
Erosion score	0.63	1.14	0.029
JSN score	0.58	1.18	0.009

[a] Based on non-parametric analysis.

In the open-label extension of Study III, 75% (n = 324) of patients initially randomized to ORENCIA®/MTX were evaluated radiographically by the TSS. Following 2 years of treatment with ORENCIA®/MTX, inhibition of progression of structural damage was observed. Fifty (50) percent of the patients had no progression of structural damage as defined by a change in the TSS of zero or less at 2 years. Eighty-six (86) percent of patients with no radiographic progression after 1 year of treatment with ORENCIA®/MTX, had no progression at 2 years. For patients treated with ORENCIA®/MTX, the mean change in TSS from year 1 to year 2 was 57% lower than the mean change in TSS from baseline to year 1.

Based on year-to-year assessment, a decrease in radiographic progression was observed for all 3 scores with the most decrease observed in the first year of the abatacept treatment in the uncontrolled, open-label, long-term (LT) period. At the end of the LT period (4 years, Day 1821),

106/235 (45.1%) subjects in the original abatacept group and 45/115 (39.1%) subjects in the original placebo group showed no radiographic progression based on the Total score).

In Study VI, the mean change in TSS at 12 months was significantly lower in patients treated with ORENCIA® plus MTX compared to those treated with MTX plus placebo as shown in Table 4. At 12 months 61% (148/242) of the patients treated with abatacept plus methotrexate and 53% (128/242) of the patients treated with methotrexate plus placebo had no progression (change from baseline in TSS ≤ 0). Among the patients who entered the open -label 12 month period, the progression of structural damage was lower in those receiving continuous abatacept plus methotrexate treatment (for 24 months) compared to patients who initially received methotrexate plus placebo (for 12 months) and were switched to abatacept plus methotrexate for the next 12 months. Of these patients, 57% (121/213) who received continuous abatacept plus methotrexate treatment and 44% (84/192) of patients who initially received methotrexate and switched to combination with abatacept had no progression.

Table 4: Mean Radiographic Changes Over 12 and 24 Months in Study VI

	Month 12			Month 24	
Parameter	**ORENCIA®/ MTX** n= 242	**Placebo /MTX** n= 242	P-value[a]	**ORENCIA®/ MTX** n= 213	**Placebo /MTX** n= 192
Total Sharp score					
Baseline (Mean)	7.50	6.67		7.73	7.24
Change from Baseline (Mean)	0.63	1.06	0.040	0.84	1.75
Erosion score					
Baseline (Mean)	5.48	4.81		5.91	5.49
Change from Baseline (Mean)	0.50	0.89	0.033	0.59	1.40
JSN score					
Baseline (Mean)	2.03	1.86		1.83	1.75
Change from Baseline (mean)	0.13	0.17	0.353	0.25	0.34

[a] Based on non-parametric analysis.

The effect of ORENCIA® on structural damage was not studied in RA patients with an inadequate response to TNF blocking agents.

Physical function response

Improvement in physical function was measured by the Health Assessment Questionnaire Disability Index (HAQ-DI) in Studies III, IV, and V, and a modified HAQ-DI in Study II. In Studies II-V, ORENCIA® demonstrated significantly greater improvement from baseline than placebo in the HAQ-DI and a significantly greater proportion of patients treated with ORENCIA® compared to placebo showed a clinically meaningful improvement (reduction in HAQ-DI of ≥0.3 units from baseline). In Study VI, significantly greater improvement from baseline in the HAQ-DI was observed in ORENCIA®+MTX-treated patients compared with MTX+placebo-treated patients, and significantly more patients in the ORENCIA®+MTX group compared with the MTX+placebo group achieved a clinically meaningful improvement at 12 months. In Study III, among HAQ responders at month 12, 88% retained the response at month 18, and 85% retained the response at month 24. The results from Studies II-IV, are shown in Table 5. During the open-label periods of Studies II, III, IV, and VI, the improvement in physical function has been maintained through 7 years, 5 years, 5 years, and 2 years, respectively.

Table 5: Mean Improvement from Baseline in Health Assessment Questionnaire Disability Index (HAQ-DI)

	Inadequate Response to Methotrexate (MTX)				Inadequate Response to TNF Blocking Agent	
	Study II		Study III		Study IV	
HAQ Disability Index	ORENCIA® [a] +MTX	Placebo +MTX	ORENCIA® [b] +MTX	Placebo +MTX	ORENCIA® [b] +DMARDS[c]	Placebo +DMARDS[c]
Baseline (Mean)	0.98[d] (n=115)	0.97[d] (n=119)	1.69[e] (n=422)	1.69[e] (n=212)	1.83[e] (n=249)	1.82[e] (n=130)
Mean Improvement from Baseline						
Month 6	0.40[d,***] (n=113)	0.19[d] (n=118)	0.59[e,***] (n=420)	0.40[e] (n=211)	0.45[e,***] (n=249)	0.11[e] (n=130)
Month 12	0.40[d,***] (n=115)	0.15[d] (n=119)	0.66[e,***] (n=422)	0.37[e] (n=212)	NA	NA
Proportion of patients with a clinically meaningful improvement[f]						
Month 6	47%[d,**]	28%[d]	61%[e,***]	45%[e]	47%[e,***]	23%[e]
Month 12	38%[d,**]	20%[d]	64%[e,***]	39%[e]	NA	NA

** p <0.01, ORENCIA® vs. placebo.

*** p <0.001, ORENCIA® vs. placebo.

[a] 10 mg/kg.

[b] Fixed dose approximating 10 mg/kg.

[c] Concurrent DMARDs included one or more of the following: MTX, azathioprine, chloroquine/hydroxychloroquine, gold, leflunomide, sulfasalazine, and anakinra.

[d] Modified Health Assessment Questionnaire; 0 = best, 3 = worst; 8 questions; 8 categories: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities.

[e] Health Assessment Questionnaire; 0 = best, 3 = worst; 20 questions; 8 categories: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities.

[f] Reduction in HAQ-DI of ≥0.3 units from baseline.

Health-related outcomes and quality of life

Health-related quality of life was assessed by the SF-36 questionnaire at 6 months in Studies II, III, and IV and at 12 months in Studies II and III. In these studies, clinically and statistically significant improvement was observed in the ORENCIA® group as compared with the placebo group in all 8 domains of the SF-36 (4 physical domains: physical function, role physical, bodily pain, general health; and 4 mental domains: vitality, social function, role emotional, mental health), as well as the Physical Component Summary (PCS) and the Mental Component Summary (MCS). In Study VI, improvement was observed at 12 months in the ORENCIA®+MTX group as compared with the MTX+placebo group in both PCS and MCS and was maintained through 24 months.

In Studies III and IV, fatigue was measured by a validated Fatigue Visual Analogue Scale, and sleep problems were assessed by the Sleep Problems Index (SPI) of the Medical Outcomes Study Sleep Module. At 12 months and 6 months, in Study III and Study IV, respectively, statistically significant reductions in fatigue and sleep problems were observed in ORENCIA®-treated patients

as compared to placebo-treated patients. In Study VI, a greater reduction in the fatigue score was observed at 6 and 12 months in ORENCIA®+MTX-treated patients than in MTX+placebo-treated patients. In open-label therapy with ORENCIA®, improvements in health-related outcomes and quality of life have been maintained for up to 4 years.

Additional clinical trials in adult rheumatoid arthritis.

