Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Abatacept

Proprietary Product Name: Orencia

Sponsor: Bristol-Myers Squibb Australia Pty Ltd

April 2012

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (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.
- To report a problem with a medicine or medical device, please see the information on the TGA website.

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.

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I. Introduction to Product Submission

Submission Details

Type of Submission	Major variation (new dosage form, new route of administration)
Decision:	Approved
Date of Decision:	23 December 2011
Active ingredient(s):	Abatacept (rch)
Product Name(s):	Orencia®
Sponsor's Name and Address:	Bristol-Myers Squibb Australia Pty Ltd PO Box 39 Noble Park North VIC 3174
Dose form(s):	Solution for injection
Strength(s):	125 mg/1 mL
Container(s):	1 mL pre-filled syringe
Pack size(s):	4 syringes
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 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). (There is no clinical trial data for the use of Orencia subcutaneous formulation in children, therefore its use in children cannot be recommended.) Orencia should not be administered concurrently with other biological DMARDs (for example, TNF inhibitors, rituximab, or anakinra).
Route(s) of administration:	Subcutaneous injection
Dosage:	Administered weekly at a dose of 125 mg regardless of weight
ARTG Number (s)	177174 (single dose syringe subcutaneous injection needle guard), 177176 (syringe flange extender)

Product Background

This AusPAR describes the application to register a new subcutaneous (SC) formulation of abatacept (Orencia) in a pre filled syringe (two types: one with a needle guard and one with a flange extender) for use in combination with methotrexate in adults with rheumatoid arthritis (the same adult indication as currently approved for the intravenous (IV) formulation).

Orencia (abatacept (rch), CTLA4Ig) is the first drug in a new class of agents, "co stimulation modulators". It is a selective co stimulation modulator and is a soluble fusion protein consisting of the extracellular domain of human cytotoxic T lymphocyte associated antigen 4 (CTLA-4) linked to the modified Fc (hinge, CH2 & CH3 domains) portion of human IgG1. Abatacept reversibly binds to CD 80/86 on antigen presenting cells via its CTLA-4 portion preventing the interaction of CD 80/86 with CD28 on T cells and thus inhibiting full T cell activation. Activated T lymphocytes are involved in the pathogenesis of rheumatoid arthritis (RA). In combination with methotrexate (MTX), IV abatacept has been shown to reduce signs and symptoms of RA, improve physical function and reduce progression of joint damage.

The registered product is an IV formulation given as an infusion. The proposal is to register a ready to use (RTU) subcutaneous formulation to allow self administration of the product by patients with rheumatoid arthritis (RA) thereby providing greater convenience and patient acceptance. The sponsor stated that the fixed dose regimen for the SC formulation was chosen to reduce dosing errors improve prescribing efficiency.

There are two commercial presentations of the SC formulation (both with 125 mg per syringe): abatacept injection prefilled syringe with Ultrasafe Passive Needle Guard and abatacept injection prefilled syringe with flange extender.

The SC formulation contains the same active pharmaceutical ingredient (API) as the IV formulation. However, as the dosing intervals and route of administration are different, the development programs aimed to show comparability via a large non inferiority study and use this data to then bridge to the data with the IV formulation. Safety and immunogenicity studies were also carried out with the SC formulation in specific situations such as withdrawal and restart of treatment and switching from IV to SC formulations.

Regulatory Status

Orencia has been registered in Australia since 27 September 2007 and has been reviewed by the Advisory Committee on Prescription Medicines (ACPM) at the Committee's 267th meeting in December 2009 when it was recommended for approval for use in children six years of age and older with juvenile idiopathic arthritis (JIA) and at the Committee's 274th meeting in February 2011 when the following extension of indications was recommended: "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".

The Current International Registration Status for Orencia is shown in Table 1.

Table 1: Current international registration status for ORENCIA® (abatacept) (Subcutaneous Dose Form Presentation).

Country	Submitted Date	Approval
US	4 October 2010	29 July 2011
Switzerland	11 November 2010	27 February 2012
Canada	13 October 2010	Currently under evaluation
EU	27 July 2011	Currently under evaluation

There have not been any withdrawals, deferrals, or rejections for Orencia (abatacept) Subcutaneous Dose Form Presentation.

Product Information

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

II. Quality Findings

Drug Substance (active ingredient)

The proposed SC formulation contains the same API (abatacept) as that of the currently marketed Orencia IV formulation (registered in September 2007). No data regarding drug substance has been submitted in the current application.

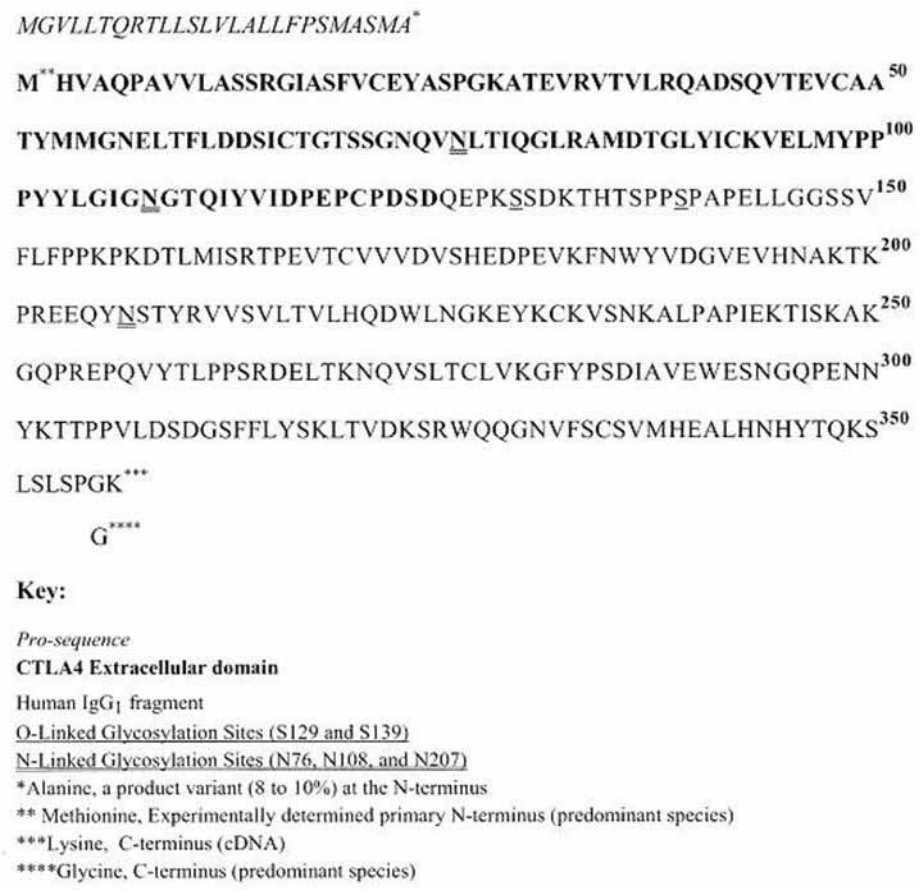
The drug substance is a clear, colourless to pale yellow and essentially particle free solution. It consists of 50 mg/mL abatacept in 25 mM sodium phosphate buffer containing 50 mM sodium chloride at pH 7.5.

Drug substance manufacturing comprises of fermentation and downstream purification.

A shelf life of 18 months at -40^{o}C and 150 days at 5^{o}C, protected from light, has been established.

Structure of the abatacept drug substance is shown in Figure 1.

Figure 1: Structure of the abatacept drug substance.



Drug Product

Formulation

Abatacept SC injection, 125 mg/syringe, is a single dose, ready to use, clear to slightly opalescent, colourless to pale yellow and essentially particulate matter free solution. It is packaged in a disposable 1mL long glass syringe barrel with fill line markings and stoppered with a Flurotec® coated 7.1mm rubber stopper. There are two commercial presentations available:

- Abatacept injection prefilled syringe with UltraSafe Passive Needle Guard (SSI Needle Guard): This presentation consists of three components, the abatacept injection prefilled syringe, plunger rod and needle guard subassembly.
- Abatacept injection prefilled syringe with flange extender: This presentation consists of three components, the abatacept injection prefilled syringe, plunger rod and flange extender.

The drug product contains apart from abatacept, sucrose, Poloxamer 188, Water for Injection and nitrogen in phosphate buffer, pH 7.2.

Manufacture

The product is sterilised by filtration through two 0.22 μm filters.

The manufacturing process involves concentration and buffer exchange of the abatacept drug substance by tangential flow filtration, formulation, sterile filtration and aseptic filling into syringes.

Specifications

Validation data were submitted in support of the test procedures controlling the specifications, including identity, potency, purity, dose delivery and other physical, chemical and microbiological properties relevant to the clinical use of the product.

Validation data have been submitted in support of the test procedures.

Stability

Stability data have been generated under real time/accelerated/stress conditions to characterise the stability profile of the product. Photo-stability data show that the drug product is light sensitive and should be kept in the primary packaging.

The submitted real time stability data support the proposed shelf life of 24 months when stored at 2°C to 8°C (protected from freezing).

Quality Summary and Conclusions

The administrative, product usage, chemical, pharmaceutical and microbiological data submitted in support of this application have been evaluated in accordance with the Australian legislation, pharmacopoeial standards and relevant technical guidelines adopted by the TGA.

There are no Quality issues outstanding.

It is a condition of registration that the first five independent batches of

Orencia® (abatacept) (rch) 125 mg/syringe, Solution for subcuteneous injection

imported into Australia are not released for sale until samples and/or the manufacturer's release data have been assessed and endorsed for release by the TGA Office of Laboratories and Scientific Services (OLSS).

The sponsor should supply:

1. Certificates of Analysis of all active ingredient (drug substance) and final product.
2. Information on the number of doses to be released in Australia with accompanying expiry dates for the product and diluents (if included).
3. Evidence of the maintenance of registered storage conditions during transport to Australia.
4. Three syringes of each batch for testing by the TGA OLSS together with any necessary standards, impurities and active pharmaceutical ingredients (with their Certificates of Analysis) required for method development and validation.

These batch release conditions will be reviewed and may be modified on the basis of actual batch quality and consistency. The conditions remain in place until the sponsor is notified in writing of any variation.

III. Nonclinical Findings

Introduction

The submission consisted of local tolerance studies to support the new route of administration and to assess the effects in the event of accidental exposure via other administration routes. A recently completed immunotoxicity study was provided in response to a TGA request. Toxicity studies conducted using the SC route of administration were included in the original submission to support the registration of abatacept. Overall,

the data are appropriate to support the new route of administration. The excipients in the SC formulation are used in other injectable products.

Toxicology

Previously submitted toxicity studies in mice and monkeys revealed no drug related toxicities, aside from those related to the pharmacology of the drug (for example, decreased serum IgG levels and decreased spleen and lymph node germinal centre activity). Exposures at the highest tested doses in mice and monkeys were 5 and 8 times the clinical area under the plasma concentration versus time curve (AUC) from the recommended IV dose. The exposure margins in the animal studies are 1.8 fold higher when based on the AUC from the clinical SC dose ($AUC_{0\text{-}28\ days}$ 23502 mg·h/mL from the SC dose compared to 41982 mg·h/mL from the IV dose[1]), thereby lessening any toxicity concerns.

In contrast to mice and monkeys, unique target organ toxicities were evident in rats. Following up to three months exposure to abatacept in rats (both adult and juvenile), lymphocytic inflammation of the thyroid and pancreatic islets were evident. These findings are indicative of an autoimmune response. The sponsor submitted an investigative study to elucidate whether these inflammatory findings were associated with anti abatacept antibody production. At doses below those required to elicit an overt pharmacological effect, but high enough for anti abatacept antibody production in adult rats, there were no significant histopathological findings in the pancreas or the thyroid gland. This study suggests that the inflammatory reactions observed at the higher doses are likely to be associated with the pharmacological action of abatacept. The clinical relevance of the autoimmune reaction in rats is uncertain. As there were no such findings in mice or monkeys, and, according to the sponsor, none have been identified during clinical use, the findings may indicate that rats are more sensitive to the effects of abatacept. However, the newly submitted study suggests that the autoimmune reactions may be associated with pharmacological activity and, therefore, similar reactions in the target patient population cannot be completely discounted. Until further studies have been undertaken to elucidate the mechanism of autoimmune reactions in rats, caution during clinical use is still warranted. It is noted that "autoimmunity" has been appropriately identified in the Nonclinical Safety Specification of the Risk Management Plan.

Local Tolerance

After SC injection of the proposed clinical formulation, there were no findings at the injection site that could be attributed to the test article. A foreign body granuloma was noted in 1/16 treated injection sites but this was considered to be related to the injection procedure. There were no drug-related injection site changes after IV, intra arterial (IA), paravenous or intramuscular (IM) administration of the clinical (SC) formulation to rabbits.

Nonclinical Summary and Conclusions

- Local tolerance studies and a mechanistic study in rats identified no major deficiencies.
- In rats, injection site reactions after SC administration of the clinical formulation were unremarkable. No drug related findings were evident after IV, IM, IA or paravenous injection to rabbits.

[1] The $AUC_{0\text{-}28days}$ for the SC dose was calculated as $4 \times AUC_{0\text{-}7\ days}$ obtained from rheumatoid arthritis patients (5875.5 mg·h/mL); data from Clinical Study IM101174.

- As the anticipated systemic exposure of abatacept with the maximum clinical dose of the SC formulation would be approximately half the exposure with the maximum IV dose, there are no additional toxicological concerns with the proposed SC dosage regimen.
- A mechanistic study in rats indicated that the unique abatacept associated autoimmune reactions seen in this species were not associated with anti abatacept antibody production. The clinical relevance of these reactions remains unknown.
- There are no nonclinical objections to the proposed registration of Orencia® (abatacept [rch]) solution for subcutaneous injection.
- Amendments to the nonclinical sections of the draft Product Information were recommended.

IV. Clinical Findings

Introduction

The sponsor's submission documented a development program of pharmacokinetics, immunogenicity, efficacy and safety for the proposed SC formulation. The pivotal efficacy study (IM101174) was a non inferiority design with the intention of then bridging to data relating to the registered IV formulation.

After the submission of data for this application, the sponsor noted that in the pivotal efficacy study (IM101174) there was a randomisation analysis error relating to weight subgroups as well as non compliance with Good Clinical Practice (GCP) regulations at one site. The data from this non compliant site was excluded, analyses with body weight groupings were redone, and the Clinical Evaluation Report was revised.

The submission contained the following clinical information:

- One pivotal Phase III efficacy/safety study (IM101174) which was a non inferiority study that compared SC and IV abatacept in subjects with RA and an inadequate response to methotrexate.
- Two clinical pharmacology studies that provided pharmacokinetic and immunogenicity data in healthy subjects (IM101013) and in an RA patient population (IM101063).
- Three supportive Phase III immunogenicity and safety studies in adults with active RA: IM101173 assessed abatacept with or without MTX and without an IV loading dose; IM101167 assessed withdrawal and reintroduction of abatacept; and IM101185 assessed the switch from long term (LT) IV to SC use.
- One follow up immunogenicity study (IM101128) of subjects from IM101013.
- Two LT, open label extension studies IM101063LT and IM101173LT.
- A pooled analysis of immunogenicity.
- Reports of bioanalytical and analytical methods for the human studies.

The current submission did not include paediatric data and at submission date there had been no paediatric investigations with the SC formulation of abatacept. The sponsor states that in Europe it has initiated a Paediatric Investigation Plan in June 2010 and that there are plans to meet with the US Food and Drug Administration (FDA) to discuss paediatric development.

The sponsor stated with each report that the clinical studies were conducted in accordance with Good Clinical Practice (GCP) guidelines and appropriate ethical and regulatory approval. Monitoring of GCP compliance led to the detection of non compliance in Study IM101174 at one site that was excluded from analyses.

Pharmacokinetics

Healthy subjects

Absorption

Not applicable.

Bioavailability

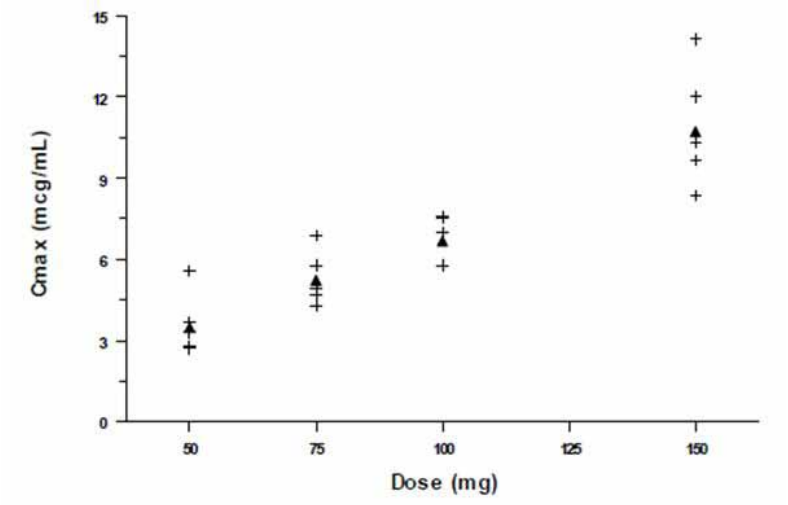
Absolute bioavailability

The absolute bioavailability of SC abatacept relative to IV abatacept was 78.6%.