Study VII: abatacept or infliximab versus placebo

A randomized, double blind study was conducted to assess the safety and efficacy of abatacept or infliximab versus placebo in patients with an inadequate response to methotrexate (Study VII, Study IM101043). Study VII patients received the same fixed dose of abatacept as that in Studies III-VI or 3 mg/kg infliximab or placebo for 6 months. Study VII continued for an additional 6 months with the abatacept and infliximab groups only. The primary outcome was the mean change in disease activity in abatacept-treated patients compared to placebo-treated patients at 6 months with a subsequent double-blind assessment of safety and efficacy of abatacept and infliximab at 12 months. The number of patients randomized was 156 to abatacept, 165 to infliximab, and 110 to placebo. In Study VII, the DAS28 mean changes from baseline at months 6 and 12 are shown in Table 6, as are the percentages of patients achieving DAS28-defined low disease activity and remission. Greater improvement ($p < 0.001$) in DAS28 was observed with abatacept and with infliximab compared to placebo at six months in the placebo-controlled portion of the trial; the results between the abatacept and infliximab groups were similar and demonstrated that the efficacy of abatacept and infliximab were both largely maintained and comparable for major efficacy variables. Further improvement was observed at 12 months with abatacept. The ACR responses in Study VII were consistent with the DAS28 score.

The open label period of Study VII provided an assessment of the ability of abatacept to maintain efficacy for subjects originally randomized to abatacept and the efficacy response of those subjects who were switched to abatacept following treatment with infliximab. The reduction from baseline in mean DAS28 score at day 365 (3.06) was maintained through day 729 (3.34) in those patients who continued with abatacept. In those patients who initially received infliximab and then switched to abatacept, there was improvement in the mean DAS28 score at day 729 (3.07) relative to day 365 (3.88).

At 6 months, the overall serious adverse events considered to be related to treatment was 1.9% (3 patients) in the abatacept group, 4.8% (8) in the infliximab group, and 2.7% (3) in the placebo group. The frequency of serious infections was 1.3% (2) in the abatacept group, 2.4% (4) in the infliximab group, and 0.9% (1) in the placebo group. The frequency of acute infusional adverse events was 5.1% (8) in the abatacept group, 18.2% (30) in the infliximab group, and 10.0% (11) in the placebo group. At 12 months, the overall serious adverse events considered to be related to treatment was 3.2% (5) in the abatacept group and 8.5% (14) in the infliximab group. The frequency of serious infections was 1.3% (2) in the abatacept group and 6.1% (10) in the infliximab group, with a total of 5 serious opportunistic infections in the infliximab group and none in the abatacept group. With regard to abnormal laboratory values at 6 months, antinuclear antibodies developed in 1.7% (2) of the abatacept group, 32.2% (38) of the infliximab group, and 4.9% (4) of the placebo group. The study was not statistically powered to determine the safety differences between abatacept and infliximab.

Table 6: Disease Activity Score 28 (DAS28 ESR) Results in Study VII

DAS28 Response	Abatacept +MTX n = 150	Infliximab +MTX n = 156	Placebo +MTX n = 102
Baseline (Mean)	6.9	6.8	6.8
Mean Change from Baseline			
Month 6	2.5 ***	2.3 ***	1.5
Month 12	2.9	2.3	NA[a]
Proportion of Patients with a Low Disease Activity			
Month 6	21%	26%	11%
Month 12	35%	22%	NA[a]
Proportion of Patients with Remission			
Month 6	11%	13%	3%
Month 12	19%	12%	NA[a]

Note: Hypothesis tests performed only on the primary endpoint of DAS28 mean change at month 6.
*** $p<0.001$ compared to placebo.
[a] Placebo administered for only six months.

Study VIII: Safety of abatacept in patients with or without washout of previous TNF blocking agent therapy

A study of open-label abatacept on a background of nonbiologic DMARDs was conducted in patients with active RA who had an inadequate response to previous (washout for at least 2 months; n=449) or current (no washout period; n=597) TNF-antagonist therapy (Study VIII, Study IM101064). The primary outcome, incidence of adverse events, serious adverse events, and discontinuations due to adverse events during 6 months of treatment, was similar between those who were previous and current TNF-antagonist users at enrollment, as was the frequency of serious infections. Results from Study VIII support the transition from TNF blocking agent therapy to ORENCIA® therapy at the next scheduled dose of the TNF blocking agent therapy.

Paediatric and Adolescent (Juvenile Idiopathic Arthritis)

The safety and efficacy of ORENCIA® were assessed in a three-part study (IM101033, AWAKEN) including an open-label extension in children with polyarticular juvenile idiopathic arthritis (JIA). The study enrolled patients 6 to 17 years of age with moderately to severely active polyarticular JIA who had an inadequate response or intolerance to one or more DMARDs, such as MTX or TNF antagonists. Patients had a disease duration of approximately 4 years with active disease at study entry, as determined by baseline counts of active joints (mean, 16) and joints with loss of motion (mean, 16); patients had elevated C-reactive protein (CRP) levels (mean, 3.2 mg/dL) and ESR (mean, 32 mm/h). The patients enrolled had subtypes of JIA that at disease onset included Oligoarticular (16%), Polyarticular (64%; 20% were rheumatoid factor positive), and Systemic (20%). Patients with systemic JIA who had intermittent fever, rheumatoid rash, hepatosplenomegaly, pleuritis, pericarditis or macrophage activation syndrome within the prior 6 months were excluded. At study entry, 74% of patients were receiving MTX (mean dose, 13.2

mg/m^2 per week) and remained on a stable dose of MTX (those not receiving MTX did not initiate MTX treatment during the study as this was not mandated as part of the protocol).

In Period A (open-label, lead-in), 190 patients (33% of which were under 12 years of age), were treated with ORENCIA®; patients received 10 mg/kg (maximum 1000 mg per dose) intravenously on days 1, 15, 29, and monthly thereafter. Response was assessed utilizing the ACR Paediatric30 definition of improvement, defined as ≥30% improvement in at least 3 of the 6 JIA core set variables and ≥30% worsening in not more than 1 of the 6 JIA core set variables. Patients demonstrating an ACR Pedi 30 response at the end of Period A were randomized into the double-blind phase (Period B) and received either ORENCIA® or placebo for 6 months or until disease flare. Disease flare was defined as ≥30% worsening in at least 3 of the 6 JIA core set variables with ≥30% improvement in not more than 1 of the 6 JIA core set variables. ≥2 cm of worsening of the Physician or Parent Global Assessment was necessary if either was used as 1 of the 3 JIA core set variables used to define flare, and worsening in ≥2 joints was necessary if the number of active joints or joints with limitation of motion was used as 1 of the 3 JIA core set variables used to define flare.

At the conclusion of Period A, paediatricACR 30/50/70 responses were 65%, 50%, and 28%, respectively. PaediatricACR 30 responses were similar in all subtypes of JIA studied.

During the double-blind randomized withdrawal phase (Period B), ORENCIA®-treated patients experienced significantly fewer disease flares compared to placebo-treated patients (20% vs 53%); 95% CI of the difference (15%, 52%). The risk of disease flare among patients continuing on ORENCIA® was less than one third that for patients withdrawn from ORENCIA® treatment (hazard ratio=0.31, 95% CI [0.16, 0.59]). Among patients who received ORENCIA® throughout the study (Period A, Period B, and the open-label extension Period C), the proportion of paediatricACR 30/50/70 responders has remained consistent for 31 months.

ORENCIA® has not been studied in children less than 6 years of age. The long-term effects of ORENCIA® therapy on skeletal, behavioural, cognitive, sexual, and immune maturation and development in children are unknown.