Dose proportionality

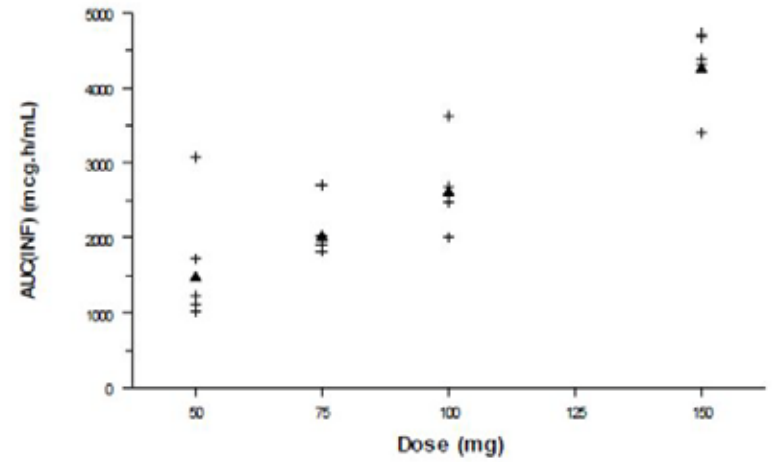
A double blind, randomised (within dose), placebo controlled, parallel group, single dose study (Clinical Study Report (CSR) IM101013) examined the pharmacokinetics (PK) of subcutaneous (SC) doses of abatacept (50, 75, 100 or 150 mg) in 48 healthy subjects (8 female), aged 23 to 56 years weighing ≤100 kg. Subjects were randomised to 1 of 8 treatment groups, which contained six subjects each. The geometric means of the maximum plasma drug concentration (C_{max}) and the area under the plasma concentration time curve from time zero to infinity (AUC_{inf}) of abatacept appeared to increase in a dose proportional manner following administration of a single subcutaneous dose of abatacept in the range of 50 to 150 mg (Figures 2-3). Median values for the time to reach maximum plasma concentration following drug administration (T_{max}) ranged from 3 to 7 days following SC administration of abatacept and were not affected by dose (Table 2). Differences in injection volume, osmolality of drug solution, and the concentration of the drug solutions had no impact on the PK of abatacept.

Figure 2: Scatter plot of individual C_{max} values versus dose of abatacept (CSR IM101013).



Source: Appendix 8.3.1 and Supplemental Table S.8.3.
▲ = Geometric mean (n = 5 subjects/dose group)

Figure 3: Scatter plot of individual AUC_{inf} values versus dose of abatacept (CSR IM101013).



Source: Appendix 8.3.1 and Supplemental S.8.3
▲ = Geometric mean (n = 5 subjects/dose group)

Table 2: Summary statistics for the pharmacokinetic parameters of abatacept by treatment (CSR IM101013).

Treatment Group	TRT A	TRT B	TRT C	TRT D	TRT E	TRT F	TRT G	TRT H
Dose (mg)	50	75	100	150	50	75	50	75
Formulation	SC	SC	SC	SC	SC	SC	IV	IV
Injection Volume (mL)	1	1	1	1.5	0.5	0.75	1	1
Osmolality (mOsm/kg)	386	386	386	386	386	386	900	900
PK Parameter								
Cmax (µg/mL)								
Geo. Mean	3.5	5.2	6.7	10.7	3.1	5.4	3.3	5.9
CV (%)	32	19	13	21	34	28	31	36
N	5	5	5	5	5	5	5	5
Tmax (hours)								
Median	96	48	96	96	96	96	168	96
(min, max)	(48, 168)	(48, 168)	(72, 168)	(48, 168)	(72, 168)	(48, 96)	(168, 168)	(48, 168)
N	5	5	5	5	5	5	5	5
AUC(INF) (µg/mL)								
Geo. Mean	1489.7	2030.2	2624.8	4270.3	1346.2	2019.4	1658.1	2714.6
CV (%)	52	18	22	12	34	20	33	40
N	5	5	5	5	5	5	5	5
T-HALF (Days)								
Mean	11.3	12.7	14.7	11.2	11.3	11.7	12.7	13.9
SD	3.3	1.1	2.0	1.6	1.1	2.5	1.9	3.7
N	3	4	3	4	4	4	4	3

Metabolism

Sites of metabolism and mechanisms / enzyme systems involved

Evaluation of the individual subject concentration versus time profiles from CSR IM101013 indicated that two of five subjects in Treatments A, C, and H, as well as one of five subjects in Treatments B, D, E, F, and G displayed increased abatacept clearance from the vascular system, which appeared to be correlated with the presence of abatacept specific antibodies as concentrations of abatacept reached below immunosuppressive levels. The elimination half life ($t_{1/2}$) of abatacept in subjects who did not exhibit a positive immune response ranged from 11.2 to 14.7 days and was independent of increasing dose; whereas, in subjects who were seropositive, $t_{1/2}$ values ranged from 3.2 to 7.5 days.

Pharmacokinetics in the target population

A double blind, randomised, placebo controlled, parallel group, multiple dose study (CSR IM101063) assessed the steady state trough serum concentrations of abatacept following

SC administration in 68 subjects (57 female), aged 40 to 81 years with RA. Subjects must have had active RA and been on MTX or on MTX plus no more than one additional oral disease modifying anti rheumatic drug (DMARD) for at least 3 months, and been on a stable dose for at least 28 days prior to Day 1. Subjects receiving oral corticosteroids should have been on a stable dose (maximum of 10 mg prednisone equivalent daily) for at least 25 of the 28 days prior to Day 1. Subjects continued on their background oral DMARD therapy at the same dose they received at the time of enrolment. Subjects were randomised in a 3:1 ratio, to receive either abatacept or placebo in one of five parallel groups based on body weight obtained at the screening visit.

Steady state trough serum concentrations of abatacept were achieved approximately 4 to 5 weeks following the combined regimen of a single IV loading dose and weekly SC injections (Figure 4). With the exception of Treatment group 4 (125 mg SC weekly dose to subjects weighing > 100 kg), the mean steady state trough concentrations across all other treatment groups were similar. Minimum plasma drug concentration (C_{min}) values on Days 71-85 were selected (when contribution from the IV dose was expected to be minimal), to estimate the steady state serum levels from SC administration without the contribution of the IV loading dose. The geometric mean steady state trough value for Treatment group 4 (abatacept 125 mg SC weekly dose to subjects weighing > 100 kg) was lower than for Treatment groups 1, 2, 3 and 5. However, the distribution of steady state trough concentrations from Treatment group 4 was within the range of trough concentrations achieved in Treatment group 3. The $AUC_{7\ days}$ of Treatment group 2 was higher, whereas the area under the plasma concentration time curve from time zero to 7 days ($AUC_{7\ days}$) of Treatment group 4 was lower compared to the other treatment groups (Table 3). The geometric mean for C_{max} in Treatment group 4 was also lower compared to the other treatment groups.

Figure 4: Steady state trough serum abatacept concentration following treatment (CSR IM101063).

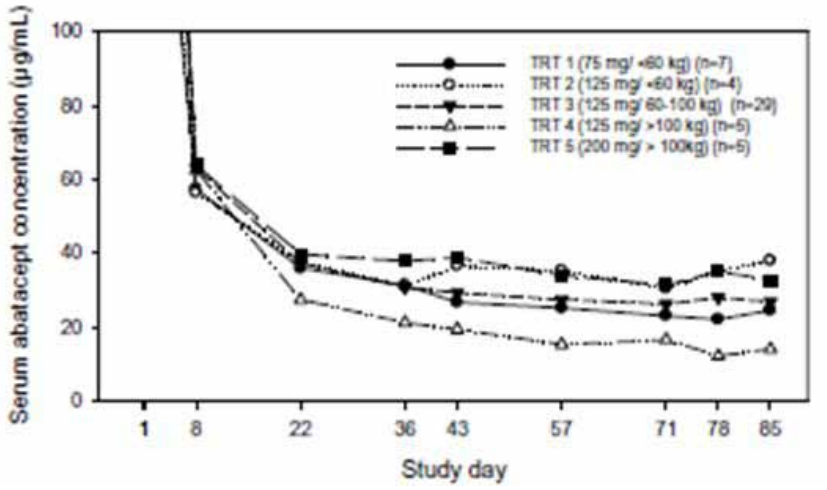


Table 3: Summary statistics for abatacept steady state pharmacokinetic parameters (CSR IM101063).

Treatment Group	Pharmacokinetic Parameter Statistic	
	Cmax (µg/mL) Geometric Mean (CV%)	AUC(TAU) (µg*h/mL) Geometric Mean (CV%)
1 (500mg IV / 75mg SC)	n = 7 26.3 (29.5)	n = 7 4066 (22.2)
2 (500mg IV / 125mg SC)	n = 4 34.9 (46.6)	n = 3 6699 (20.7)
3 (750mg IV / 125mg SC)	n = 26 31.9 (42.8)	n = 24 4607 (38.6)
4 (1000mg IV / 125mg SC)	n = 5 14.7 (44.3)	n = 4 2555 (30.1)
5 (1000mg IV / 200mg SC)	n = 5 41.7 (41.2)	n = 5 5849 (40.5)

Source: Supplemental Table S.8.2.3
n = number of subjects, TAU = 7 days
Cmax and AUC(TAU) were calculated between a SC dosing interval from Day 71 to Day 78 profile.

Pharmacokinetics in other special populations

Not applicable

Pharmacokinetic interactions

Not applicable

Pharmacodynamics

Mechanism of action

Abatacept is a co stimulation modulator of the interaction of CD80 and CD86 on antigen presenting cells with CD28 on T lymphocytes and 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 DMARDs such as MTX or tumour necrosis factor (TNF) blocking agents.

In the reviewed PD studies, disease activity was assessed using the Disease Activity Score 28 (DAS28) questionnaire.[2] Improvement in physical function was measured by the Health Assessment Questionnaire Disability Index (HAQ-DI).[3] The ability of abatacept to provoke an immune response (immunogenicity) was measured using two validated enzyme linked immunosorbent assay (ELISA) methods, that is, an anti abatacept assay, which measured the antibody response to the whole molecule (that is, both the CTLA4 and immunoglobulin portion) and an anti CTLA4-T assay, which measured the antibody response to only the CTLA4 portion. In addition, rheumatoid factor (RF) levels were measured in CSR IM101063.

[2] Disease Activity Score 28 (CRP) is a composite of four variables: the 28 tender joint count (14 joints on each side of the body) and the 28 swollen joint count (14 joints on each side of the body), CRP, and the subject assessment of disease activity measure on a VAS.

[3] A questionnaire that includes 20 questions assessing physical function in 8 domains: dressing, arising, eating, walking, hygiene, reach, grip, and common activities. The questions are evaluated on a 4-point scale: 0 = without any difficulty, 1 = with some difficulty, 2 = with much difficulty and 3 = unable to do. Higher scores indicate greater dysfunction. The HAQ-DI score was calculated by summing the worst scores in each domain and dividing by the number of domains answered. The use of aids and devices to help with function was adjusted in the scoring.

Pharmacodynamic effects

Primary pharmacodynamic effects

In healthy subjects

CSR IM101013 examined the immunogenicity following a SC injection of the SC formulation and the current IV formulation of abatacept in 48 healthy subjects. Eleven of the 40 subjects (27.5%) developed antibodies to the CTLA4 binding portion of the abatacept molecule: 8 of the 30 subjects (26.7%) who received the SC formulation (osmolality 386 mOsm/kg) and 3 of the 10 subjects (30%) who received the IV formation (osmolality 900 mOsm/kg) given SC. The earliest identified onset of seroconversion was on Day 43 in the group given 50 mg of the IV formulation SC. The endpoint titres in healthy subjects who received the SC formulation ranged from 33 to 106 and from 62 to 872 in subjects who received the IV formulation given SC. No dose dependent increases in immunogenicity were observed. Only one subject had a serum sample that possessed neutralisation activity. Immunogenicity was not associated with adverse safety outcomes; that is, the safety profile of abatacept in subjects with and without immune response was comparable.

CSR IM101128 was conducted to determine the development and/or persistence of immunogenicity in the 48 healthy subjects following the administration of a subcutaneous abatacept dose approximately 3 years previously in CSR IM101013. At least two attempts were made to have the subjects return for this study and 31 subjects (6 female), aged 26 to 82 years participated. Six of the 11 subjects who demonstrated CTLA4 T specific antibody reactivity in CSR IM101013 participated in the current study. A 10 mL blood sample was collected for immunogenicity analyses. One subject did not have sufficient pre dose sera available to complete anti abatacept antibody screening; however, none of the remaining 30 subjects were positive for anti abatacept antibodies. In addition, none of the subjects were positive for anti CTLA4 T specific antibody.

In the target population

CSR IM101063 assessed the immunogenicity of abatacept administered SC and its effects on serum RF levels in 68 subjects with active RA. On Day 71, only one of the 51 abatacept treated subjects was seropositive for anti abatacept antibody, their blood sample having a titre of 758 with specificity towards the IgG portion of the abatacept molecule; however, the immune response was transient and by Day 85 this subject was negative for anti abatacept antibody. None of the 51 abatacept treated subjects were positive for anti CTLA4 antibody through Day 85; therefore, the cell based abatacept neutralising antibody assay was not undertaken. The low incidence of an immune response to abatacept in RA subjects receiving repeated administration of SC abatacept is in contrast to the 27.5% incidence rate observed in healthy subjects who received a single dose of abatacept SC in CSR IM101013.

A multi centre study (CSR IM101173) evaluated the immunogenic potential of SC abatacept with or without background MTX and in the absence of an initial IV loading dose of abatacept in 100 subjects (75 female), aged 26 to 84 years, with active RA. It consisted of a screening period, short term (ST) treatment period of four month's duration, and a LT extension period. Subjects were stratified 1:1 into two cohorts based on their current use of MTX. During the ST treatment period, all subjects received abatacept 125 mg SC, once weekly; subjects in the SC abatacept + MTX cohort remained on a stable dose of MTX. Subjects who completed the ST treatment period were eligible for entry into the LT extension period, the results of which are reported separately. Subjects had to satisfy the

diagnostic criteria for definite RA[4] with no other rheumatic disease, having a Subject Global Assessment of Disease Activity visual analogue scale (VAS) score of > 20 mm, and requiring a new therapeutic intervention for RA. Subjects in the SC abatacept monotherapy cohort must have been MTX naive and considered a non responder to at least one non biological disease modifying anti rheumatic drug, or discontinued MTX therapy due to lack or efficacy or tolerability at least four weeks prior to the first dose of SC abatacept. Subjects in the SC abatacept + MTX cohort must have currently been receiving MTX at a stable dose of ≥10 mg once weekly for at least four weeks prior to first injection of SC abatacept. Blood samples for immunogenicity assessments were obtained just prior to the SC injection of abatacept on Days 1, 15, 29, 43, 57, 85, and 113 of the ST treatment period, and at 7, 28, 56, and 85 days after the last SC injection for subjects who withdrew from the study prematurely during the ST treatment period. The primary efficacy endpoint for this study was the mean change from baseline in DAS 28 (CRP) and HAQ-DI score at Day 113 (Month 4), and proportion of subjects with ≥1.2 unit reduction from baseline in DAS 28 (CRP) at Day 113. The primary immunogenicity endpoint was the proportion of subjects with positive antibody (anti abatacept and anti CTLA4 T) response at Day 113 (Month 4) based on ELISA.

Similar improvements were observed in the efficacy measures for the two cohorts during ST treatment. At Day 113, the mean change from baseline [95% CI (confidence interval)] in the DAS 28 (CRP) score was -1.67 (-2.06, -1.28) [SC abatacept + MTX cohort] and -1.94 (-2.46, -1.42) [SC abatacept monotherapy cohort]. The proportion of subjects with a Clinically Significant Improvement, defined by a reduction from baseline in the DAS 28 (CRP) score of ≥1.2, was 62.5% and 66.7%, respectively. At the end of the ST treatment period (Day 113), none of the 95 subjects with immunogenicity data (50 in SC abatacept + MTX cohort; 45 in SC abatacept monotherapy cohort) were seropositive for anti abatacept or anti CTLA4 T antibodies. Transient and infrequent positive antibody responses were observed at earlier time points, generally before Day 85, during the ST treatment period or during the follow up and were associated with low titres. During the ST treatment period, the overall immunogenicity rate at any time in the SC abatacept monotherapy and SC abatacept + MTX cohorts was 4.1% (2/49) and 3.9% (2/51), respectively. Only one seropositive response was observed following treatment discontinuation. One subject in the SC abatacept monotherapy cohort was seropositive for anti CTLA4 T antibodies at post treatment Day 85 and did not develop neutralising antibodies; this subject was withdrawn for lack of efficacy after receiving 12 SC injections. There did not appear to be any correlation between the development of antibodies with clinical safety or efficacy findings.

Pharmacodynamic interactions

Not applicable.

Dosage Selection for the Pivotal Studies

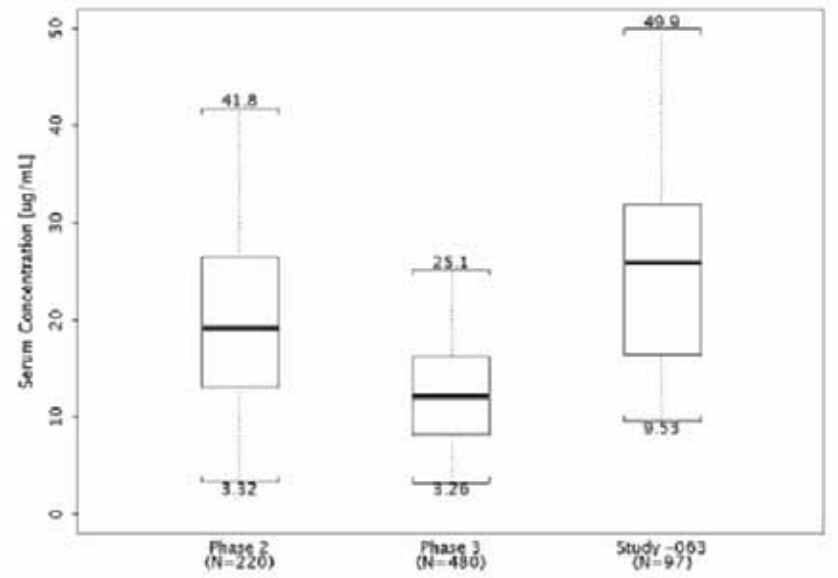
The sponsor states that the nonclinical data found that concentrations ≥10 μg/ml provided maximal T cell inhibition as measured by T cell proliferation and cytokine responses. In addition, in the Phase II and III trials, steady state trough concentrations with IV abatacept in a range of 2 to 28 μg/mL. C_{min} were the best predictor of clinical efficacy while concentrations that were approximately 5 μg/mL were associated with lower efficacy. From these data, the aim with SC abatacept was to target a trough concentration in a range of 10 to 30 μg/mL.

In Study IM101063, the steady state trough concentrations with 125 mg SC abatacept once weekly were within the target range and over 90% of subjects dosed with 125 mg had C_{min}

[4] Hochberg MC, et al. The American College of Rheumatology 1991 revised criteria for the classification of global functional status in rheumatoid arthritis. *Arthritis & Rheumatism*, 1992; 35: 498-502.

≥10 µg/mL. The findings were comparable across the weight groups of <60 kg and 60-100 kg. The steady state trough concentrations were lower in those weighing above 100 kg, although they were still within the target range. When compared to data from Phase II and III studies with IV abatacept, the trough exposure was higher (Figure 5); however the overall exposure, as measured by AUC and C_{max}, for the weekly SC formulation was lower that what is achieved with monthly IV abatacept.

Figure 5: Distribution of trough serum abatacept concentrations from Phase 2 and Phase 3 IV studies and from RA subjects administered weekly SC adatacept at 125 mg (IM101063).



The thick line in the middle of the box is the median, the box is the inter-quartiles, the whiskers are the 5th and 95th percentiles.

A fixed dose of SC abatacept was chosen for the Phase III program for simplicity. It was acknowledged that this could result in a potential safety risk for those of low body weight and inadequate clinical efficacy for those of high body weight so subgroup analyses by weight group were planned.

Efficacy

Pivotal efficacy studies

Study IM101174

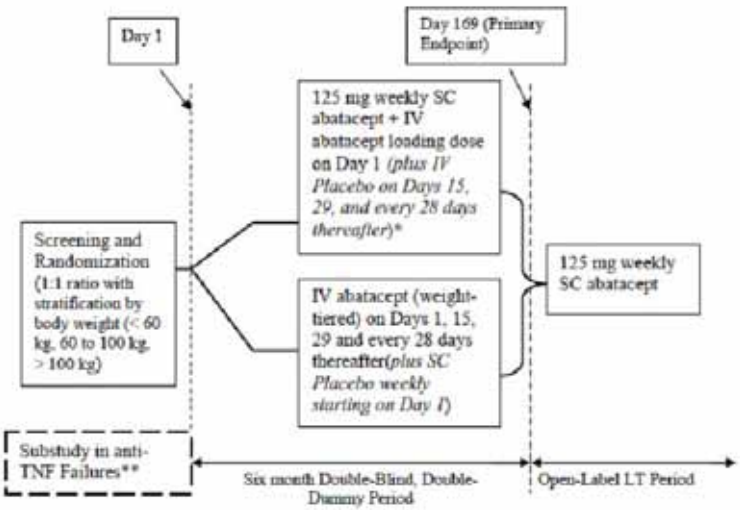
Study design, objectives, locations and dates

Study IM101174 was a Phase IIIb multicentre, randomised, double blind, double dummy study to compare the efficacy and safety of abatacept administered subcutaneously and intravenously in subjects with RA receiving background MTX and experiencing an inadequate response to MTX. The study was conducted at 242 centres in the Europe, Australia, North and South America, South Africa, Asia and Russia. It ran between January 2008 and October 2009 for the ST period. The LT period was reported as ongoing and the sponsor stated it may continue until the SC formulation is commercially available in the relevant country.

The study consisted of a 6 month (169 day) ST blinded and controlled period, followed by an open label, LT period (Figure 6). There was a variable length screening period prior to randomisation. The primary objective of the ST period was to demonstrate non inferiority of SC abatacept versus IV abatacept. There was a sub study which assessed

immunogenicity, efficacy and safety in 18 subjects who had failed or had inadequate prior response to anti TNF therapy.

Figure 6: Design of Study IM101174.



A revised CSR (dated 10 Jan 2011) was provided as two issues were identified after the initial report was finalised. There was an error in the body weight stratification analysis dataset, though randomisation was reported to have been correctly undertaken. The second issue was GCP non compliance at one site in South Korea. The site had enrolled 8 subjects and they were all excluded from the efficacy analyses in the revised report.

Inclusion and exclusion criteria

The main inclusion criteria were adults (≥18 years) with RA as defined by the American Rheumatism Association and the American College of Rheumatology (ACR) functional Classes[4] I, II or III who were considered inadequate responders to MTX. Subjects needed to have received MTX for at least 3 months at a minimal weekly dose of 15 mg (or 10 mg if 15 mg not tolerated). Other DMARDs were prohibited and required wash out of at least 4 weeks. The dose of prednisolone needed to be stable at ≤10 mg daily. Subjects who had received an anti TNF therapy and discontinued for reasons other than lack of efficacy were limited of 10% of the study population. Other medical conditions were required to be stable. Disease activity requirements were dependent on whether treatment washout was required.

The main exclusion criteria were other rheumatic disease, active vasculitis, severe, progressive or uncontrolled medical conditions, serious acute or chronic bacterial infection, had a history of cancer within 5 years, at risk of tuberculosis (TB), herpes zoster within two months, requiring a prohibited medication such as rituximab, anti TNF therapy, anakinra, or another biologic therapy.

Study treatments

During the ST period, subjects received either abatacept 125 mg SC weekly, together with an IV abatacept loading dose on Day 1 based on weight, or abatacept IV infusion on Days 1, 15, 29 and then every 28 days. The IV dose was 500 mg for subjects weighing <60 kg, 750 mg for subjects weighing 60 to 100 kg, and 1000 mg for subjects weighing >100 kg. Subjects received IV abatacept in a fixed volume of 100 mL at a constant rate of flow over approximately 30 minutes. Subjects were trained to self administer the weekly SC injection. Matching placebo SC ready to use syringes and IV infusion were used so that all subjects received weekly SC and monthly IV study medication.

MTX was continued at the current dose and dose increases were not permitted during the ST period. Low dose corticosteroids (≤10 mg prednisolone) were permitted. A short course or single IA injection of corticosteroids were allowed but not within 28 days of Day 169 visit. Treatment with non steroidal anti inflammatory drugs (NSAIDs) needed to remain stable. All other biologics or DMARDs were prohibited during the ST period. In the LT period, all subjects received weekly open label 125 mg SC abatacept.

Efficacy variables and outcomes

The primary main efficacy variable was ACR response criteria[5] for 20% (ACR 20) response at Day 169. ACR 20 response is a validated index which has previously been used as the primary endpoint in other abatacept studies. ACR 20 response was defined as proportion of subjects meeting the ACR criteria of 20% improvement in tender and swollen joint counts and 20% improvement in 3 of the remaining 5 core set measures (subject global assessment of pain, subject global assessment of disease activity, physician global assessment of disease activity, subject assessment of physical function and one acute phase reactant value [CRP]). ACR 50 and ACR 70 responses were similarly defined with 50% and 70% improvement, respectively. Standardised tender and swollen joint counts for 34 locations were conducted and investigators trained in the assessment.

The Health Assessment Questionnaire (HAQ) was completed by subjects. A HAQ response was defined as a reduction of at least 0.3 unit from baseline in the HAQ score. VAS was used for the subject's global assessment of pain and disease severity and the physicians assessment of disease activity. Disease Activity Score (DAS) 28-CRP score was derived from four components: tender swollen joint counts, subject global assessment of disease activity and hsCRP. Using the European League Against Rheumatism (EULAR) definitions,[6] a low DAS28-CRP score (LDAS) was a DAS28-CRP ≤3.2 and remission was a DAS28-CRP <2.6.

The primary efficacy outcome was to demonstrate that SC abatacept was non-inferior to IV abatacept in ACR 20 responses after 6 months (Day 169) of treatment in subjects who had active RA, were receiving MTX and experiencing an inadequate response to MTX.

Other efficacy outcomes included:

- To assess the proportion of subjects with ACR 50 response at Month 6 (Day 169)
- To assess the proportion of subjects with ACR 70 response at Month 6 (Day 169)
- To assess the PK of SC injections of abatacept
- To assess the immunogenicity of abatacept
- To assess the change in physical function as measured by the HAQ disability index (HAQ-DI) at Month 6 (Day 169)
- To assess the proportion of subjects with a HAQ response as measured by a reduction of at least 0.3 unit from baseline in the HAQ at Month 6 (Day 169)
- To assess the safety and tolerability of SC injections of abatacept
- To assess the change from baseline in disease activity as measured by DAS-28 using CRP by visit in the ST period

[5] ACR response criteria include changes in number of swollen joints, tender joints, physician global assessment of disease, patient global assessment of disease, patient assessment of pain, C-reactive protein or erythrocyte sedimentation rate, and health assessment questionnaire score.
[6] van Tuyl LH, et al. Evidence for predictive validity of remission on long-term outcome in rheumatoid arthritis: a systematic review. *Arthritis Care Res. (Hoboken)* 2010; 62:108-117.

- To assess the safety and LT tolerability of SC injections of abatacept as well as the maintenance of responses in subjects who had completed the initial 6 month treatment period.

Randomisation and blinding methods

Subjects were randomised to SC or IV abatacept by an IVRS in a 1:1 ratio stratified by body weight (<60 kg, 60 to 100 kg and >100 kg). A double dummy design was used to protect the study blind. Subjects in the IV abatacept group received SC placebo injections and those in the SC abatacept group received IV placebo infusions (except on Day 1 when they received their IV abatacept loading dose). Study personnel and subjects were blinded to treatment.

During the study two subjects were accidently unblinded. A pharmacokineticist and bioanalytical scientist were unblinded for PK data analysis prior to database lock, although the sponsor states they did not have access to safety or efficacy data.

Analysis populations

The intention-to-treat (ITT) population was all randomised subjects who received at least one dose of study medication. The per protocol (PP) population was the ITT population without any relevant protocol deviations. The primary and key secondary efficacy analyses (ACR and HAQ responses) were based on the PP population.

Sample size

A treatment difference of 25% between IV abatacept and placebo in ACR 20 response was the minimum expected benefit based on previous trials. The sponsor stated that for demonstrating non-inferiority, SC abatacept would need to demonstrate at least 70% of the treatment effect of IV abatacept, that is, a non-inferiority margin of 7.5% [(1-0.7) x 25%] and SC abatacept would be deemed non inferior to IV abatacept if the lower bound of the 95% CI for the difference on ACR 20 was greater or equal to -7.5%. This equates to a point estimate of the difference of 2.1%.

Assuming an equivalent ACR 20 response rate of 60% as sample of 1370 (685 per group) would give the study an 80% power to detect non inferiority at a 0.025 significance level. A sample of 1440 randomised patients was chosen to allow for protocol deviations leading to exclusion from the PP analysis.

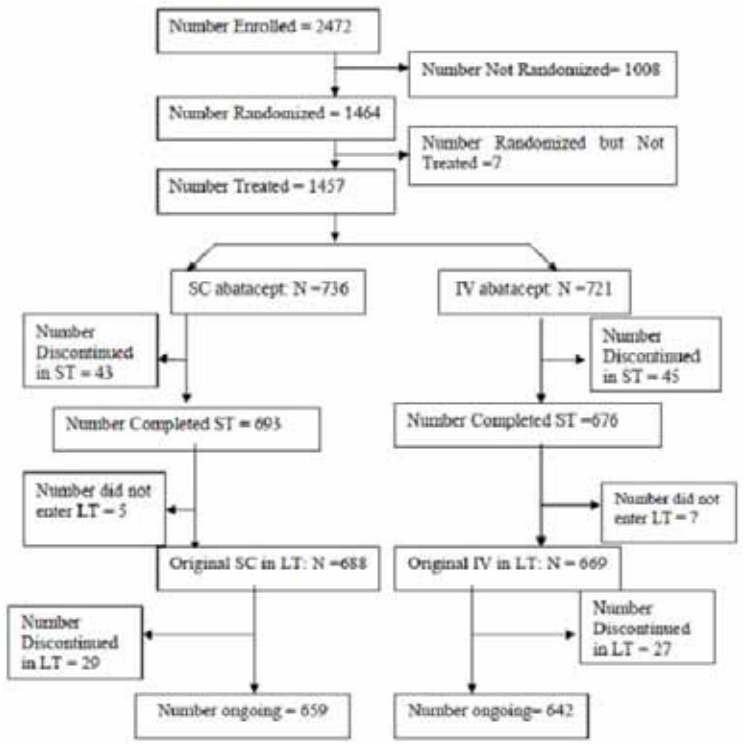
Statistical methods

ACR and HAQ response rate point estimates and 95% CI were summarised by treatment group. Treatment group differences and 95% CI, adjusted for stratification, were calculated. Change in HAQ-DI and DAS-CRP were analysed using an analysis of covariance (ANCOVA) model which included treatment as the main factor, baseline values and weight stratification as covariates. Subgroup analyses (by age, gender, race, weight, baseline weight quartiles, geographic location, duration of RA, anti TNF historical use, baseline DAS28-CRP, and baseline RF Status) were conducted.

Participant flow

There were 2472 subjects enrolled, 1464 randomised and 1457 treated. There were seven subjects randomised and not treated. Subject disposition is presented in Figure 7. There were 736 SC abatacept and 721 IV abatacept subjects, with 693 (94.2%) and 676 (93.8%), respectively, completing the 6 month ST treatment period. Premature discontinuation from the ST period occurred in 43 (5.8%) and 45 (6.2%) of the SC abatacept and IV abatacept groups, respectively. Adverse events (AEs) were the most common reason for premature termination (2.3% versus 3.5%).

Figure 7: Subject disposition in Study IM101174.



There were 12 subjects who did not continue onto the LT treatment period. At 21 January 2010, there were 1301 subjects in the LT period. Premature discontinuation from the LT period occurred in 4.2% and 4.1% of the SC and IV abatacept groups, respectively, with the main reason being lack of efficacy (1.9% versus 1.5%) and adverse event (0.9% versus 1.0%). There were 1379 subjects, 693 SC abatacept and 678 IV abatacept, in the PP analysis population which just met the sample size requirements (685 per group).

Major protocol violations/deviations

There were 78 subjects (5.4% SC abatacept and 5.3% IV abatacept) with protocol deviations deemed to have a potential significant impact on the primary efficacy analysis. The most frequent (22 subjects) was receipt of IA/IM/IV steroid injection or high dose oral steroid within 28 days for the final assessment. There were 17 subjects with insufficient number of swollen or tender joints and 10 subjects had received more than two anti TNF therapies in the past.

Baseline data

The treatment groups were comparable on demographics and baseline disease characteristics. Study subjects were mainly female (82.3%), had a mean age of 49.9 years and a mean weight of 71.8 kg. About half were from South America with the rest from the range of other countries and 74% were white. The subjects had moderate to severe arthritis with a mean disease duration of 7.6 and 7.7 years in the SC abatacept and IV abatacept groups, respectively. In the PP population, other disease characteristics were similar between groups such as the mean number of tender joints (30.0 versus 29.2), swollen joints (20.5 versus19.6), mean HAQ-DI score (1.73 versus 1.69), mean DAS28-CRP score (6.25 versus 6.22) and mean hsCRP (2.65 versus 2.72 mg/dL). About 85% of subjects were rheumatoid factor positive and the mean baseline MTX dose was 16.4 mg/wk.

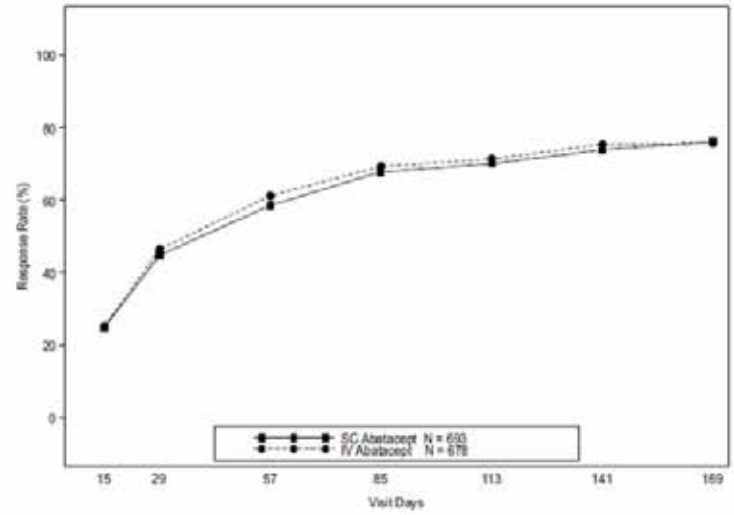
Prior to enrolment, all except two subjects had received MTX, 12-16% used non biologic DMARDs and 73% used corticosteroids. There were 3.4% and 4.5% of the SC abatacept and IV abatacept groups, respectively, who had been treated with biologics, predominantly TNF antagonists. Concomitant corticosteroid use during the study was similar (71.3% versus 74.2%) as was NSAID use (80.7% versus 79.6%). The mean weekly MTX dose during the study was 16.0 and 16.2 mg, respectively. Other common concomitant medications were vitamin B12, folic acid, analgesics, peptic ulcer treatment and cardiovascular treatments. There were 2 subjects in the IV abatacept group who received prohibited DMARDs during the study.

For the ST period in the SC abatacept group, all subjects received the IV abatacept loading dose, the mean treatment duration was 166.8 days and 94.7% received at least 21 of the planned 24 SC injections. In the IV abatacept group, the mean duration of treatment was 166.0 days, with 96.9% receiving at least 4 of the 7 planned infusions. Treatment discontinuation due to non compliance occurred in 3 subjects of the SC abatacept group and none of the IV abatacept group. There were 83.7% and 81.4% of the groups, respectively, who did not miss any injections/infusions.

Results for the primary efficacy outcome

In the PP population at Day 169, the proportion of subjects with an ACR 20 response was 76.0% (527/693) and 75.8% (514/678) in the SC abatacept and IV abatacept groups, respectively. The treatment difference was 0.3% (95% CI: -4.2%, 4.8%). As the lower bound of the 95% CI was greater than the non inferiority margin of -7.5% the primary objective was met. The response was similar on the ITT population analysis with a treatment difference of 0.5% (95% CI: -4.0%, 4.9%). The ACR 20 response improved similarly over time in both groups, from 25% at the first assessment at Day 15 (Figure 8).