INDICATIONS

ORENCIA® in combination with methotrexate is indicated for the treatment of moderate to severe active rheumatoid arthritis in adult patients who have had an insufficient response or intolerance to other disease modifying anti-rheumatic drugs (DMARDs), such as methotrexate or tumour necrosis factor (TNF) blocking agents. A reduction in the progression of joint damage and improvement in physical function have been demonstrated during combination treatment with ORENCIA® and methotrexate.

ORENCIA® in combination with methotrexate is also indicated in the treatment of severe, active and progressive rheumatoid arthritis in adults not previously treated with methotrexate

ORENCIA® is indicated for reducing signs and symptoms in paediatric patients 6 years of age and older with moderately to severely active polyarticular juvenile idiopathic arthritis who have had an inadequate response to one or more disease-modifying anti-rheumatic drugs (DMARDs). ORENCIA® may be used as monotherapy or concomitantly with methotrexate (MTX).

ORENCIA® should not be administered concurrently with other biological DMARDs (eg, TNF inhibitors, rituximab, or anakinra).

CONTRAINDICATIONS

ORENCIA® should not be administered to patients with known hypersensitivity to ORENCIA® or any of its components (see **PRODUCT DESCRIPTION**). ORENCIA® should not be administered to patients with severe infections such as sepsis, abscesses, tuberculosis, and opportunistic infections.

PRECAUTIONS

Combination with TNF blocking agents

There is limited experience with the use of ORENCIA® in combination with TNF blocking agents. In placebo-controlled clinical trials in patients with adult RA, patients receiving concomitant ORENCIA® and TNF blocking agent therapy experienced more infections (24%) and serious infections (2.2%) compared to patients treated with only TNF blocking agents (19% and 0.8%, respectively). Concurrent therapy with ORENCIA® and a TNF blocking agent is not recommended.

While transitioning from TNF blocking agent therapy to ORENCIA® therapy, patients should be monitored for signs of infection.

Other biologic RA therapy. There is insufficient experience to assess the safety and efficacy of ORENCIA administered concurrently with other biologic RA therapy, such as anakinra or rituximab, and therefore such use is not recommended.

Hypersensitivity

Hypersensitivity reactions can be observed during treatment with any injectable protein. Such reactions have been reported with ORENCIA® administration in clinical trials, where patients were not required to be pretreated to prevent hypersensitivity reactions. The occurrence of anaphylaxis remained rare between the double blind trials and long-term open-label experience. (see ADVERSE EFFECTS – Infusion-related reactions and hypersensitivity reactions) Hypersensitivity was reported uncommonly. Other events potentially associated with drug hypersensitivity, such as hypotension, urticaria, and dyspnea, that occurred within 24 hours of ORENCIA® infusion were uncommon.

Effects on the immune system

The possibility exists for drugs that affect the immune system, including ORENCIA®, to affect vaccination responses and host defenses against infections and malignancies.

In a small study with healthy subjects ORENCIA® reduced the quantitative immune response (measured via antibody titer against the tetanus toxoid vaccine and pneumococci antigens). However the 2-fold increase in titer response to these antigens was not altered.

Infections

Serious infections, including sepsis and pneumonia, have been reported in patients receiving ORENCIA®. Some of these infections have been fatal. Many of the serious infections have occurred in patients on concomitant immunosuppressive therapy which in addition to their underlying disease, could further predispose them to infections. Physicians should exercise caution when considering the use of ORENCIA® in patients with: a history of recurrent infections; underlying conditions which may predispose them to infections; or chronic, latent, or localized infections. Patients who develop a new infection while undergoing treatment with ORENCIA® should be monitored closely. Administration of ORENCIA® should be discontinued if a patient develops a serious infection. A higher rate of serious infections has been observed in adult RA patients treated with concurrent TNF blocking agents and ORENCIA®.

In placebo-controlled clinical studies in adults, of 1955 ORENCIA® patients and 989 placebo patients, two cases of tuberculosis were reported, one each in the ORENCIA® and placebo groups. When treating patients with therapies that modulate the immune system, it is appropriate to screen

for tuberculosis infections, as was the case with patients in these clinical trials. ORENCIA® has not been studied in patients with a positive tuberculosis screen, and the safety of ORENCIA® in individuals with latent tuberculosis is unknown. Patients testing positive in tuberculosis screening, should be treated by standard medical practice prior to therapy with ORENCIA®.

Anti-rheumatic therapies have been associated with hepatitis B reactivation. Therefore, screening for viral hepatitis should be performed in accordance with published guidelines before starting therapy with ORENCIA®.

Malignancies

In the placebo-controlled clinical trials in adult RA, the frequencies of malignancies in abatacept- and placebo-treated patients were 1.4% and 1.1%, respectively (see ADVERSE REACTIONS). Patients with known malignancies were not included in these clinical trials. In carcinogenicity studies in mice, an increase in lymphomas and mammary tumours were noted. The clinical significance of this observation is unknown (see CARCINOGENICITY). The potential role of ORENCIA® in the development of malignancies, including lymphoma, in humans is unknown.

Infusion-related reactions

Infusion Related reactions can be observed during treatment with any injectable protein. Such reactions have been reported with ORENCIA® administration in clinical trials, where patients were not required to be pretreated to prevent hypersensitivity reactions. (see ADVERSE EFFECTS – Infusion-related reactions and hypersensitivity reactions).

Immunizations

Live vaccines should not be given concurrently with ORENCIA® or within 3 months of its discontinuation. No data are available on the secondary transmission of infection from persons receiving live vaccines to patients receiving ORENCIA®. No data are available on the effects of vaccinations in patients receiving ORENCIA®. Drugs that affect the immune system, including ORENCIA®, may blunt the effectiveness of some immunizations.

It is recommended that patients with juvenile idiopathic arthritis be brought up to date with all immunizations in agreement with current immunization guidelines prior to initiating ORENCIA® therapy.

Autoimmune processes

There is a theoretical concern that treatment with ORENCIA® might increase the risk for autoimmune processes, for example deterioration of multiple sclerosis. In the placebo-controlled clinical trials, abatacept treatment did not lead to increased autoantibody formation, such as antinuclear and anti-dsDNA antibodies, relative to placebo treatment

Interactions with other medicines

Formal drug interaction studies have not been conducted with ORENCIA®.

The majority of patients in the RA placebo-controlled clinical trials received concomitant DMARDs, NSAIDs, and/or corticosteroids. Most patients were taking MTX. Other less frequently used concomitant DMARDs included chloroquine/hydroxychloroquine, sulfasalazine, and leflunomide. There is limited experience with abatacept in combination with other DMARDs such as azathioprine, gold and anakinra. Population pharmacokinetic analyses revealed that MTX, NSAIDs, corticosteroids, and TNF blocking agents did not influence abatacept clearance (see **PHARMACOLOGY: PHARMACOKINETICS**)

Concurrent administration of a TNF blocking agent with ORENCIA® has been associated with an increased risk of serious infections. Concurrent therapy with ORENCIA® and TNF blocking agents is not recommended.

There is insufficient experience to assess the safety and efficacy of ORENCIA® administered concurrently with anakinra or rituximab, and therefore such use is not recommended.

ORENCIA® has not been studied in combination with agents which deplete lymphocyte count. Such combination therapy could potentiate the effects of ORENCIA® on the immune system.

Other Interactions

Blood Glucose Testing.

Parenteral drug products containing maltose can interfere with the readings of blood glucose monitors that use test strips with glucose dehydrogenase pyrroloquinolinequinone (GDH-PQQ). The GDH-PQQ based glucose monitoring systems may react with the maltose present in ORENCIA®, resulting in falsely elevated blood glucose readings on the day of infusion. When receiving ORENCIA®, patients that require blood glucose monitoring should be advised to consider methods that do not react with maltose, such as those based on glucose dehydrogenase nicotine adenine dinucleotide (GDH-NAD), glucose oxidase, or glucose hexokinase test methods.

Genotoxicity

Abatacept was not genotoxic in *in vitro* tests for reverse gene mutation in bacteria, forward gene mutation in mammalian cells, and clastogenicity in human lymphocytes.

Carcinogenicity

In a long term carcinogenicity study in mice, weekly subcutaneous abatacept treatment for up to 84-88 weeks resulted in increased incidences of malignant lymphomas at all doses (0.8 to 3-fold the human drug exposure based on AUC). Increased incidences of female mammary gland tumours were also observed at drug exposures (AUC) 2 to 3-fold the human exposure. While these tumours may be related to activation of murine leukaemia virus and mouse mammary tumour virus, respectively, by prolonged immumosuppression, there is no conclusive evidence to support this hypothesis.

Effects in non-human primates

In a one-year toxicity study in 30 cynomolgus monkeys at weekly doses of 10-50 mg/kg, abatacept (2-9-fold the human exposure based on the AUC), drug related effects consisted of minimal transient decreases in serum immumoglobulin G and minimal to severe lymphoid depletion of germinal centres in the spleen and/or lymph nodes, which were consistent with the pharmacological activities of the drug. No lymphomas or pre-neoplastic morphological changes were observed, despite the presence of a virus (lymphocryptovirus) known to cause these lesions in imunosuppressed monkeys.

Effects on fertility

Fertility in rats was unaffected by abatacept doses of up to 200 mg/kg every 3 days (11-fold the human drug exposure based on AUC).

Use in pregnancy (Category C)

Abatacept may affect the immune system in the fetus. Embryofetal development was unaffected by doses of up to 300 mg/kg/day in mice, 200 mg/kg/day in rats, and 200 mg/kg every 3 days in rabbits (approximately 29-fold the human drug exposure based on AUC). Abatacept was shown substantially to cross the placenta in rats, and minimally in rabbits. Offspring were unaffected by abatacept doses of up to 45 mg/kg given every 3 days to rats from early gestation through to the end of lactation (3-fold the human drug exposure based on AUC). With a dose of 200 mg/kg every 3 days (approximately 11-fold the human drug exposure based on AUC) female pups showed enhanced T cell dependent antibody responses and a single case (out of 20 pups) of thyroid chronic inflammation. Whether these findings indicate a potential for the development of autoimmune

diseases in humans exposed *in utero* is uncertain. There are no adequate and well-controlled studies in pregnant women. The use of ORENCIA during pregnancy is not recommended.

Use in lactation

Abatacept has been shown to be present in rat milk and in the serum of suckling pups. It is not known whether abatacept is excreted in human milk or absorbed systemically after ingestion. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in breast-fed infants from abatacept, women on abatacept should not breast feed. The long half-life of abatacept should also be considered when discontinuing therapy.

PaediatricUse

ORENCIA® is indicated for reducing signs and symptoms in paediatric patients 6 years of age and older with moderately to severely active polyarticular juvenile idiopathic arthritis who have had an inadequate response to one or more disease-modifying anti-rheumatic drugs (DMARDs). ORENCIA® may be used as monotherapy or concomitantly with methotrexate (MTX).

The safety and effectiveness of ORENCIA® in paediatric patients below 6 years of age have not been established. Therefore, ORENCIA® is not recommended for use in patients below the age of 6 years.

Safety and efficacy of ORENCIA® in paediatric patients for uses other than juvenile idiopathic arthritis have not been established.

The long-term effects of ORENCIA® therapy on skeletal, behavioural, cognitive, sexual, and immune maturation and development in children are unknown.

Non-clinical studies relevant for use in the paediatric population

Studies in rats exposed to abatacept have shown immune system abnormalities including a low incidence of infections leading to death (juvenile rats) as well as inflammation of the thyroid and pancreas (both juvenile and adult rats). Studies in adult mice and monkeys have not demonstrated similar findings. The increased susceptibility to opportunistic infections observed in juvenile rats is likely associated with the exposure to abatacept prior to development of memory responses. The relevance of these results to humans greater than 6 years of age, where memory responses have more time to develop, is unknown.

Use in the elderly

A total of 323 patients 65 years of age and older, including 53 patients 75 years and older, received ORENCIA® in clinical studies. Similar efficacy was observed in these patients and younger patients. The frequency of serious infection and malignancy among ORENCIA® -treated patients over age 65 was higher than for those under age 65. Because there is a higher incidence of infections and malignancies in the elderly population in general, caution should be used when treating the elderly.

Patients on controlled sodium diet

This medicinal product contains 1.5mmol (or 34.5mg) sodium per maximum dose of 4 vials(0.375 mmol or 8.625 mg sodium per vial). To be taken into consideration when treating patients on a controlled sodium diet

Use in Patients with Chronic Obstructive Pulmonary Disease (COPD)

COPD adult patients treated with ORENCIA® developed adverse events more frequently than those treated with placebo, including COPD exacerbations, cough, rhonchi, and dyspnea. Use of ORENCIA® in patients with rheumatoid arthritis and COPD should be undertaken with caution and such patients should be monitored for worsening of their respiratory status

Information for Patients

Patients should be provided the ORENCIA® Patient Information leaflet and provided an opportunity to read it prior to each treatment session. Because caution should be exercised in administering ORENCIA® to patients with active infections, it is important that the patient's overall health be assessed at each visit and any questions resulting from the patient's reading of the Patient Information be discussed.

ADVERSE EFFECTS

Adult

General

ORENCIA® has been studied in patients with active rheumatoid arthritis in placebo-controlled clinical trials (1955 patients with ORENCIA®, 989 with placebo). The trials had either a double-blind, placebo-controlled period of 6 months (258 patients with ORENCIA®, 133 with placebo) or 1 year (1697 patients with ORENCIA®, 856 with placebo). Most patients in these trials were taking methotrexate (81.9% with ORENCIA®, 83.3% with placebo). Other concomitant medications included: NSAIDs (83.9% with ORENCIA®, 85.1% with placebo); systemic corticosteroids (74.7% with ORENCIA®, 75.8% with placebo); non-biological DMARD therapy, most commonly chloroquine/hydroxychloroquine, leflunomide and/or sulfasalazine (26.9% with ORENCIA®, 32.1% with placebo); TNF blocking agents, mainly etanercept (9.4% with ORENCIA®, 12.3% with placebo); and anakinra (1.1% with ORENCIA®, 1.6% with placebo).

In placebo-controlled clinical trials with ORENCIA®, adverse drug reactions (ADRs) (adverse events at least possibly causally-related to treatment) were reported in 52.2% of ORENCIA®-treated patients and 46.1% of placebo-treated patients. The most frequently reported adverse drug reactions ($\geq$ 5%) among ORENCIA®-treated patients were headache and nausea. The proportion of patients who discontinued treatment due to ADRs was 3.4% for ORENCIA®-treated patients and 2.2% for placebo-treated patients.

Overall adverse events reported irrespective of consideration to causality to treatment in the placebo-controlled clinical trials in RA patients are listed in Table 7.

The majority of these adverse events were mild to moderate and the severity was similar in patients that had previously taken traditional DMARDs, such as MTX, or biological therapies, such as TNF blocking agents (Table 8).