Figure 8: ACR 20 response over time during ST period (PP analysis): PP population in ST period (Study IM101174).



Results for other efficacy outcomes

In the ITT population, the ACR 50 response at Day 169 was 50.2% and 48.6% in the SC abatacept and IV abatacept groups, respectively. The response over the ST study period was similar between groups (Figure 9). The ACR 70 response rates were also similar between groups (25.8% versus 24.2%) (Figure 10). PP population analysis was consistent with these findings.

Figure 9: ACR 50 response over time during ST period (ITT analysis): all randomised and treated subjects in ST period (Study IM101174).

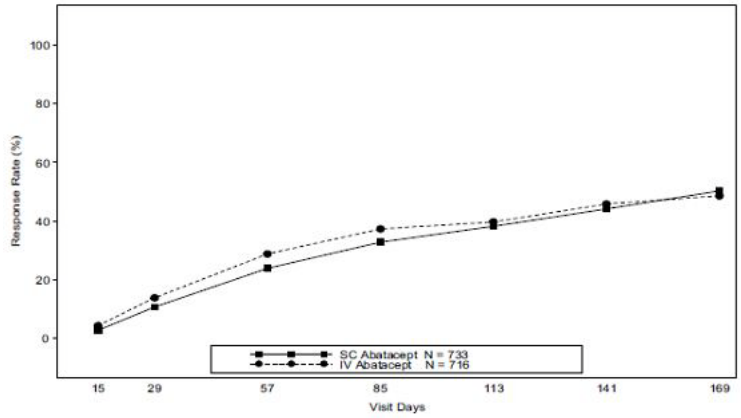
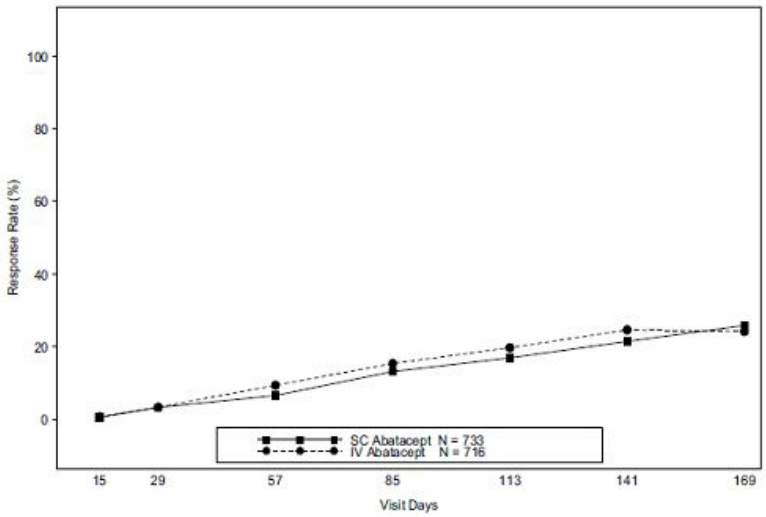


Figure 10: ACR 70 response over time during ST period (ITT analysis): all randomised and treated subjects in ST period (Study IM101174).



Physical function was measured by the HAQ with a reduction of at least 0.3 units from baseline deemed as a positive response. At Day 169, the HAQ response rate was 69.7% and 65.2% in the SC and IV abatacept groups, respectively. The adjusted mean change from baseline to 6 months in the HAQ-DI score was -0.69 and -0.70 in the two groups, respectively.

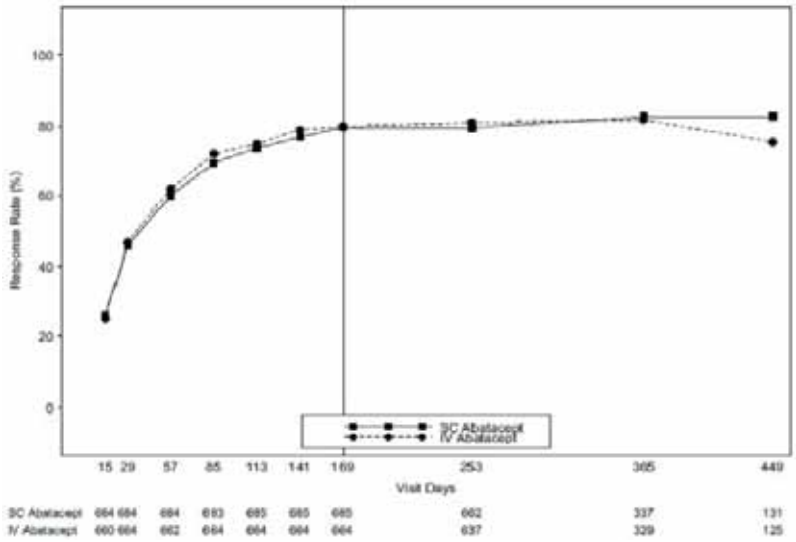
The adjusted mean change from baseline in DAS28-CRP was similar between groups. LDAS response (DAS28-CRP ≤3.2) was 39.5% (268/679) and 41.3% (272/658) in the SC abatacept and IV abatacept groups respectively. The rate of DAS remission (defined as DAS28-CRP <2.6) was also comparable (24.2% versus 24.8%). The mean change from baseline to Day 169 in hsCRP was -15.2 in both groups.

Subgroup analysis was conducted on the ACR 20 and HAQ response at Day 169 on the PP population. Response to the SC and IV abatacept treatment was similar for the subgroups of gender, race, geographic region, duration of RA, baseline DAS-CRP, baseline RF status, and prior anti-TNF use. In the weight subgroups (<60, 60-100, >100 kg) efficacy on ACR 20 response and HAQ response was similar between the two formulations. It was noted, however, for both the SC and IV formulations that there was a trend for increasing efficacy with decreasing body weight. Efficacy in the subgroups of age (<65, ≥65, ≥75 years) showed a lower ACR 20 response with SC abatacept in the elderly ≥65 years treated with

SC abatacept (61.1% versus 74.4%) while the response on HAQ was similar in this age group (54.4% versus 59.0%). Results for the <65 years age group were similar between treatments.

LT efficacy: At database lock (21 January 2010) there were 1301 of the 1357 (95.9%) subjects in the open label LT study receiving SC abatacept. The mean cumulative duration of exposure to abatacept was 13.8 months for the SC abatacept group and 13.8 months for the IV abatacept group. Approximately 85% of subjects in both groups did not miss any injections during the LT period. During this period, over 70% received NSAIDs and over 99% of subjects continued MTX. Sulfasalazine, chloroquine, hydroxychloroquine or azathioprine could be added, although this was only done in a few subjects. The response on ACR 20 was maintained throughout the LT period to Day 449 (Figure 11). Maintenance of ACR 50 and ACR 70 response was also seen. The mean change from baseline in HAQ-DI score at day 449 was -0.79 and -0.71 in the SC abatacept and IV abatacept groups, respectively. Response rates on the HAQ, LDAS, and DAS remission were also maintained.

Figure 11: ACR 20 response over time: all treated subjects in LT period (Study IM101174).



Other efficacy studies

Study IM101167

Methods: IM101167 was a Phase IIIb, multicentre, randomised, withdrawal study to evaluate the immunogenicity and safety of subcutaneously administered abatacept in 120 adults with active rheumatoid arthritis on MTX. The methodology is outlined in Figures 12-15.

Figure 12: Design of Study IM101167.

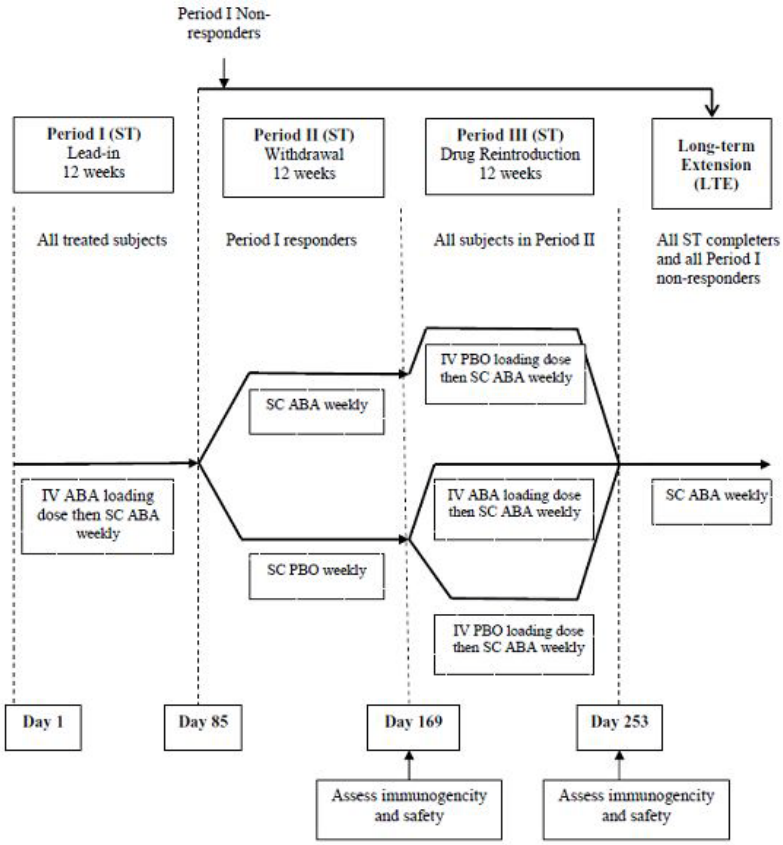


Figure 13: Subject disposition in Study IM101167, Period I.

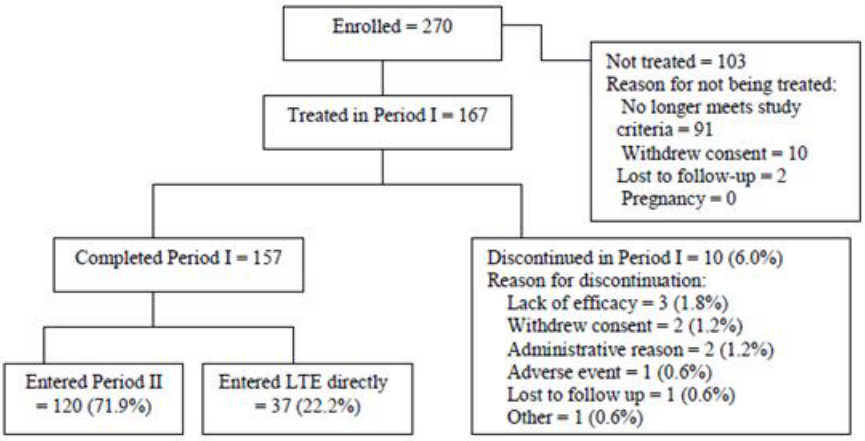
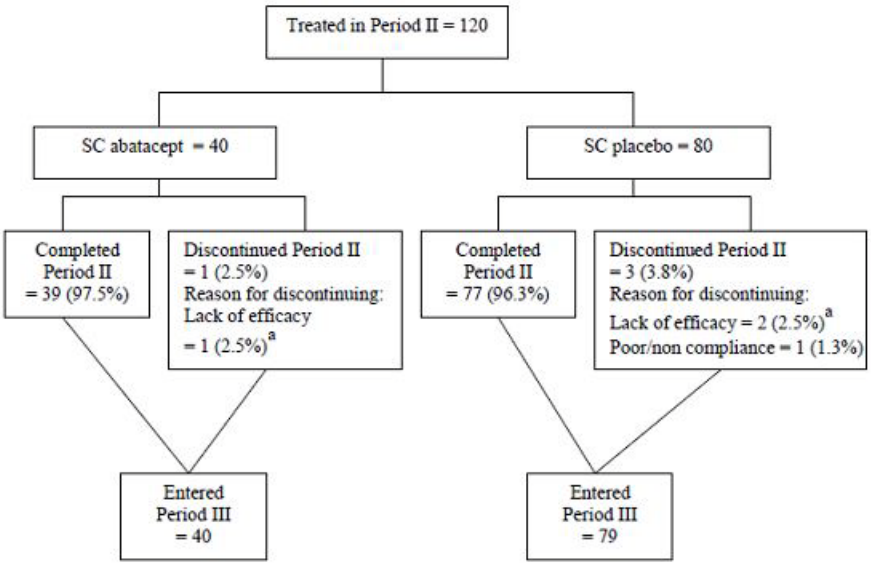
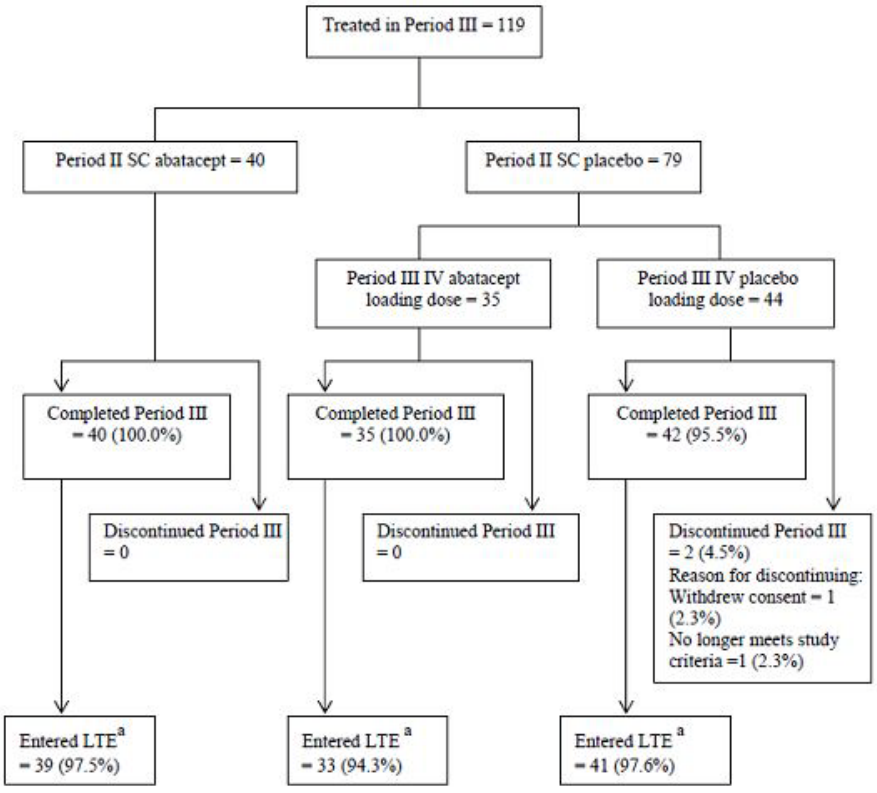


Figure 14: Subject disposition in Study IM101167, Period II.



[a] One subject in SC abatacept group and 2 subjects in SC placebo group who discontinued due to 'lack of efficacy' met the criteria for disease flare during Period II. These subjects discontinued from Period II to enter Period III early.

Figure 15: Subject disposition in Study IM101167, Period III.



[a] Four subjects who completed Period III did not enter the LTE due to lack of effiacy (1 subject) or subjects elected not to continue because the site closed at the end of the ST period (3 subjects).

Results: In Period I (Day 85) there was a reduction from baseline in DAS28-CRP (mean -1.88 and -1.97 in the Period II SC abatacept and SC placebo groups, respectively) which was maintained in Period II (withdrawal) in the SC abatacept group (-2.03) and increased slightly in the SC placebo group (-1.49). After reintroduction of abatacept, the results were similar between groups at the end of Period III (Figure 16). There was a worsening of low disease activity (DAS28-CRP ≤3.2) and clinical remission rates (DAS28-CRP <2.6) when subjects were treated with SC placebo in Period II and an improvement with reintroduction of SC abatacept (clinical remission at the end of each period was 35.0%, 47.4% and 51.3% in the SC abatacept group and 37.2%, 28.0% and 63.5% in the SC placebo group).

The results of hsCRP were consistent with the DAS28-CRP results. The mean change from baseline in the HAQ-DI score was maintained in the SC abatacept group (-0.74, -0.72 and -0.86 at the end of Period I, II and III, respectively) while in the SC placebo group showed some worsening on abatacept withdrawal and improvement on reintroduction (-0.63, -0.50, -0.72 the end of the three periods, respectively). There were three subjects (one in SC abatacept and two in SC placebo groups) who had an RA flare during the withdrawal period, none of whom had positive immunogenicity responses.

For those who were responders to SC abatacept in Period I, the mean change in DAS28-CRP was maintained during the LT extension period to Day 449 regardless of the treatment withdrawal (Figure 17). Low disease activity and clinical remission rates were also maintained. With longer term treatment, subjects who were classed as non responders to SC abatacept at Day 85 (and directly entered the LT extension) did have some improvement in disease activity (Figure 18).

Figure 16: DAS28-CRP mean change from baseline over time during the ST period: all subjects treated in Period II (Study IM101167).

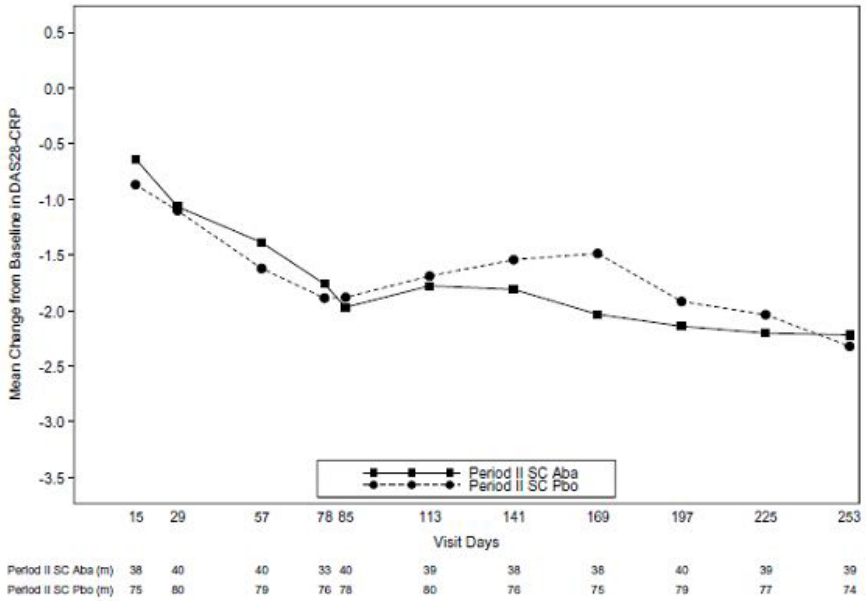


Figure 17: DAS28-CRP mean change from baseline over time, as-observed analysis: all subjects treated in the LT extension who were Period I responders (Study IM101167).