Table 7: Overview of Adverse Events in Placebo-Controlled Clinical Trials in Rheumatoid Arthritis Patients

	ORENCIA® (n=1955) Percentage	Placebo (n=989) Percentage
All adverse events	88.8	85.1
Serious adverse events	14.0	12.5
Infections and infestations	54.1	48.7
Malignancies	1.4	1.1
Acute infusion-related events (reported within 1 hour of the start of the infusion)	9.8	6.7

Table 8: Intensity of Adverse Events in Double-Blind, Controlled Study Periods: Study IV vs Study III

	Percent of Patients			
	Mild	**Moderate**	**Severe**	**Very Severe**
Study IV, Inadequate Response to TNF Blocking Agent				
ORENCIA®	61.2%	47.3%	8.1%	1.9%
Placebo	51.1%	42.1%	9.8	0.8%
Study III, Inadequate Response to MTX				
ORENCIA®	75.1%	60.3%	15.2%	1.2%
Placebo	73.5%	55.3%	12.8%	0.9%

In general, adverse events are more common with biological agents as compared with other types of medications used in the management of rheumatoid arthritis.

Adverse drug reactions greater in frequency (difference >0.2%) in ORENCIA®-treated patients compared to placebo patients are listed below by system organ class and frequency (very common ≥10%; common ≥1% <10%; uncommon ≥0.1% <1%; rare ≥0.01% <0.1%).

Infections and infestations

Common: Lower respiratory tract infection (including, bronchitis), urinary tract infection, herpes simplex, upper respiratory tract infection (including tracheitis, nasopharyngitis), rhinitis

Uncommon: Tooth infection, infected skin ulcer, onchomycosis

Neoplasms benign and malignant (including cysts and polyps)

Uncommon: Basal cell carcinoma

Blood and the lymphatic system disorders

Uncommon:	Thrombocytopenia, leukopenia
Psychiatric disorders	
Uncommon:	Depression, anxiety
Nervous system disorders	
Very Common:	Headache
Common:	Dizziness
Uncommon:	Paraesthesia
Eye disorders	
Uncommon:	Conjunctivitis, visual acuity reduced
Ear and labyrinth disorders	
Uncommon:	Vertigo
Cardiac disorders	
Uncommon:	Tachycardia, bradycardia, palpitations
Vascular disorders	
Common:	Hypertension, flushing
Uncommon:	Hypotension, hot flush
Respiratory, thoracic and mediastinal disorders	
Common:	Cough
Gastrointestinal disorders	
Common:	Abdominal pain, diarrhoea, nausea, dyspepsia
Uncommon:	Gastritis, mouth ulceration, aphthous stomatitis
Skin and subcutaneous tissue disorders	
Common:	Rash (including dermatitis)
Uncommon:	Increased tendency to bruise, alopecia, dry skin
Musculoskeletal, connective tissue and bone disorders	
Uncommon:	Arthralgia, pain in extremity
Reproductive system and breast disorders	
Uncommon	Amenorrhea
General disorders and administration site conditions	
Common:	Fatigue, asthenia
Uncommon:	Influenza like illness
Investigations	
Common:	Blood pressure increased, liver function test abnormal (including transaminases increased)
Uncommon:	Blood pressure decreased, weight increased

Infections

In the placebo-controlled trials, infections at least possibly related to treatment were reported in 23.2% of ORENCIA®-treated patients and 19.5% of placebo patients.

Serious infections at least possibly related to treatment were reported in 1.8% of ORENCIA®-treated patients and 1.0% of placebo patients. The most frequent (0.1-0.3%) serious infections at least possibly related to treatment reported with ORENCIA® were pneumonia, cellulitis, localized infection, urinary tract infection, bronchitis, diverticulitis, and acute pyelonephritis **(see PRECAUTIONS)**.

In double blind and open-label clinical trials in 4,149 patients treated with abatacept during 11,658 patient-years, the incidence rate of serious infections was 2.87 per 100 patient -years, and the annualized incidence rate remained stable.

Malignancies

In placebo-controlled clinical trials, malignancies were reported in 27 of 1955 ORENCIA®-treated patients observed during 1687 patient-years, and in 11 of 989 placebo-treated patients observed during 794 patient-years.

In double-blind and open-label clinical trials in 4149 patients treated with ORENCIA® during 11,658 patient-years, (of which over 1,000 were treated with abatacept for over 5 years), the incidence rate of malignancy was 1.43 per 100 patient-years, and the annualised incidence rate remained stable. The incidence rates per 100 patient-years were 0.72 for non-melanomatous skin cancer, 0.59 for solid malignancies and 0.13 for hematologic malignancies. The most frequently reported solid organ cancer was lung cancer (0.17 per 100 patient-years), and the most common hematologic malignancy was lymphoma (0.06 per 100 patient-years). The incidence rate did not increase for malignancies overall, by major type (non-melanomatous skin cancer, solid tumors, and hematologic malignancies), or for individual tumor types in the double-blind and open label period compared to the double-blind experience. The type and pattern of malignancies reported during the open-label period of the trials were similar to those reported for the double-blind experience.

The incidence rate of observed malignancies was consistent with that expected in an age- and gender-matched rheumatoid arthritis population.

With regard to the general population, the observed and expected malignancies and the standardised incidence ratios are shown in Table 9.

Table 9: Observed and Expected Malignancies and Standarised Incidence Ratios (SIRs) Compared with the General Population[a]

Malignancy	Observed[b]	Expected[c]	SIR (95% CI)[d]
Overall Solid Organ Malignancies	28	37.25	0.75 (0.50, 1.09)
Lung	11	4.88	2.25 (1.12, 4.03)
Breast	4	9.66	0.41 (0.11, 1.10)
Prostate	3	3.92	0.77 (0.15, 2.24)
Colon/Rectum	0	3.54	0 (0.00, 1.04)
Lymphoma	4	1.34	3.00 (0.81, 7.67)

a General Population Rate estimates from United States Surveillance and End Results (SEER).

b Observed number in ORENCIA®-exposed patients in double-blind and open-label clinical trials.

c Based on General Population (SEER) rate estimates; adjusted for age and gender and takes into account duration of ORENCIA® exposure.

d SIR -Standardised incidence ratio (Observed/Expected) 95% CI - confidence interval.

Infusion-related reactions and hypersensitivity reactions

Infusion Related reactions can be observed during treatment with any injectable protein. Such reactions have been reported with ORENCIA® administration in clinical trials, where patients were not required to be pretreated to prevent hypersensitivity reactions.

Acute infusion reactions (within 1 hour of infusion) the incidence rate of 4.04 per 100 p-y. The annual incidence rate of acute-infusional events was elevated in the first year of exposure, decreased in the second, and then remained stable with increasing duration of exposure to abatacept. The 4 most common events contributing to this incidence rate per 100 p-y were dizziness (0.70), headache (0.69), hypertension (0.62), and nausea (0.40)). The frequencies of these 4 events were 1.9%, 1.8% 1.7% and 1.1%, respectively. Greater than 95% of all subjects with acute-infusional events were mild or moderate in intensity

Peri-infusion reactions (up to 24 hrs after infusion) the incidence rate was 11.63 per 100 p-y. The 4 most common events contributing this overall incidence rate per 100 p-y were headache (3.09), nausea (1.69), dizziness (1.56), and hypertension (1.16). Approximately 95% of all subjects with peri-infusional events had events that were mild or moderate in intensity.