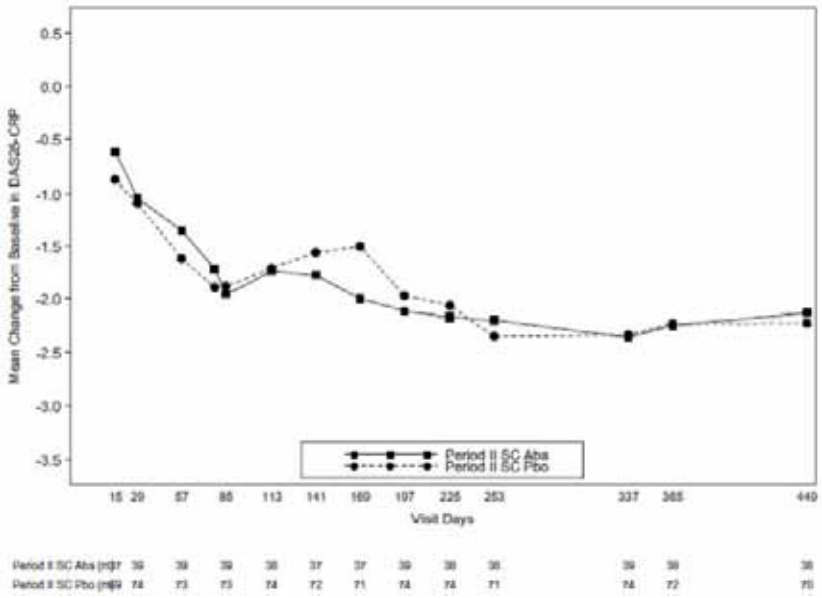
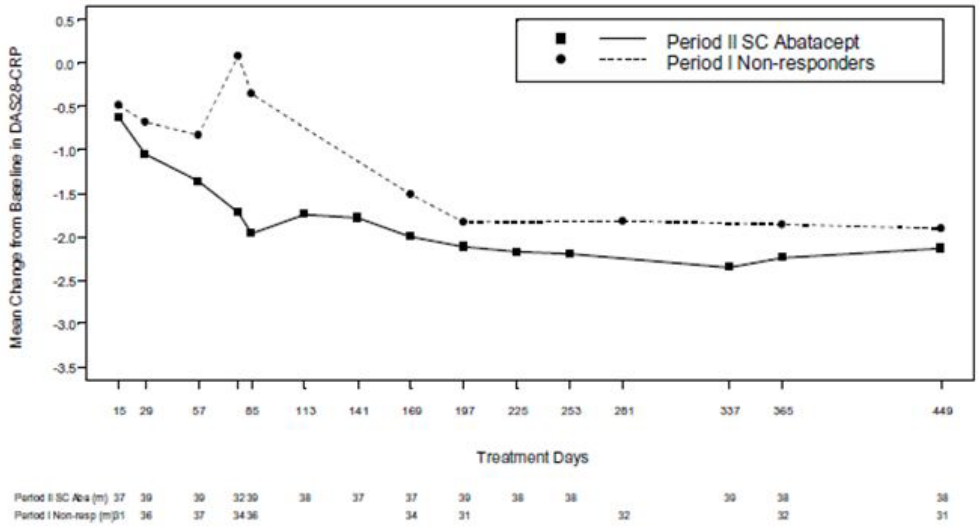


Figure 18: DAS28-CRP mean change from baseline over time, as-observed analysis: all subjects treated in the LT extension Period I non-responders and Period II SC abatacept treatment group (Study IM101167).

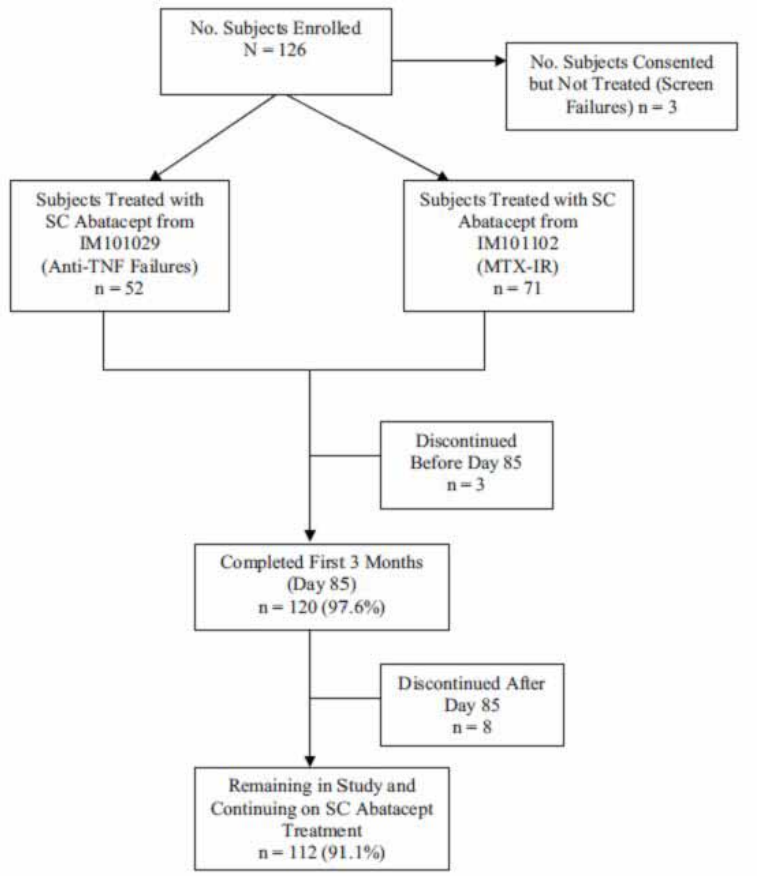


Summary: Withdrawal of abatacept treatment for 12 weeks led to a small increase in disease activity which improved on treatment reintroduction. Efficacy was maintained to day 449. Those with an initial poor treatment response had a reduction in DAS28-CRP with ongoing 16 weeks of treatment.

Study IM101185

Methods: Study IM101185 was a Phase IIIb, multicentre, open label, single arm study evaluating the safety of abatacept in 123 subjects who switched from IV to SC therapy. Participant flow is shown in Figure 19.

Figure 19: Subject disposition in Study IM101185.



Results: Subjects had low disease activity at enrolment (after approximately 5 years of IV abatacept treatment) with a mean tender joint count of 8.9, mean swollen joint count of 4.8, DAS28-CRP score of 3.39, HAQ-DI score of 0.94 and hsCRP of 0,93 mg/dL. At enrolment 37.4% were on corticosteroids (mean dose 2.3 mg), 71.5% NSAIDs, 82.1% on DMARDs (77.2% MTX). During the first 3 months 92.7% of subjects received all scheduled SC injections. Anti-rheumatic medications received up to day 85 were consistent with those at study entry as were those received up to the last dose of SC abatacept (20 months of cumulative treatment).

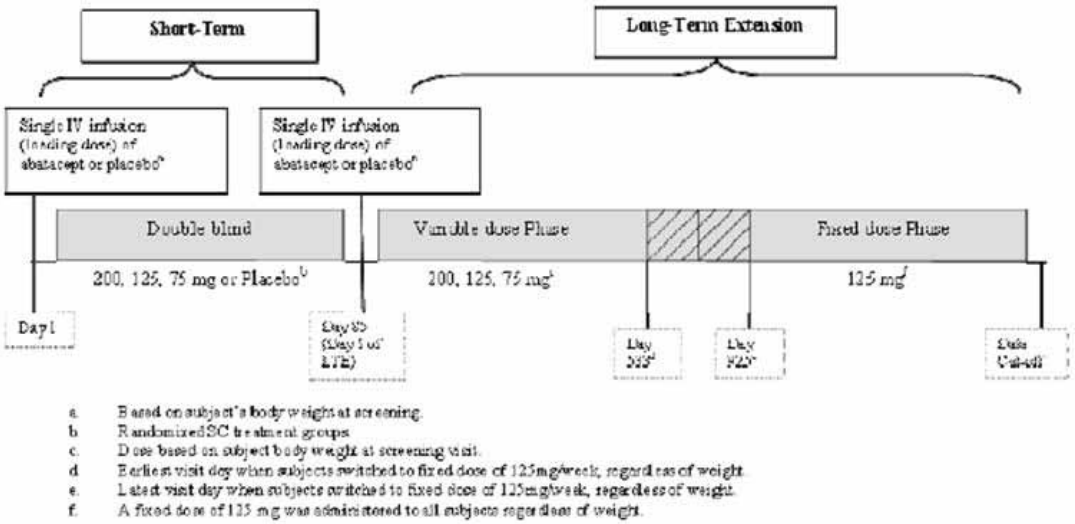
At Day 85, the mean DAS28-CRP score was 3.13 and at Day 365, it was 3.21. At baseline, the low disease activity score (LDAS) and remission (DAS28-CRP <2.6) proportions were 43.4% and 32.0%, respectively. These scores were 54.6% and 38.7% at Day 85, and 51.3% and 39.8% at Day 365, respectively. Likewise, the HAQ-DI score was maintained at baseline levels to Day 365 (mean score 0.94 at baseline and 0.90 at Day 365) as was the mean hsCRP value.

Summary: In IM101185, subjects (from two IV abatacept trials where initial inclusion was either inadequate response to MTX or had failed anti TNF therapy) were switched to weekly open label SC abatacept after a minimum of 4 years treatment with IV abatacept. Efficacy was maintained after up to 1 year of open label treatment, as demonstrated by stable results on DAS28-CRP and HAQ-DI scores as well as the proportion with low disease activity and remission (as based on the DAS28-CRP).

Study IM101063LT

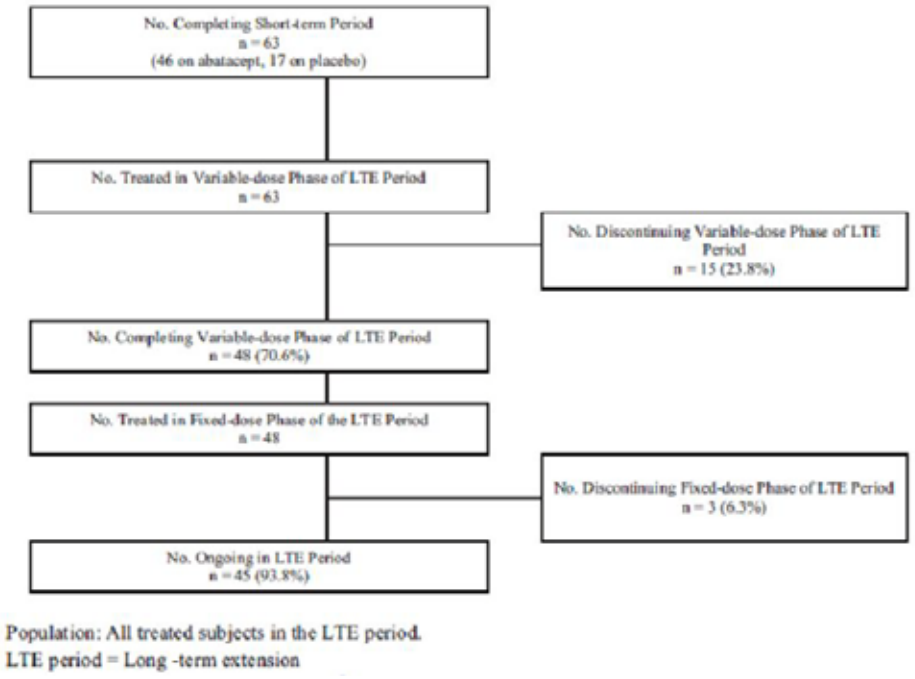
Methods: Study IM101063LT was an open label, LT extension study of IM101063, a PK study assessing dosing regimens for SC abatacept in RA subjects receiving DMARDs. The primary objective of this study was safety, immunogenicity and LT tolerability. Efficacy assessments were minimal and limited to tender and swollen joint counts. The open label extension commenced in April 2006 and was ongoing at reported database cut off of December 2009. There were 12 sites in the US. After completing the initial study 12 week treatment period, subjects entered a variable dose phase and then a fixed dose phase. A weight-based loading dose of IV abatacept or IV placebo was given to maintain the ST study blind at the commencement of the LT period, then weekly SC abatacept with weight-based dosing as per the ST period (<60 kg received 75mg, 60-100kg 125 mg and >100 kg 200mg). Dosing was adjusted based on reweighing at Day 365. In the second year, after approval of protocol amendments, all subjects received fixed dose SC abatacept of 125 mg/wk (Figure 20). RA medications could be adjusted during the extension study and prohibited medications were the same as Study IM101185. Efficacy was assessed on joint counts in the treated population (all subjects who received at least one SC abatacept dose in the LT period) Data analysis was descriptive.

Figure 20: Design of Study IM101063LT.



Results: Sixty-three subjects completing the initial study were enrolled into the variable dose phase and 48 (76.2%) continued to the fixed dose phase. Of the 15 (23.8%) who prematurely discontinued, 5 (7.9%) were for lack of efficacy and 4 (6.3%) for AEs (Figure 21). At baseline subjects had moderate disease activity with a mean number of tender and swollen joints of 22.1 and 14.9, respectively. Compliance was low during the variable phase with 41.3% of subjects missing 3 or more injections. During the fixed dose phase compliance was higher with 25% missing 3 or more injections. Most (98.4%) of subjects were taking MTX. On Day 1 (n=22) of the fixed dose phase, the mean (SD) number of tender and swollen joints were 8.5 (9.5) and 7.0 (6.1), respectively. At Day 365 (n=46) the mean (SD) number of tender and swollen joints were 6.0 (8.2) and 5.1 (5.3), respectively.

Figure 21: Subject disposition flowchart: LT extension period (Study IM101063LT).



Comment: This study provides little useful efficacy data due to the small subject numbers with large response variability, the open label nature and the limited efficacy assessments.

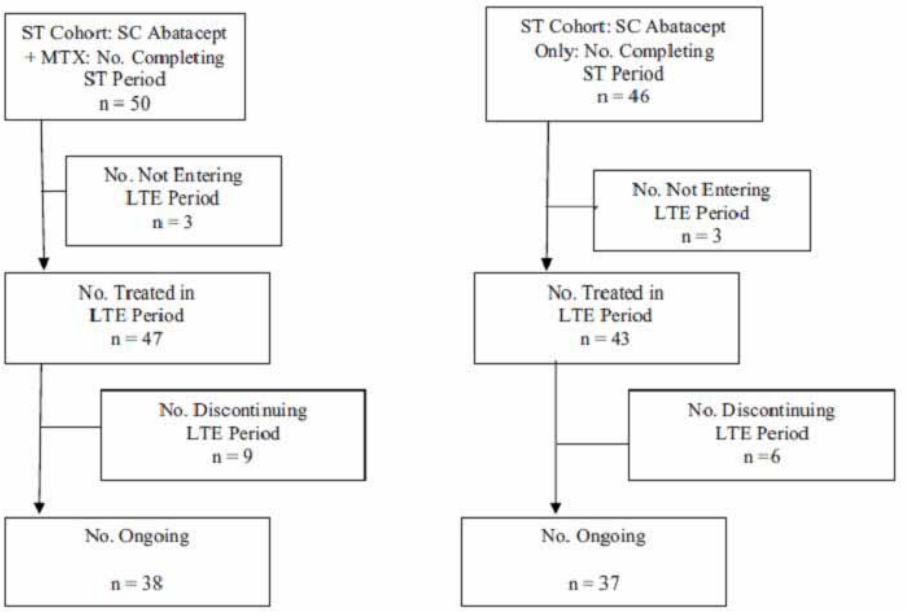
Study IM101173LT

Methods: Study IM101173LT was an open label, LT extension study of IM101173 which evaluated the immunogenicity and PK of SC abatacept in RA subjects with or without MTX. In the initial study, subjects were stratified to those receiving stable MTX and those who had not received MTX. The primary objective of this study was safety and LT tolerability. The open label extension commenced in December 2007 and was ongoing at reported database cut off of December 2009. There were 22 sites in the US, South Africa, Australia and Mexico. After completing the initial study 4 month treatment period, subjects continued on SC abatacept 125 mg/week. RA medications, including MTX, could be added and adjusted during the extension study. Permitted DMARDs were sulfasalazine, chloroquine, hydroxychloroquine and azothioprine. Efficacy was assessed on DAS28-CRP and HAQ in the treated population (all subjects who received at least one SC abatacept dose in the LT period).

Results: Of the 96 subjects completing the initial study, 90 entered the LT extension with 75 (83.3%) ongoing at database lock. Of the 15 (16.7%) who prematurely discontinued, 9 (10%) were for lack of efficacy and 4 (4.4%) for AEs (Figure 22). At baseline, subjects were mainly white (77.8%) and female (74.4%) with a mean age of 53.7 years and mean duration of RA of 9.6 years. The ST cohorts were not balanced on race, region or gender. Subjects had moderate disease activity at entry to the LT period with a mean number of tender and swollen joints of 22.8 and 16.0, respectively. The mean HAQ-DI was 1.4. At the start of the LT period the disease activity was not balanced between the original cohorts, with greater activity in the SC abatacept monotherapy compared to the SC abatacept and MTX group. NSAIDs were used by about two thirds of the subjects, 42% were receiving corticosteroids and 63.3% were using MTX. The mean cumulative exposure to abatacept

was 19.4 months. Most subjects (72.2%) did not miss more than one injection during the LT period.

Figure 22: Subject disposition flowchart: LT extension period (Study IM101173LT).



After approximately 14 months (Day 533) in the LT study, the mean change from baseline in disease activity as measured by the DAS28-CRP was -2.86 and -1.84 in the SC abatacept monotherapy and SC abatacept plus MTX groups, respectively. The proportion with LDAS (DAS28-CRP ≤3.2) was maintained over the LT period (57.5% to 69.4% at day 533) (Figure 23). Remission rates (DAS28-CRP <2.6) at Day 533 were 58.3% and 42.5% in the SC abatacept monotherapy and SC abatacept plus MTX groups, respectively (Figure 24). The mean change from baseline in the HAQ-DI was -0.74 and -0.35 in the SC abatacept monotherapy and SC abatacept plus MTX groups, respectively.

Figure 23: Proportion of subjects with DAS 28 (CRP) low disease activity over time by ST period cohort: all treated subjects in LT extension period (Study IM101173LT).

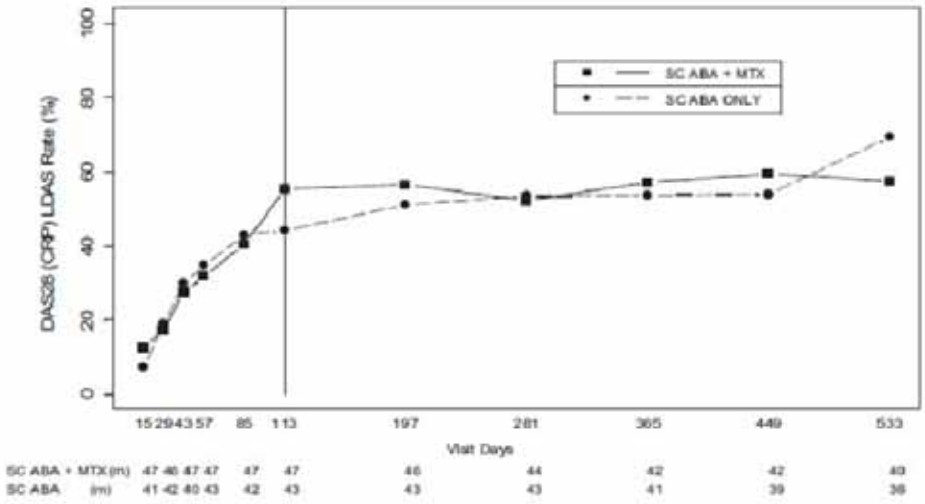
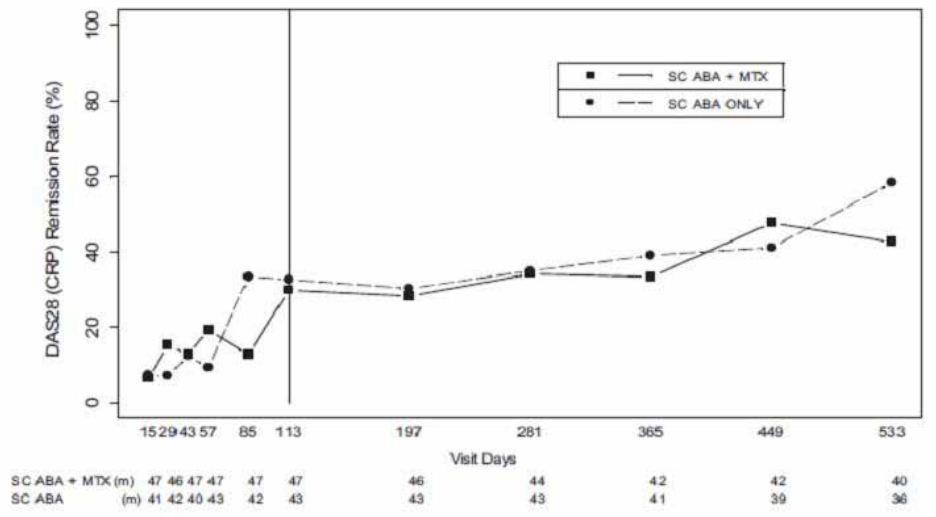


Figure 24: Proportion of subjects with DAS 28 (CRP) remission over time by ST period cohort: all treated subjects in LT extension period (Study IM101173LT).



Comment: This small open label study provided some supportive evidence for maintained efficacy over an 18 month treatment period as measured by DAS28-CRP and HAQ-DI.

Analyses performed across trials (pooled analyses and meta-analyses)

There were no pooled efficacy analyses.

IV loading dose: In IM101174 and IM101167 all subjects received an IV loading dose prior to SC administration while in IM101173 no loading dose was given. As these studies had differences in baseline disease severity, the sponsor reported change from baseline in the continuous variables DAS-CRP and HAQ-DI. It is noted that IM101173 was an open label study and the only randomised controlled data comes for IM101167. In this study, after the withdrawal period, subjects were re-randomised at Period III to IV abatacept or IV placebo loading dose before SC abatacept.

In patients receiving SC abatacept, at Day 85, the mean change from baseline in DAS28-CRP was 31.6%, 33.1 and 27.8% in IM101167, IM101174 and IM101173, respectively, and in HAQ-DI was 44.6%, 31.4% and 32.2%, respectively, indicating that the lack of loading dose in IM101173 did not impact on clinical response. In IM101167 after 12 weeks treatment in Period III, the mean change from baseline in DAS28-CRP was similar between groups (-0.93 and -0.89 in the IV abatacept and IV placebo groups, respectively).

Safety

Studies providing evaluable safety data

Evaluable safety data was available from five Phase II and III studies (that is, all studies except IM101013) and their long term extensions. These data were included in the pooled safety population.

Pivotal efficacy study

In the pivotal efficacy study, IM101174, the following safety data were collected:

- General AEs were assessed by routine monitoring, physical examination and vital signs at study visits.

- AEs of particular interest were infections, malignancies, autoimmune disorders, acute infusional AEs (within first hour after infusion), peri infusional AEs (within first 24 hours after infusion), local injection site reactions, systemic injection reactions (systemic AEs within first 24 hours of injection). These were assessed from routine monitoring and examination. They were analysed as composite terms using preferred terms (PTs) under the Medical Dictionary for Regulatory Activities (MedDRA) term or System Organ Class (SOC) or under an event category based on customised listings of PTs created by the sponsor.
- Laboratory tests, including haematology, clinical chemistry, pregnancy test, high sensitivity C-reactive protein (hsCRP) assays were performed at screening, prior to infusion or injection of abatacept at each scheduled visit during the ST period (Days 15, 29, 57, 85, 113, 141, and 169) at 12 week intervals and at a yearly visit in the LT period. Anti nuclear antibodies (ANA) and double stranded DNA (dsDNA) assessments were conducted on Days 1 and 169. RF was assessed on the first and last day of the ST period. Laboratory tests were conducted at a central laboratory.
- Immunogenicity. Serum samples were obtained at Days 1, 85 and 169 in the ST period, and every 3 months thereafter in the LT period. Two ELISA assays was used, one to measure antibody to the whole molecule of abatacept and one for the CTLA4 portion. In the LT period, the electrochemiluminescence (ECL) assay was used.

Pivotal studies that assessed safety as a primary outcome

The Phase IIIb Studies IM101167 (withdrawal) and IM101185 (switch) were studies that assessed safety as a primary outcome. In addition, the two open label LT extension studies, IM101063LT and IM101173LT, were primarily safety studies. These are discussed with the pooled safety data. The safety variables assessed in these studies were AEs, vital signs, physical examination, body weight, breast palpation (and screening if applicable), pregnancy tests, haematology, clinical chemistry and urinalysis. Immunogenicity was assessed in all studies and ANA, dsDNA and RF were also assessed in IM101167.

Dose-response and non pivotal efficacy studies

Not applicable.

Other studies evaluable for safety only

Clinical pharmacology studies:

- Study IM101013: a Phase I single dose PK and tolerability in healthy subjects, provided data on AEs, vital signs, electrocardiograms (ECGs), haematology and clinical chemistry. Study IM101128 was a follow up to assess immunogenicity and only serious AEs (SAEs) were assessed, of which there were none.
- Study IM101063: a PK, safety and immunogenicity in subjects with active RA receiving DMARDs treated for 12 weeks, provided data on AEs, vital signs, ECGs, haematology, clinical chemistry and urinalysis.
- Study IM101173: an immunogenicity study with 4 months treatment duration, provided data on AEs, vital signs, physical examination, body weight, haematology, clinical chemistry, urinalysis, ANA and dsDNA.

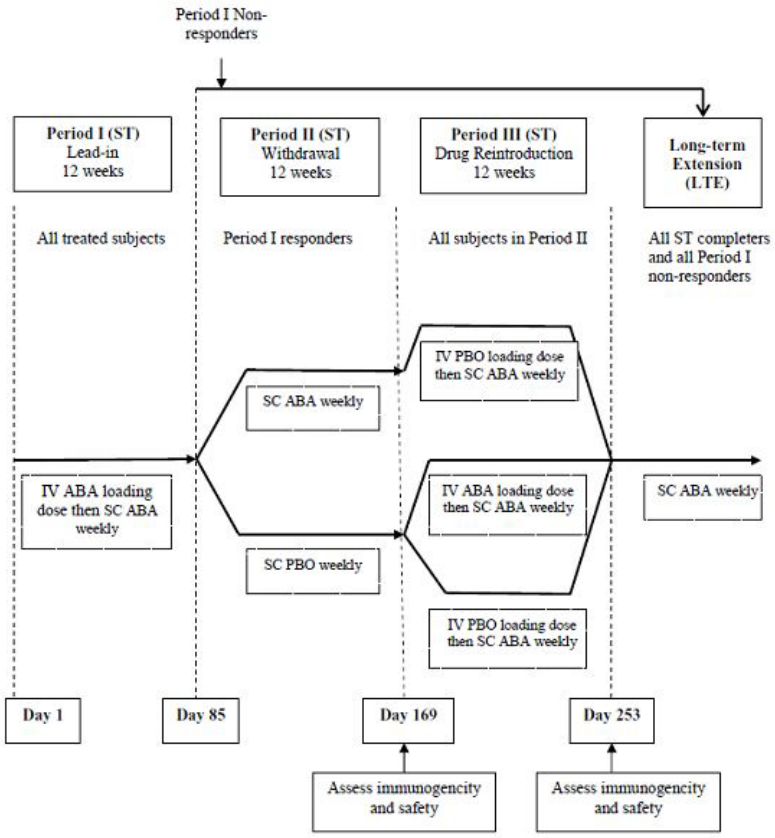
Pivotal studies that assessed safety as a primary outcome

Study IM101167

Study design, objectives, locations and dates

IM101167 was a Phase IIIb, multicentre, randomised, withdrawal study to evaluate the immunogenicity and safety of subcutaneously administered abatacept in adults with active RA on MTX. It was conducted between November 2007 and July 2009 at 32 sites in the USA, Canada, South Africa, Argentina and Mexico. There was a ST period consisting of three 12 week periods. In Period I, subjects received weekly open label SC abatacept 125 mg after a single IV loading dose of abatacept. In Period II, subjects who were responders at the end of Period I (decrease from baseline in DAS28-CRP of ≥ 0.6) were randomised 2:1 to double blind, weekly SC placebo or SC abatacept. In Period III, all subjects received weekly open label SC abatacept with a single IV loading dose of abatacept or placebo. After completing Period III, subjects could enter the open label, LT extension of weekly SC abatacept (Figure 25).

Figure 25: Design of Study IM101167.



The primary objective was the assessment of safety and immunogenicity in subjects where, after clinical response, SC abatacept was withdrawn for 12 weeks or maintained for 12 weeks. Secondary objectives were safety and immunogenicity after reintroduction of SC abatacept, the effect of immunogenicity on trough abatacept serum concentration and efficacy assessments during Period I and II.

Inclusion and exclusion criteria

Adult subjects needed to be taking a dose of ≥10 mg MTX for at least 3 months. Other inclusion and exclusion criteria were essentially the same as IM101174.

Study treatments

All enrolled subjects received weekly SC abatacept 125 mg (or SC placebo for those randomised to it in Period II). Loading doses of weight-based IV abatacept were given on Day 1 and Day 169 (or IV placebo on Day 169). Subjects also received background MTX (minimum 10 mg/wk).

Safety variables and outcomes

The main safety variables were AEs, clinical laboratory evaluations (haematology, clinical chemistry, urinalysis, pregnancy test), ANA and dsDNA, vital signs and body weight. The main efficacy variable was DAS28-CRP.

Randomisation and blinding methods

A central randomisation system was used for subject enrolment. Period II was double blind with matching placebo for SC administration. Subjects were randomised in a 2:1 ratio of SC placebo to SC abatacept. At the start of Period III the loading dose of IV abatacept or IV placebo was single blind and the hospital pharmacist prepared the solution and so was aware of treatment allocation, although this was not revealed to other study staff. Subjects who received SC placebo in Period II, were randomised in a 1:1 ratio to receive a loading dose of IV abatacept or IV placebo at the start of Period III.

Analysis populations

Efficacy was analysed on the ITT population and safety base on the "as treated" population which was all subjects who had received at least 1 dose of study medication during that period. Immunogenicity was based on the as treated population who had at least 1 immunogenicity result reported.

Sample size

A sample of 105 subjects randomised in a 2:1 ratio (70 SC placebo, 35 SC abatacept) gave the study a 90% power to detect 30% difference in immunogenicity rate between the treatment group at 5% significance level.

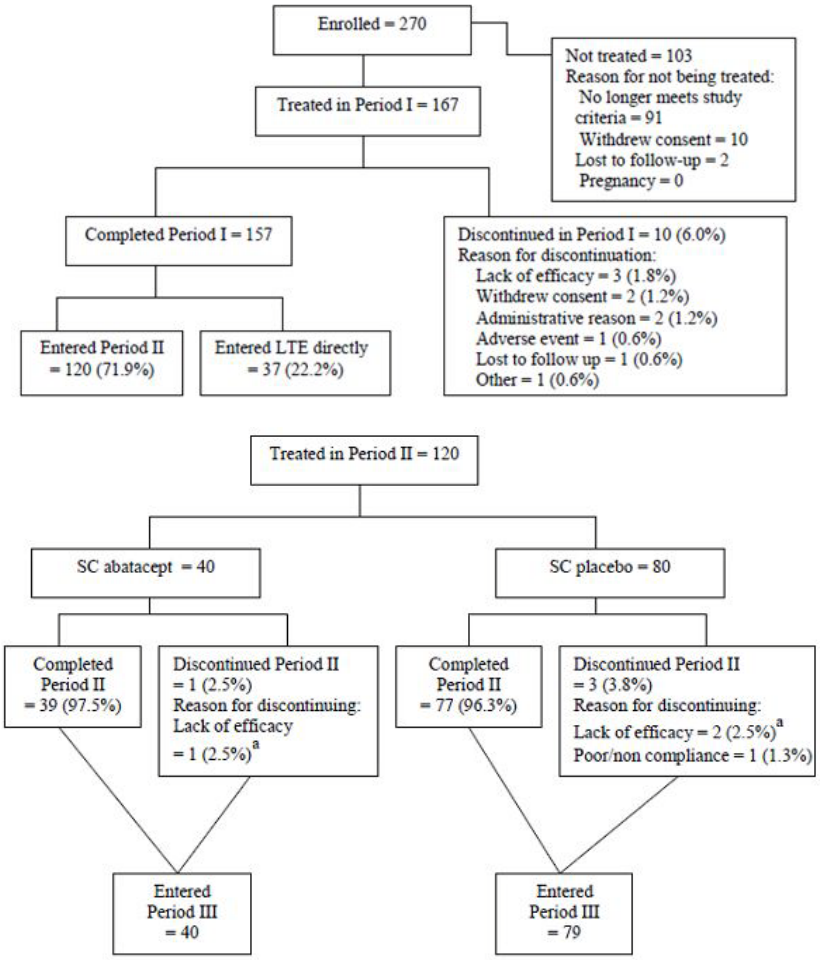
Statistical methods

A continuity corrected Chi-square test was used to compare immunogenicity rates based on the ELISA at Day 169 at a 5% significance level. A two sided 95% CI for the rate difference was calculated at Day 169 and 253. Safety and efficacy analyses were descriptive.

Participant flow

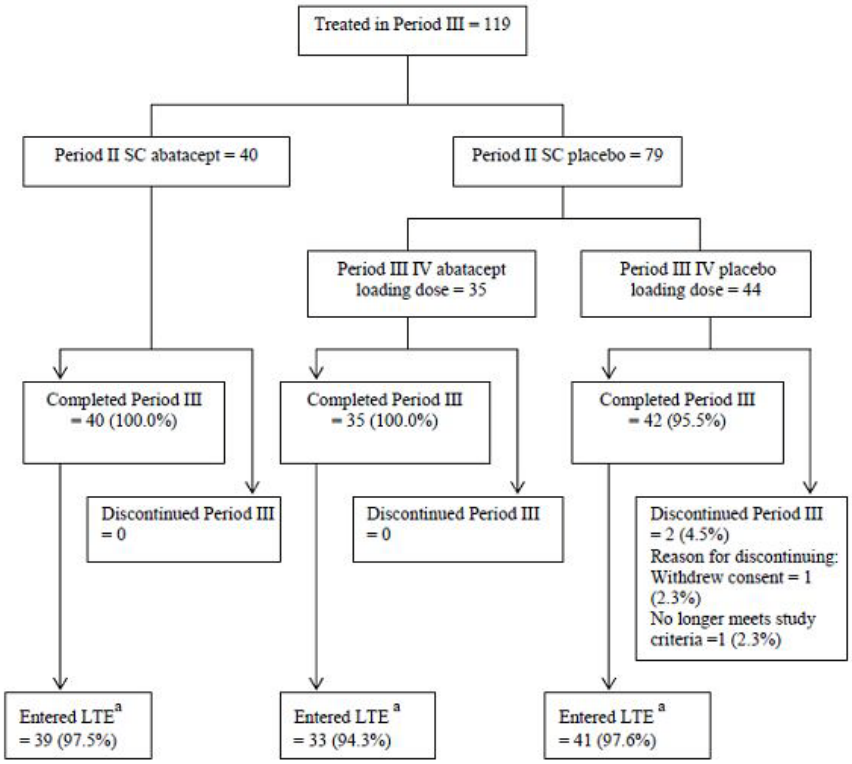
Subject disposition is in Figures 26-27. There were 167 subjects treated with open label abatacept in Period I. At the end of Period I there were 120 responders who were randomised to SC abatacept or SC placebo. There were 119 subjects treated in Period III and 150 entered the LT extension (37 after Period I and 113 after Period III).