Adverse drug reactions in patients with chronic obstructive pulmonary disease (COPD)

In Study V, there were 37 patients with COPD treated with ORENCIA® and 17 treated with placebo. The COPD patients treated with ORENCIA® developed adverse drug reactions more frequently than those treated with placebo (51.4% vs. 47.1%, respectively). Respiratory disorders occurred more frequently in ORENCIA®-treated patients than in placebo-treated patients (10.8% vs. 5.9%, respectively); these included COPD exacerbation, and dyspnea. A greater percentage of ORENCIA®- than placebo-treated patients with COPD developed a serious adverse reaction (5.4% vs. 0%), including COPD exacerbation (1 of 37 patients [2.7%]) and bronchitis (1 of 37 patients [2.7%]).

Autoantibodies

ORENCIA® therapy did not lead to increased formation of antinuclear or anti-double stranded DNA antibodies compared with placebo.

Immunogenicity

Antibodies directed against the ORENCIA® molecule were assessed by ELISA assays in 3,985 rheumatoid arthritis patients treated for up to 8 years with ORENCIA®. One hundred and eighty-seven of 3,877 patients developed anti-abatacept antibodies while on treatment. In patients assessed for anti-abatacept antibodies after discontinuation of ORENCIA® (>42 days after last dose), 103 of 1,888 (5.5%) were seropositive.

Samples with confirmed binding activity to CTLA-4 were assessed for the presence of neutralizing antibodies. Twenty-two of 48 evaluable patients showed significant neutralizing activity. The potential clinical relevance of neutralizing antibody formation is not known.

Overall, there was no apparent correlation of antibody development to clinical response or adverse events. However, the number of patients that developed antibodies was too limited to make a definitive assessment

Clinical experience in MTX-naive patients

Study VI was an active-controlled clinical trial in MTX-naive patients. Data from Study VI were not integrated into the safety dataset described above in this section; however, the safety experience

in MTX-naive patients was consistent with that described above in patients with an inadequate response to MTX or a TNF blocking agent. The adverse reaction profile observed in patients receiving MTX alone in Study VI was as expected, and the adverse reaction profile observed in patients receiving ORENCIA® plus MTX was similar to that in patients receiving MTX alone.

Table 10 below lists the adverse drug reactions (ADRs - adverse events at least possibly causally related to treatment) occurring in ≥1% of patients treated with ORENCIA + MTX in AGREE (IM101023).

Table 10 Adverse Drug Reactions (ADR's) Occuring in ≥1% of Patients in the ORENCIA®+MTX in AGREE (IM101023)

Related Adverse Event (Preferred Term)	ORENCIA® + MTX n = 256 %	Placebo + MTX n = 253 %
infections and infestations		
bronchitis	3.9	1.2
nasopharyngitis	3.1	2.0
urinary tract infection	2.3	2.8
upper respiratory tract infection	2.3	2.4
oral herpes	2.0	1.2
pharyngitis	2.0	0.4
influenza	1.6	2.8
herpes zoster	1.2	1.2
gastrointestinal disorders		
nausea	4.3	4.3
mouth ulceration	1.6	0.4
diarrhoea	1.2	2.4
nervous system disorders		
headache	3.5	3.6
dizziness	3.5	2.4
investigations		
alanine aminotransferase increased	3.1	2.4
aspartate aminotransferase increased	2.0	1.6
weight increased	1.2	0
respiratory, thoracic and mediastinal disorders		
cough	2.7	1.6
general disorders and administration site conditions		
fatigue	1.2	1.2
vascular disorders		
hypertension	1.2	1.6

Less common Clinical Trial Adverse Drug Reactions (<1.0%)

ADRs reported in less than 1% of patients receiving ORENCIA® + MTX in the AGREE Trial and not listed in **Table 10** are listed below by body system.

Blood and lymphatic system disorders: anaemia
Ear and labyrinth disorders: vertigo
Eye disorders: eye irritation, presbyopia
Gastrointestinal disorders: vomiting, abdominal pain upper, dry mouth, dyspepsia, abdominal pain, gastritis, gastrointestinal haemorrhage, gastrointestinal pain, gingival ulceration, lip dry

General disorders and administration site conditions: malaise, chest pain, asthenia, chest discomfort, axillary pain, chills, feeling hot, infusion related reaction, infusion site erythema, infusion site pain, sudden death
Hepatobiliary disorders: hepatic function abnormal
Immune system disorders: hypersensitivity
Infections and infestations: gastroenteritis, tooth abscess, pneumonia, respiratory tract infection, sinusitis, tonsillitis, viral upper respiratory tract infection, acariasis, furuncle, genital herpes, tinea pedis, acarodermatitis, bacterial infection, bronchopneumonia, cystitis, ear infection, fungal rash, laryngitis, lung infection pseudomonal, rhinitis, sepsis, soft tissue infection, tinea versicolour, vaginal infection
Injury, poisoning and procedural complications: contusion
Investigations: transaminases increased, gamma-glutamyltransferase increased, blood alkaline phosphatase increased, blood pressure increased
Metabolism and nutrition disorders: diabetes mellitus
Musculoskeletal and connective tissue disorders: back pain, joint swelling, ligament disorder, musculoskeletal stiffness, pain in extremity, systemic lupus erythematosus
Neoplasms benign, malignant and unspecified (incl cysts and polyps): lung neoplasm, skin papilloma
Nervous system disorders: dysgeusia, paraesthesia
Psychiatric disorders: depression, insomnia, nervousness
Reproductive system and breast disorders: breast mass, breast pain
Respiratory, thoracic and mediastinal disorders: nasal congestion, pharyngolaryngeal pain, rhinorrhoea, sinus congestion, dyspnoea exertional, nasal discomfort, nasal dryness
Skin and subcutaneous tissue disorders: rash, alopecia, urticaria, acne, eczema, nail dystrophy, pruritus, psoriasis, skin lesion
Vascular disorders: flushing, hyperaemia, hypotension

Clinical experience in Study VII (IM101043)

At 6 months, the overall serious adverse events considered to be related to treatment was 1.9% (3 patients) in the abatacept group, 4.8% (8) in the infliximab group, and 2.7% (3) in the placebo group. The frequency of serious infections was 1.3% (2) in the abatacept group, 2.4% (4) in the infliximab group, and 0.9% (1) in the placebo group. The frequency of acute infusional adverse events was 5.1% (8) in the abatacept group, 18.2% (30) in the infliximab group, and 10.0% (11) in the placebo group. At 12 months, the overall serious adverse events considered to be related to treatment was 3.2% (5) in the abatacept group and 8.5% (14) in the infliximab group. The frequency of serious infections was 1.3% (2) in the abatacept group and 6.1% (10) in the infliximab group, with a total of 5 serious opportunistic infections in the infliximab group and none in the abatacept group. With regard to abnormal laboratory values at 6 months, antinuclear antibodies developed in 1.7% (2) of the abatacept group, 32.2% (38) of the infliximab group, and 4.9% (4) of the placebo group.

Study VIII: Safety of abatacept in patients with or without washout of previous TNF blocking agent therapy

A study of open-label abatacept on a background of nonbiologic DMARDs was conducted in patients with active RA who had an inadequate response to previous (washout for at least 2 months; n=449) or current (no washout period; n=597) TNF-antagonist therapy (Study VIII, Study IM101064). The primary outcome, incidence of adverse events, serious adverse events, and discontinuations due to adverse events during 6 months of treatment, was similar between those who were previous and current TNF-antagonist users at enrollment, as was the frequency of serious infections. Results from Study VIII support the transition from TNF blocking agent therapy to ORENCIA® therapy at the next scheduled dose of the TNF blocking agent therapy.