Figure 26: Subject disposition flowchart: Period I and II (Study IM101167).



[a] One subject in SC abatacept group and 2 subjects in SC placebo group who discontinued due to 'lack of efficacy' met the criteria for disease flare during Period II. These subjects discontinued from Period II to enter Period III early.

Figure 27: Subject disposition flowchart: Period III (Study IM101167).



[a] Four subjects who completed Period III did not enter the LTE due to lack of effiacy (1 subject) or subjects elected not to continue because the site closed at the end of the ST period (3 subjects).

Major protocol violations/deviations

Twenty subjects had significant protocol deviations during the ST period with 12 in Period II of whom 5 (12.5%) and 7 (8.8%) were in the SC abatacept and SC placebo groups, respectively.

Baseline data

Subjects entering Period II were balanced on baseline characteristics. Most were White (94.2%), female (84.2%), with a mean age of 49 years and mean weight of 68.6 kg. The mean baseline DAS28-CRP score was 4.8. Exposure to study medication and other anti-rheumatic medication during Periods II and III was comparable between groups.

Results for the primary safety outcome

At Day 169, none of the SC abatacept group had a positive antibody response. There were 7/73 (9.6%) of the SC placebo group who were positive, 1 (1.4%) to abatacept and 6 (8.2%) to CTLA4-T. The difference of 9.6% (95% CI: 0.8, 18.3) was not significant (p=0.119). At Day 252, there was 1/38 (2.6%) and 2/73 (2.7%) subjects in the SC abatacept and SC placebo groups, respectively, with a positive antibody response. The treatment difference was 0.11% (95% CI: -8.21, 8.43). All 3 had anti-CTLA4-T antibodies.

Results for other safety outcomes

There was one death from a pulmonary thromboembolism (Period I) in a subject with cellulitis. This was deemed unrelated to study treatment. In Period I, there were three subjects with SAEs (1.8%); cholelitiasis, fatigue and pulmonary embolism/cellulitis. In Period II, there were two (2.5%) subjects with SAEs in the placebo group and none in the

abatacept group. The AE rate was 32.5% and 36.3% and the rate of infections was 12.5% and 8.8% in the SC abatacept and SC placebo groups, respectively. In Period III, the AE rate was 37.5% and 41.8% in the SC abatacept and SC placebo groups, respectively, and there were no local injection site reactions or acute infusional events when SC abatacept was reintroduced, although there was one peri infusional event and one systemic injection reaction in the SC placebo group. There were no safety issues identified from laboratory data, no malignancies and no autoimmune disorders.

Study IM101185

Study design, objectives, locations and dates

Study IM101185 was a Phase IIIb, multicentre, open label, single arm study evaluating the safety of abatacept in 123 subjects who switched from IV to SC therapy. It was conducted between May 2008 and January 2010 at 32 sites in the USA, Canada and Mexico. The primary objective was safety assessment at Day 85 (3 months) after switching to SC abatacept. Immunogenicity and PK were secondary objectives and efficacy a tertiary objective. After a screening visit subjects entered a 12 month ST period which was followed by a LT extension period until the product becomes commercially available.

Inclusion and exclusion criteria

Subjects were recruited from the open label LT extension periods of IV abatacept Studies IM101102 and IM101029. These were subjects with active RA and inadequate response to MTX or who had failed anti TNF therapy, respectively. All had received IV abatacept for at least 4 years.

Study treatments

Concomitant DMARDs and NSAIDs were maintained at stable doses to Day 85, other biologics, cyclosporine, D-penicillamine, mycophenylate mofetil and immunoadsorption columns were prohibited. Subjects self administered (if able) weekly SC abatacept (125mg/syringe). The first dose was within 4 weeks of the last IV infusion.

Safety variables and outcomes

The main safety variables were AEs, SAEs, vital signs and clinical laboratory results. The proportion of subjects with positive anti-abatacept and anti CTLA4 antibodies on ELISA in the first 3 months of SC abatacept compared to historical IV abatacept data. Efficacy assessments were DAS28-CRP, HAQ-DI score, LDAS and remission proportions, and mean change in hsCRP.

Randomisation and blinding methods

The study was open label and single group.

Analysis populations

Safety and efficacy analysis was based on the all treated population, immunogenicity was based on subjects with at least one SC abatacept injection and at least one immunogenicity result. Primary analysis was on data to Day 85.

Sample size

A sample size of 200 was targeted, there were no sample size calculations.

Statistical methods

Data analysis was descriptive.

Participant flow

There were 126 subjects screened and 123 enrolled, all of whom received at least 1 dose of SC abatacept and 120 (97.6%) who completed three months of SC treatment. At Day 85, three (2.4%) subjects had prematurely discontinued.

Major protocol violations/deviations

Protocol deviations were not recorded.

Baseline data

The mean age was 54.3 years, 95.1% were White, 82.1% female and 70.0% weighed between 60 and 100 kg. Subjects had low disease activity at enrolment (after approximately 5 years of IV abatacept treatment) with mean tender joint count 8.9, mean swollen joint count of 4.8, DAS28-CRP score of 3.39, HAQ-DI score of 0.94 and hsCRP of 0,93 mg/dL. At enrolment, 37.4% of subjects were on corticosteroids (mean dose 2.3 mg), 71.5% on NSAIDs and 82.1% on DMARDs (77.2% MTX). During the first three months, 92.7% of subjects received all scheduled SC injections. Anti rheumatic medications received up to Day 85 were consistent with those at study entry as were those received up to the last dose of SC abatacept (20 months of cumulative treatment).

Results for the primary safety outcome

During the first three months (Day 85), there were no deaths, malignancies or autoimmune disorders. There was one SAE (worsening RA). AEs were reported in 39.8% with 8.9% assessed as treatment related. Infections were reported in 16.3% of subjects, none were severe or resulted in treatment withdrawal. Local injection site reactions or systemic reactions within 24 hours occurred in 1.6% (n=2) of subjects.

Results for other safety outcomes

After the cumulative treatment period of up to 20 months, 3.6% of subjects withdrew. There were no deaths and 13 (10.6%) subjects with SAEs of which 2 were deemed treatment related (sarcoidosis and pneumonia). The subject with sarcoidosis discontinued treatment. There were 2 (1.6%) malignancies (breast and uterine cancer). There were no notable laboratory findings.

Patient exposure

Safety data in the dossier was analysed in three ways: a comparison of SC to IV abatacept in the ST period of IM101174 (739 SC abatacept and 721 IV abatacept); the cumulative SC population based on pooled data from the five Phase II and III studies which provides long term data; and data from special groups from individual studies. The comparator for the cumulative SC population was the LT cumulative IV safety population which includes 12,132 person years of exposure with 1165 subjects with at least 5 years of exposure.

In the comparative SC/IV populations (IM101174) the mean exposure to SC and IV abatacept was 166.5 days and 165.6 days, respectively. In the Phase II/III program, there were 1915 subjects in the ST and 1783 in the LT period, with a cumulative total of 1879 subjects exposed to SC abatacept for 1945 patient years. The mean duration of exposure was 12.6 months with a range of 2 to 47 months.

Adverse events

All adverse events (irrespective of relationship to study treatment)

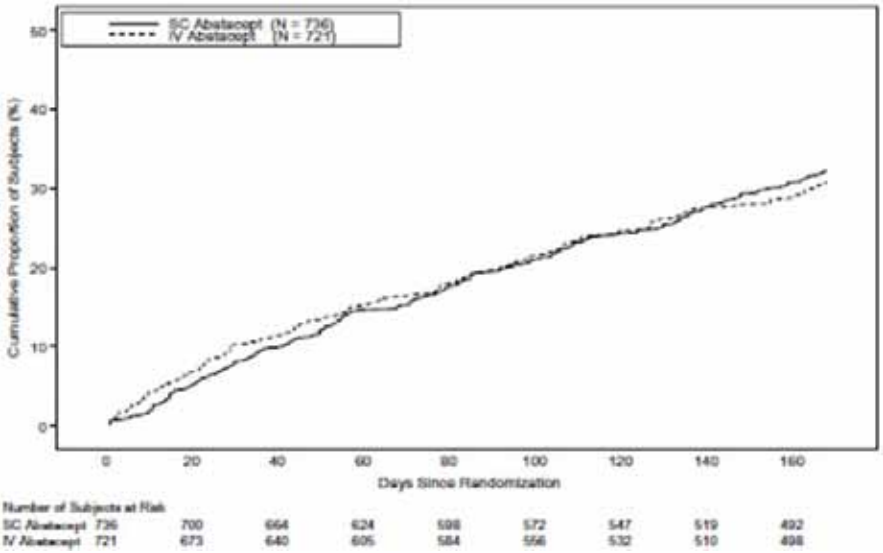
Pivotal studies

In the ST period of IM101174, the AE rate was 67.0% and 65.2% in the SC abatacept and IV abatacept groups, respectively. AEs reported in ≥5% of subjects were headache (6.0%

versus 7.6%), nasopharyngitis (5.6% versus 5.8%), Upper respiratory tract infections (URTI; 4.8% versus 5.1%), diarrhoea (4.1% versus 5.7%) and nausea (5.3% versus 3.1%). Severe AEs were slightly more frequent with SC abatacept (4.8% versus 3.3%).

Infections: AE in the SOC of infections/infestations occurred at a similar rate (31.8% versus 30.7%). Only sinusitis occurred with a more than 2% increase in the SC abatacept compared to the IV abatacept group (3.4% versus 0.8%). The time to first infection in the ST period was similar between groups (Figure 28). Most infections were mild or moderate with 7 (1.7%) subjects in the SC abatacept group and 6 (0.8%) in the IV abatacept group having a severe infection related AEs. There was one staphylococcal sepsis leading to death in the SC abatacept group and two cases of very severe pneumonia in the IV abatacept group. There were also two cases of severe herpes zoster in the SC abatacept group and one severe varicella in the IV abatacept group.

Figure 28: Kaplan-Meier curve for time from start of SC abatacept to first occurrence of infection during the ST period: all randomised treated subjects (Study IM101174).



Malignancies and Autoimmune disorders: The rate of malignancies was similar in the SC abatacept group compared to the IV group (0.4% versus 0.7%). The rate of autoimmune disorders was also similar (1.0% versus 0.8%).

Injection reactions: Pre-specified systemic injection reaction AEs occurring within 24 hours of SC injection occurred at a similar rate (7.6% versus 7.8%) and were mainly headache (2.6% versus 3.2%) and nausea (1.6% versus 1.8%). Local injection site reactions were also similar between SC abatacept and SC placebo (2.6% versus 2.5%), though injection site erythema (0.7% versus 0.1%) and pruritus (0.8% versus 0.1%) were more frequent with SC abatacept.

Infusion reactions: Acute infusion reactions (with one hour) occurred in 2.7% and 2.2% of the SC abatacept and IV abatacept groups, respectively, with 2 cases in each group that were severe. Pre-specified reactions with 24 hours of infusion occurred in 8.0% and 8.2% of the groups, respectively, and were mainly headache and nausea.

Other studies - Cumulative

In the cumulative SC period, AE were reported in 67.4% of subjects with an incidence of 144.36 per 100 patient years. The most frequent (≥5% of subjects) were URTI (8.4%), nasopharyngitis (7.4%), urinary tract infections (UTI; 5.8%), bronchitis (5.7), sinusitis

(5.4%) and headache (5.4%). The frequency of mild, moderate, severe and very severe AEs was 28.6%, 30.2%, 7.7% and 0.9%, respectively.

Infections: Overall, infections/infestations SOC AE occurred in 40.2% of subjects with an incidence rate of 54.94 per 100 pattine years (p-y). The sponsor reported the historical cumulative incidence rate in the LT IV abatacept population was 75.68 per 100 p-y. The most common infections were URTI (8.4%), nasopharyngitis (7.4%), UTI (5.8%), bronchitis (5.7%) and sinusitis (5.4%). Severe or very severe infections included pneumonia, gastroenteritis, UTI, herpes zoster, swine influenza, wound infection, cellulitis, pelvic inflammatory disease, perinephric abscess, Ludwig's angina, staphylococcal sepsis and pneumocystis jiroveci pneumonia. Frequent herpetic events included herpes zoster (1.4%), oral herpes 1.0%, and herpes simplex 0.5%.

Malignancies: The malignancy frequency was 1.1% with an incidence of 1.04 per 100 p-y and excluding non melanoma skin cancer (NMSC) was 0.46. The historical IV abatacept population had a reported rate of 1.42 and 0.73 per 100 p-y, respectively. There were five cases leading to discontinuation: B cell lymphoma, uterine cancer, lung adenocarcinoma, lung malignancy and breast cancer.

Autoimmune disorders: These occurred in 0.9% of subjects with an incidence of 0.88 in the cumulative SC period compared to 1.99 in the IV abatacept historical population. One event, vasculitis, was considered severe and one, sarcoidosis, serious and led to discontinuation. The subject with sarcoidosis (Study IM101185) was positive for anti-CLTA4-T antibodies. The most frequent autoimmune disorders were psoriasis (three subjects, 0.2%) and Sjorgren's syndrome (two subjects, 0.1%).

Injection reactions: Systemic injection reactions occurred in 7.0% of subjects with an incidence of 7.21 per 100 p-y. The reactions were mainly headache (1.7%), nausea (1.2%), hypertension (1.1%) and dizziness (0.9%). There was one case of angioedema (moderate severity and led to discontinuation) and two cases of severe headache. Local site reactions (3.1% of subjects) had an incidence of 3.09 per 100 p-y with two cases leading to discontinuation.

Infusion reactions: After the IV abatacept loading dose, acute reactions were reported in 1.6% of subjects and included urticaria (0.4%) and increased blood pressure (0.3%). Peri infusional AE were reported in 3.6% of subjects.

Treatment related adverse events (adverse drug reactions)

Pivotal studies

Treatment related AE occurred in 27.7% and 29.1% of the SC abatacept and IV abatacept groups, respectively, and the largest SOC was Infections and Infestations (11.3% versus 12.3%). The most frequent treatment related AE were headache (2.2% versus 4.0%), URTI (2.0% versus 1.8%), bronchitis (1.6% versus 2.1%), and diarrhoea (1.1% versus 2.2%).

Other studies - cumulative

Treatment related AE were reported in 27.6% of subjects with an incidence of 33.97 per 100 patient years (p-y). The most frequent were again Infections, particularly URTI (3.4%) and bronchitis (2.2%). Most were mild (14.3%) or moderate (11.6%) with 1.5% severe and 0.2% very severe. The three very severe AE were gastroenteritis, pneumocystis pneumonia and staphylococcal sepsis.

Deaths and other serious adverse events

Pivotal studies

In the ST period of IM101174 there were six deaths: five on IV abatacept (two pneumonia, subarchnoid haemorrhage, gall bladder cancer, and intestinal infarction) and one on SC abatacept (staphylococcal sepsis) (Table 4). There were four deaths in the LT period (motor vehicle accident, respiratory failure and bilateral pulmonary fibrosis, acute myocardial infarction and one of unknown cause). The SAE rate was 4.2% and 4.9% in the SC abatacept and IV abatacept groups, respectively. The most common SAEs were myocardial infarction (0.4% versus 0.1%) and pneumonia (0.1% versus 0.4%).

Table 4: AEs with outcome of death: ST period (Study IM101174).

Subject No. (Age/Sex)	Treatment	Cause of Death	Study Day	Relationship
IM101174-113-563 (76/F)	IV Abatacept	Pneumonia	42	Possible
IM101174-126-766 (51/F)	IV Abatacept	Subarachnoid Hemorrhage	15	Unlikely
IM101174-206-652 (64/F)	IV Abatacept	Gallbladder Cancer Metastatic	179	Unrelated
IM101174-215-252 (49/M)	IV Abatacept	Pneumonia	29	Unrelated
IM101174-217-1661 (67/M)	IV Abatacept	Intestinal Infarction	81	Unrelated
IM101174-219-1418 (66/F)	SC Abatacept	Staphylococcal Sepsis	146	Probable

Abbreviations: F = Female; IV = intravenous; M = male; SC = subcutaneous
Relationship: Certain, Probable, Possible, Unlikely, Unrelated

Other studies - cumulative

There were nine (0.5%) deaths in the cumulative SC data with an incidence rate of 0.46 per 100 p-y. The additional deaths (apart from the ones in Study IM101174 listed above) were cardiac arrest, pneumonia, pneumonia/acute renal failure, upper gastrointestinal haemorrhage and pulmonary embolism (with associated cellulitis) (Table 5). SAE occurred in 8.6% of subjects with an incidence rate of 8.63 per 100 p-y. The most frequent SAE, by SOC, were Infections/Infestations (2.1%), Musculoskeletal disorders (1.5%) and Neoplasms (1.2%) (Table 8.4, p**Error! Bookmark not defined.**). Treatment related SAE occurred at a rate of 1.91 per 100 p-y, with the most frequent being pneumonia (0.4%), herpes zoster (0.1%), lobar pneumonia (0.1%), UTI (0.1%) and breast fibroadenoma (0.1%).