Postmarketing experience

Adverse reactions have been reported during the post-approval use of ORENCIA®. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to ORENCIA®. Based on the postmarketing experience with ORENCIA® in adult rheumatoid arthritis (RA) patients, the adverse event profile of ORENCIA® does not differ from that listed/discussed above in adults.

Laboratory findings

Based on the results of clinical studies, no special laboratory evaluations are necessary in addition to careful medical management and supervision of patients.

Paediatric and Adolescent

In general, the adverse events in paediatric patients were similar in frequency and type to those seen in adult patients (see PRECAUTIONS AND ADVERSE EFFECTS).

ORENCIA® has been studied in 190 paediatric patients; 6 to 17 years of age, with polyarticular juvenile idiopathic arthritis (see CLINICAL TRIAL EFFICACY INFORMATION). Overall frequency of adverse events in the 4-month, lead-in, open-label period of the study was 70%; infections occurred at a frequency of 36%. The most common infections were upper respiratory tract infection and nasopharyngitis. The infections resolved without sequelae, and the types of infections were consistent with those commonly seen in outpatient paediatric populations. Other events that occurred at a prevalence of at least 5% were headache, nausea, diarrhea, cough, pyrexia, and abdominal pain.

A total of 6 serious adverse events (acute lymphocytic leukemia, ovarian cyst, varicella infection, disease flare [2], and joint wear) were reported during the initial 4 months of treatment with ORENCIA®

For the 122 patients who responded in the lead-in period and entered the placebo-controlled, 6-month, withdrawal phase, there were no serious adverse events in 60 ORENCIA®-treated patients and 3 serious adverse events in 2 of the 62 placebo-treated patients (hematoma in one patient, varicella and encephalitis in the other).

Of the 190 patients with JIA treated with ORENCIA® in this study, one (0.5%) patient discontinued due to non-consecutive infusion reactions, consisting of bronchospasm and urticaria. During Periods A, B, and C, acute infusion-related reactions occurred at a frequency of 4%, 2%, and 3%, respectively, and were consistent with the types of events reported in adults.

Upon continued treatment in the open-label extension period, 27.5% (42/153) of patients discontinued treatment, and the types of adverse events were similar in frequency and type to those seen in adult patients, except for a single 14 year old patient diagnosed with temporal lobe epilepsy secondary to multiple sclerosis while on open-label treatment. The subject was reported to have a probable seizure four days after the 12th infusion of abatacept. The subject had no known personal or family history of multiple sclerosis prior to study entry. This has been the only case of MS in the JIA study with abatacept and there is no evidence to date that there is a increased risk of MS or other demyelinating events due to abatacept treatment.

Adverse events regardless of causality occurring in ≥5% of pediatric patients receiving ORENCIA® in period B (double-blind phase) of the three part study conducted in paediatric and adolescent patients with polyarticular JIA are listed below by system organ classification. All adverse events listed below fall into the frequency category of common (≥1% <10%), as defined above for adult RA.

Table 11: Adverse Events in Placebo-Controlled Trials (regardless of causality) at ≥ 5% for Period B(double-blind phase)		
System Organ Classification / Preferred Term	**ORENCIA®** n (%)	**Placebo**[a] n (%)
Number treated	60 (100)	62 (100)
Infections and infestations		
Influenza	5 (8.3)	4 (6.5)
Bacteriuria	4 (6.7)	0
Nasopharyngitis	4 (6.7)	3 (4.8)
Upper respiratory tract infection	4 (6.7)	5 (8.1)
Gastroenteritis	3 (5.0)	1 (1.6)
Sinusitis	3 (5.0)	2 (3.2)
Gastrointestinal disorders		
Abdominal pain	3 (5.0)	1 (1.6)
General disorders and administration site conditions		
Pyrexia	4 (6.7)	5 (8.1)
Nervous system disorders		
Headache	3 (5.0)	1 (1.6)

[a] Preceding the double-blind phase of the study (Period B), all patients were treated with ORENCIA® for 4 months in the open-label, lead-in phase (Period A). At the conclusion of Period A, patients who exhibited a predefined clinical response were randomized into one of 2 arms (in Period B), and either continued on ORENCIA® or withdrew from ORENCIA® to receive placebo. See CLINICAL TRIAL EFFICACY INFORMATION: Paediatric and Adolescent (Juvenile Idiopathic Arthritis).

Clinical Trial Adverse Drug Reactions (< 5%)

ADR's reported in less than 5% for Period B (double-blind) for patients receiving ORENCIA® in the paediatric clinical trials are listed below by body system. Each ADR was a single ADR case yielding an incidence of 1.7%, no ADR with a frequency of less than 1% was reported.

Infections and Infestations: Sinusitis, influenza, rhinitis, tinea versicolour, upper respiratory tract infection, bacteriuria, otitis externa

Gastroinintestinal disorders: Abdominal pain, nausea, aphthous stomatitis

Skin and subcutaneous tissue disorders: Pityriasis, skin lesion

Nervous system disorders: headache

Renal and urinary disorders: Leukocyturia

Vascular disorders: Hypotension

Infections

Adverse events of infections were reported in 36% of patients in the 4-month, lead-in, open-label period. The most common infections were upper respiratory tract infections [14 (7.4%)] and nasopharyngitis [11 (5.8%)]. Other than upper respiratory tract infections and nasopharyngitis, few infectious adverse events were reported. No pneumonias or opportunistic infections were observed.

During the double-blind phase, adverse events of infections were reported in the abatacept and placebo groups [45% and 44%]; influenza 5 [8.3%] vs 4 [6.5%], bacteriuria 4 [6.7%] vs 0 [0%],

nasopharyngitis 4 [6.7%] vs 3 [4.8%], and upper respiratory tract infections 4 [6.7%] vs 5 [8.1%], were the most frequently reported events.

Infusion-related Reactions
In the open-label lead-in phase of the study, eight (4.2%) patients experienced acute infusional adverse events; all but one was mild in intensity and none was serious. Most infusional adverse events were reported as single events in one patient each with no recurrences; headache and dizziness occurred in four and two patients, respectively. During the double-blind phase, acute infusional adverse events were reported in 1.7% and 3.2% of the abatacept and placebo groups, respectively; all were either mild or moderate in intensity and none were serious.

Autoantibodies
In Period A of the paediatric clinical trial, 10.6% of ORENCIA® treated patients that had negative antinuclear antibody titers at baseline had positive titers at Day 113. In Period B, 5.9% of ORENCIA® treated patients and 4.0% of placebo patients that had negative antinuclear antibody titers at baseline had positive titers at Day 169.

In Period A, newly detected anti-dsDNA antibodies were observed in 6.2% of ORENCIA® treated patients at Day 113. In Period B, newly detected anti-dsDNA antibodies were observed in 2.3% of ORENCIA® treated patients and 0% of placebo patients at Day 169.

Immunogenicity

Antibodies directed against the entire abatacept molecule or to the CTLA-4 portion of abatacept were assessed by ELISA assays in patients with polyarticular JIA following repeated treatment with ORENCIA®. The rate of seropositivity while patients were receiving abatacept therapy was 0.5% (1/189) during Period A; 13.0% (7/54) during Period B; and 11.4% (17/149) during Period C. For patients in Period B who were randomized to placebo (therefore withdrawn from therapy for up to 6 months) the rate of seropositivity was 40.7% (22/54). Anti-abatacept antibodies were generally transient and of low titer. The absence of concomitant methotrexate (MTX) did not appear to be associated with a higher rate of seropositivity in Period B placebo recipients. The presence of antibodies was not associated with adverse events or infusional reactions, or with changes in efficacy or serum abatacept concentrations. Of the 54 patients withdrawn from ORENCIA® during the double-blind period for up to 6 months, none had an infusion reaction upon re-initiation of ORENCIA®.

Malignancies

A single case of acute lymphocytic leukaemia was reported in the paediatric trial. No other malignancies were reported

DOSAGE AND ADMINISTRATION

For adult patients with RA, ORENCIA® should be administered as a 30-minute intravenous infusion utilizing the weight range-based dosing specified in Table 12 Following the initial administration, ORENCIA® should be given at 2 and 4 weeks after the first infusion, then every 4 weeks thereafter. Methotrexate, other non-biologic DMARDs, corticosteroids, salicylates, nonsteroidal anti-inflammatory drugs (NSAIDs), or analgesics may be used during treatment with ORENCIA®.

Table 12: Dose of ORENCIA® [a] in Adult RA

Body Weight of Patient	Dose	Number of Vials[a]
< 60 kg	500 mg	2
60 to 100 kg	750 mg	3
> 100 kg	1 gram	4

[a] Each vial provides 250 mg of abatacept for administration.

For paediatric juvenile idiopathic arthritis, a dose calculated based on each patient's body weight is used (see Paediatric and adolescent).

Hypersensitivity Reactions

Hypersensitivity reactions are uncommon with the infusion of ORENCIA®, however these may occur. To minimize the incidence of hypersensitivity reactions, the patient should be monitored closely before and after ORENCIA® administration. Should any such reaction occur, then appropriate responses and treatments are to be initiated. The necessary equipment, treatments and procedures sufficient to initiate management of acute infusion reactions (anaphylaxis) should be in place.

The risk of hypersensitivity reactions including anaphylaxis and how they are managed should be discussed with the patient by the prescriber prior to the patient receiving ORENCIA®, so that the patient is aware of such risks and has an understanding of these risks.

Renal impairment, hepatic impairment

ORENCIA® has not been studied in theses patient populations. No dose recommendations can be made.

Paediatric and adolescent

Juvenile Idiopathic Arthritis. The recommended dose of ORENCIA® for patients 6 to 17 years of age with juvenile idiopathic arthritis who weigh less than 75 kg is 10 mg/kg calculated based on the patient's body weight at each administration. Paediatric patients weighing 75 kg or more should be administered ORENCIA® following the adult dosing regimen, not to exceed a maximum dose of 1000 mg. ORENCIA® should be administered as a 30-minute intravenous infusion. Following the initial administration, ORENCIA® should be given at 2 and 4 weeks after the first infusion and every 4 weeks thereafter. Any unused portions in the vials must be immediately discarded.

Use in the elderly

No dose adjustment is required (see PRECAUTIONS).

Concomitant therapy

Methotrexate, other non-biologic DMARDs, corticosteroids, salicylates, nonsteroidal anti-inflammatory drugs (NSAIDs), or analgesics may be used during treatment with ORENCIA®.

PREPARATION AND ADMINISTRATION INSTRUCTIONS

Use aseptic technique.

ORENCIA® is provided as a lyophilized powder in preservative-free, single-use vials. Each vial of ORENCIA® must be reconstituted with 10 mL of sterile water for injection, BP. Immediately after reconstitution, the product must be further diluted to 100 mL with 0.9% sodium chloride injection, BP. To reduce microbiological hazard, use as soon as practicable after dilution. If storage is necessary hold at 2 – 8 ºC for not more than 24 hours.

1) Each ORENCIA® vial provides 250 mg of abatacept for administration.
2) Reconstitute the ORENCIA® powder in each vial with 10 ml of sterile water for injection BP, **USING ONLY the SILICONE-FREE DISPOSABLE SYRINGE PROVIDED WITH EACH VIAL** and an 18-21-gauge needle. Remove the flip-top from the vial and wipe the top with an alcohol swab. Insert the syringe needle into the vial through the center of the rubber stopper and direct the stream of sterile water for injection BP, to the glass wall of the vial. Do not use the vial if the vacuum is not present. To minimize foam formation in solutions of ORENCIA®, the vial should be rotated with gentle swirling until the contents are completely dissolved. Avoid prolonged or vigorous agitation. Do not shake. Upon complete dissolution of the lyophilized powder, the vial should be vented with a needle to dissipate any foam that may be present. The solution should be clear and colorless to pale yellow. Do not use if opaque particles, discoloration, or other foreign particles are present. After reconstitution, the concentration of abatacept in the vial will be 25mg/mL
3) The reconstituted ORENCIA® solution must be further diluted to 100 ml as follows. From a 100 ml infusion bag or bottle, withdraw a volume of 0.9% sodium chloride injection BP, equal to the volume of the reconstituted ORENCIA. Slowly add the reconstituted ORENCIA® solution from each vial to the infusion bag or bottle, **USING ONLY the SILICONE-FREE DISPOSABLE SYRINGE PROVIDED WITH EACH VIAL**. Gently mix. **DO NOT SHAKE THE BAG OR BOTTLE**. The final concentration of abatacept in the bag or bottle will depend upon the amount of drug added, but will be no more than 10mg/mL.Any unused portion in the vials must be immediately discarded.
4) Prior to administration, the ORENCIA® solution should be inspected visually for particulate matter and discolouration. Discard the solution if any particulate matter or discolouration is observed.
5) The entire, fully diluted ORENCIA® solution should be administered over a period of 30 minutes and must be administered with an infusion set and a sterile, non-pyrogenic, low-protein-binding filter (pore size of 0.2 to 1.2 μm).
6) ORENCIA® should not be infused concomitantly in the same intravenous line with other agents. No physical or biochemical compatibility studies have been conducted to evaluate the co-administration of ORENCIA® with other agents.
7) EACH VIAL OF ORENCIA® IS FOR SINGLE USE IN ONE PATIENT ONLY. DISCARD ANY RESIDUE.

If the **SILICONE-FREE DISPOSABLE SYRINGE** is dropped or becomes contaminated, use a new **SILICONE-FREE DISPOSABLE SYRINGE** from inventory. For information on obtaining additional **SILICONE-FREE DISPOSABLE SYRINGES**, contact Bristol-Myers Squibb Australia 1800-RENCIA or contact Bristol-Myers Squibb Australia 1800-067567.

OVERDOSE

ORENCIA® is administered as an intravenous infusion under medically controlled conditions. Doses up to 50 mg/kg have been administered without apparent toxic effect. In case of overdosage,

it is recommended that the patient be monitored for any signs or symptoms of adverse reactions and appropriate symptomatic treatment instituted.

In the event of an overdose or poisoning contact the Poisons Information Centre on 131126.

PRESENTATION

ORENCIA® is a lyophilized powder for intravenous infusion; it is supplied as an individually packaged, single-use vial with a silicone-free disposable syringe. All components of the syringe are latex-free. The product is available in the strength of 250 mg of abatacept in a 15-mL vial.

Storage and Stability conditions:

ORENCIA® lyophilized powder must be refrigerated at 2°C to 8°C. For storage of the fully diluted ORENCIA® solution, (see **PREPARATION AND ADMINISTRATION**)

Do not use beyond the expiration date.

Protect the vials from light by storing in the original package until time of use.

Poisons Schedule: S4

DISTRIBUTED BY:

Bristol-Myers Squibb Australia Pty Ltd
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NOBLE PARK VIC 3174

AUSTRALIAN REGISTRATION NUMBERS:

ORENCIA® is a lyophilized powder for intravenous infusion:	AUST R 130100
SYRINGE:	AUST R 12743

DATE OF TGA APPROVAL: 23rd March 2011

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Reference/Publication #