Table 5: AEs with outcome of death: cumulative SC period.

Subject No. (Age/Sex)	Treatment/ Dose	Cause of Death	Study Day	Relationship
IM101063-6-5 (57/F)	SC abatacept 75 mg[a]	Cardiac Arrest[b]	996	Unlikely
IM101063-11-13 (79/M)	SC abatacept 125 mg[a]	Death[c]	1055	Unlikely
IM101063-16-5 (51/M)	SC abatacept 125 mg[a]	Pneumonia	424	Possible
IM101167-41-175 (70/F)	SC abatacept	Upper Gastrointestinal Hemorrhage	427	Unlikely
IM101167-52-259 (55/F)	SC abatacept	Pulmonary Embolism	99	Unrelated
IM101174-130-646 (74/M)	IV abatacept ST/ SC abatacept LT	Road Traffic Accident	416	Unrelated
IM101174-162-635 (49/F)	SC abatacept	Respiratory Failure	353	Unrelated
IM101174-232-2040 (56/M)	SC abatacept	Acute Myocardial Infarction	172	Unrelated
IM101174-258-2244[d] (50/M)	SC Abatacept	Unknown*	303	Not reported*

a Treatment groups represent SC abatacept dose received weekly during the variable-dose phase of the LT period.[6]

b Death reported after the 56-day post dose period in the fixed dose period.

c Subject IM101063-11-13 reported SAEs of lobar pneumonia (Day 1041) and acute renal failure (Day 1041).

d Subject IM101174-258-2244 died in the LT period however the event was reported in the ST period due to incomplete AE onset date at the time of database lock.

* The cause of death, treatment required, and the action taken regarding study medication were not available.

Abbreviations: F – Female; IV – intravenous; M – male; SC – subcutaneous

Relationship: Certain, Probable, Possible, Unlikely, Unrelated

Discontinuation due to adverse events

Pivotal studies

In the ST period of IM101174, the discontinuation rate due to AE and SAE was slightly lower in the SC abatacept group compared to the IV abatacept group (2.0% versus 3.5% and 1.1% versus 1.9%, respectively). The most frequent AE leading to discontinuation were pneumonia (three subjects) and UTI (two subjects), all of whom were in the IV abatacept group.

Other studies

In the cumulative SC safety data, AE led to treatment discontinuation in 2.4% of subjects with an incidence rate of 2.37 per 100 p-y. The most frequent were cellulitis (0.2%), URTI (0.1%), MI (0.1%) and headache (0.1%). SAE led to the discontinuation of 1.3% of subjects, with an incidence of 1.23 per 100 p-y. The most frequent were pneumonia and myocardial infarction (0.1% each).

Laboratory tests

Liver function

Pivotal studies

There were no cases of alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 5x ULN (Upper Limit of Normal), 5 cases in each group of AST > 3x ULN and 12 and 16 subjects in the SC abatacept and IV abatacept groups, respectively, with ALT > 3x ULN.

Other studies

Increase in AST and ALT[7] occurred in 0.6% and 1.5% of subjects, respectively with a mean change from baseline to day 365 of 1.89 and 1.51 U/L, respectively.

Kidney function

Pivotal studies

There were no cases of serum creatinine >3x ULN, and 19 and 20 subjects in the SC abatacept and IV abatacept groups, respectively, had an elevation of >1.5x baseline value.

Other studies

A high creatinine value[8] was reported in 3.2% of subjects in the integrated SC population and the mean change from baseline at Day 365 was 0.03 mg/dL.

Other clinical chemistry

Pivotal studies

Low potassium[9] occurred in 1.2% and 1.3% of the SC abatacept and IV abatacept groups, respectively.

Other studies

Cumulative data on other parameters were not reported.

Haematology

Pivotal studies

During the 6 month treatment period in IM101174, there were slightly more SC abatacept subjects with low leucocytes[10] (0.8% versus 0.3%). Two cases in the SC abatacept and one case in the IV abatacept group had a temporal association with injection. One subject in the SC abatacept group had markedly low platelet counts (47-92 x 10^9 c/L).

Other studies

In cumulative SC data, the rate for a low leucocyte count was 1.1%, low haemoglobin[11] was 0.4% and a low platelet count[12] was 0.1%. At Day 365, the mean change from baseline in haemogloblin was 0.52 g/dL, the mean change from baseline in platelets was -56.9 x 10^9/L, and the mean change from baseline in leucocytes was -0.82 x10^3/uL.

Autoimmunity biomarkers

Pivotal studies

In Study IM101174, the conversion rate in ANA from positive at baseline to negative at Day 169 was 65.2% and 40.9% of the SC abatacept and IV abatacept groups, respectively. The rate of conversion from negative ANA at baseline to positive at Day 169 was 5.4% and 4.8%, respectively. The conversion from positive to negative anti dsDNA was 41.1% and 48.1%, respectively, and from negative to positive anti dsDNA was 4.2% and 5.1%.

[7] High AST or ALT was defined as >3 x ULN or if pre-treatment was > ULN then > 4x pre-treatment.
[8] High serum creatinine was defined as >1.5 x pre-treatment value.
[9] Low potassium was defined as < 0.95 x LLN or if pre-treatment < LLN then < 0.95 x pre-treatment value.
[10] Low leucocytes was defined as <0.75 x LLN or if pre-treatment was < LLN then <0.8 x pre-treatment value.
[11] Low haemoglobin was defined as >3 g/dL decrease from pre-treatment.
[12] Low platelets was defined as <0.67 x LLN.

Other studies

In the cumulative SC data, the conversion from positive to negative ANA was 35.6% and from negative to positive was 6.0%. Of those who were positive to anti dsDNA at baseline, 42.0% converted to negative. In addition, 4.0%, converted from negative to positive dsDNA.

Vital signs

Pivotal studies

Vital signs were similar between groups and over the ST period in Study IM101174.

Other studies

There were no remarkable findings on the mean values for systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate or temperature over the cumulative SC period.

Weight

Pivotal studies

In Study IM101174, 25% of subjects were <60 kg, 67% were 60 to 100 kg and 8% were >100 kg. Subjects weighing >100 kg had a higher rate of AE (77.6% and 77.4% in the SC and IV abatacept groups, respectively) than subjects in the lower weight groups (60-100 kg: 66.1% and 63.4%, <60 kg: 66.1% and 66.5%). The incidence of Infection/Infestation SOC AE was also higher in those >100 kg (44.8% and 43.4% compared to 27.6%-35.2%). When treated with SC abatacept compared to with IV abatacept, subjects with low body weight (<60kg) did not have a higher rate of AE (66.1% versus 66.5%), SAE (4.8% versus 6.1%) or discontinuations due to AE (1.1% versus 5.0%). There were slightly higher rates of local injections site reactions (3.8% versus 0.6%) and systemic injection reactions (8.1% versus 6.1%). These rates were, however, not markedly different to those seen in the other body weight groups with SC abatacept (local reactions 2.0-3.4% and systemic reactions 6.9-7.5%). Examination of data by body weight quartiles showed similar findings. Data for the lowest weight group (<40 kg, ≥40 - <50 kg, ≥50 - <60 kg) showed the that the burden of infections was no greater than in the higher weight subjects, though the numbers were small.

Other studies

In the cumulative data, there were 24%, 67% and 8% of subjects in the <60kg, 60-100 kg and >100 kg weight groups, respectively. The mean duration of exposure to SC abatacept was 12.4, 12.5 and 13.7 months, respectively. Table 6 has a summary of safety events, exposure and incidence rates by weight group. Of note, there is an increased incidence of AE, SAE and AE in the Infection/Infestation SOC in subjects weighing >100 kg compared to those weighing less than this. There were no evident safety signals low body weight subjects. The numbers in the very low body weight group, <40 kg, were very small (n=8).

Table 6: Summary of safety events by weight group: cumulative SC period.

Baseline Weight	SC Abatacept Exposure			
	Subjects with Event (%)	Exposure (p-y)	Incidence Rate (per 100 p-y)	Poisson 95% CI
< 40 kg (N = 8)				
AEs	5 (62.5%)	3.80	131.48	(54.73, 315.88)
SAEs	2 (25.0%)	6.41	31.20	(7.80, 124.77)
Infections and Infestations	1 (12.5%)	7.08	14.13	(1.99, 100.31)
≥ 40 - < 50 kg (N = 105)				
AEs	64 (61.0%)	56.16	113.96	(89.20, 145.60)
SAEs	12 (11.4%)	102.70	11.68	(6.64, 20.57)
Infections and Infestations	31 (29.5%)	86.55	35.82	(25.19, 50.93)
Malignant Neoplasms	1 (1.0%)	106.54	0.94	(0.13, 6.66)
Autoimmune Disorders	2 (1.9%)	106.60	1.88	(0.47, 7.50)
≥ 50 - < 60 kg (N = 337)				
AEs	225 (66.8%)	160.36	140.31	(123.12, 159.89)
SAEs	21 (6.2%)	334.89	6.27	(4.09, 9.62)
Infections and Infestations	125 (37.1%)	251.73	49.66	(41.67, 59.17)
Malignant Neoplasms	1 (0.3%)	342.11	0.29	(0.04, 2.08)
Autoimmune Disorders	1 (0.3%)	341.94	0.29	(0.04, 2.08)
< 60 kg (N = 450)				
AEs	294 (65.3%)	220.32	133.44	(119.03, 149.60)
SAEs	35 (7.8%)	444.00	7.88	(5.66, 10.98)
Infections and Infestations	157 (34.9%)	345.36	45.46	(38.88, 53.16)
Malignant Neoplasms	2 (0.4%)	456.19	0.44	(0.11, 1.75)
Autoimmune Disorders	3 (0.7%)	456.08	0.66	(0.21, 2.04)
≥ 60 to ≤ 100 kg (N = 1264)				
AEs	842 (66.6%)	604.66	139.25	(130.16, 148.98)
SAEs	100 (7.9%)	1252.93	7.98	(6.56, 9.71)
Infections and Infestations	506 (40.0%)	927.72	54.54	(49.99, 59.51)
Malignant Neoplasms	15 (1.2%)	1289.53	1.16	(0.70, 1.93)
Autoimmune Disorders	11 (0.9%)	1294.38	0.85	(0.47, 1.53)
> 100 kg (N = 162)				
AEs	128 (79.0%)	51.79	247.17	(207.85, 293.92)
SAEs	25 (15.4%)	165.78	15.08	(10.19, 22.32)
Infections and Infestations	90 (55.6%)	101.97	88.26	(71.78, 108.51)
Malignant Neoplasms	2 (1.2%)	179.11	1.12	(0.28, 4.46)
Autoimmune Disorders	3 (1.9%)	180.11	1.67	(0.54, 5.16)

Source: SCS-A - Appendices 3.14, 3.16, 6.7, 6.9, 7.2, 7.4, 7.8, 7.10, 7.16, and 7.18.
Abbreviations: AE = adverse event; CI - confidence interval; p-y = person-years; SAE = serious adverse event; SC = subcutaneous

Gender

Pivotal studies

Subgroup safety analysis by gender was not provided.

Other studies

The rates of AEs, SAEs and discontinuation due to AEs were similar between males and females.

Age

Pivotal studies

Subgroup safety analysis by age was not provided.

Other studies

The rate of AEs, SAEs and discontinuations due to AE increased with increasing age. The incidence per 100 p-y of discontinuation due to AEs was 12.1 in those aged ≥75 years, compared to 5.7 in ≥65 years and 1.8 in the < 65 year age group.

Race

Pivotal studies

Subgroup safety analysis by age was not provided.

Other studies

The majority to subjects were White (78%), with only 4% Black and 8% Asian. There was a higher rate of AEs, SAEs and discontinuations in Black subjects, compared to White, though the numbers were small (n=75).

Postmarketing experience

No data was provided.

Safety issues with the potential for major regulatory impact

Unwanted immunological events

Blood samples for immunogenicity were collected for ELISA and ECL assays. Both the ELISA and ECL assays were used in the SC abatacept development program. In general, ELISA was used in the ST study periods of Studies IM101174, IM101173, IM101167, IM101185 and IM101063 (and LT in this study) and the ELC assay in the ST and LT periods of Studies IM101173, IM101167 and IM101185. ECL was also used in the LT period of Study IM101174 and in 10% of the ST period subjects. As the ECL assay is more sensitive and was introduced during the development of SC abatacept, the sponsor reported that the ELISA was used to compare the ST study period data to historical IV abatacept data, while the ECL assay was used for immunogenicity assessment with the LT study periods. The integrated ELISA (or ECL) immunogenicity population included all subjects who received at least 1 dose of study medication and had at least one postbaseline immunogenicity result by ELISA (or ECL) reported. Seropositive defined as having a positive response for anti CTLA4-T and/or anti abatacept antibodies. Data was assessed on treatment (from Day 2 to 21 days post last dose) and post treatment (from Day 22 post last dose of SC abatacept).

Results for ELISA: In Study IM101174 ST period, the immunogenicity rates were 1.1% (8/725) and 2.3% (16/710) of the SC and IV abatacept groups, respectively. In the SC abatacept group, 0.4% and 0.7% were positive for anti abatacept and anti CTLA4-T antibodies, respectively, and in the IV abatacept group the rates were 0.7% and 1.5%, respectively. Anti abatacept titres ranged from 434 to 1273 with SC abatacept and 416 to 2783 with IV abatacept. While on treatment, anti CTLA4-T titres ranged from 25-33 and from 41-174 in the two groups, respectively, and there was a small rise in titres on post treatment samples (53-200 and 58-726, respectively). In subjects weighing <60 kg the immunogenicity rates were similar (1.6% versus 1.8% in the SC and IV abatacept groups, respectively). There were no reported hypersensitivity reactions or autoimmune disorders in the seropositive subjects.

In the ST period of IM101173, the immunogenicity rates were 3.8% and 4.1% in the SC abatacept+MTX and SC abatacept monotherapy groups, respectively. There were no safety events identified that were possibly related to seropositivity in the ST or LT periods. In IM101167 there was an increase in positive antibody response on treatment withdrawal, with 9.6% of the SC placebo group and 0% of the SC abatacept group being seropositive on

Day 169 (end of the withdrawal period). On reintroduction of abatacept, 4 of the 7 seropositive subjects became seronegative. There were no significant safety events when abatacept was reintroduced in this group.

In subjects switching from IV abatacept to SC abatacept in Study IM101185, the seropositivity rate after three months on SC abatacept was 6.6% (8/122) compared to an overall rate of 5.9% and 7.0% in the two previous feeder studies. Of the eight subjects, one had anti-CTLA4-T and 7 had anti abatacept antibodies. The subject with anti CTLA4-T antibodies was withdrawn due to serious sarcoidosis. In IM101063 there was one seropositive subject in the ST period and 6 (9.7%) in the LT period, all of whom where anti-abatacept positive.

ECL results: There were 1430 subjects with 4446 samples for evaluation in the cumulative SC period, with a mean exposure of 12.7 months (range: 1.9 to 24.7). Most data came from Study IM101174 (1046 subjects and 1872 samples). Overall, the seropositive rate was 1.7% (24/1430) with 1.2% with anti-CTLA4 and possibly Ig and 0.6% with anti Ig and/or junction region antibody. Eight subjects had a baseline titre higher than their post-baseline titre. Examination of seropositivity by weight showed no major differences, though numbers were small. The rate of seropositivity on treatment was 1.3% (18/1420) with an incidence rate of 1.23 (95% CI: 0.73, 1.94) per 100 p-y. Antibody titres were low (generally <25).

Antibody persistence (detectable antibodies at two or more consecutive visits) occurred in 4/861 (0.5%) subjects. There were 256 subjects who missed one injection and 5 (2.0%) of these had abatacept induced immunogenicity. There were 71 subjects (152 samples) with post treatment immunogenicity data and of these 9.9% (7/71) were seropositive during the follow up period (to Day 85). Titres were generally low (<25) except in 2 subjects where the titres were 104 and 58. Of the 24 seropositive subjects, nine discontinued, six of whom become seropositive in post treatment follow up and three while one treatment.

In these 24 seropositive subjects, there was one SAE (4.2%) (gastroenteritis), the AE rate was 87.5%, and the discontinuation rate due to AEs was 12.5% (3/24). The most frequent AE were in the SOC of infections (62.5% of subjects), mainly URTI. There were no local injection site reactions and 3/24 (12.5%) had systemic injection reactions (two with moderately severe rash and one moderate headache). There were no autoimmune events in this population.

List of Questions

During 2010, the TGA began to change the way applications were evaluated. As part of this change, after an initial evaluation, a List of Questions to the sponsor is generated.

Safety

1. The rate of abatacept-induced immunogenicity was noted to increase post treatment in a small sample of subjects (n=71). Was there more data available on post treatment immunogenicity and if so, the sponsor was requested to provide details of this and any related to safety issues.
2. Were there plans for further assessment of this issue as this potential risk had not been included in the draft PI nor the Risk Management Plan (RMP) and this decision needed to be explained.

Clinical Summary and Conclusions

Clinical aspects

Pharmacokinetics

The geometric means of C_{max} and AUC_{inf} of abatacept appeared to increase in a dose proportional manner in the dose range of 50 to 150 mg following administration of a single subcutaneous dose of SC dose of abatacept.

Median T_{max} values ranged from three to seven days following SC administration of abatacept and were not affected by dose.

Differences in injection volume, osmolality of drug solution and the concentration of the drug solutions had no impact on the PK of abatacept.

In subjects who did not exhibit abatacept specific antibodies, $t_{1/2}$ ranged from 11.2 to 14.7 days, and were independent of increasing dose, whereas, $t_{1/2}$ values ranged from 3.2 to 7.5 days in subjects who were seropositive.

In subjects with active RA, steady state trough serum concentrations of abatacept occurred approximately 4 to 5 weeks following the combined regimen of a single IV loading dose and weekly SC injections.

In subjects with active RA, the geometric mean steady state trough value of abatacept for subjects weighing >100 kg given 125 mg abatacept was lower than for subjects weighing ≤100 kg given 75 to 125 mg abatacept and subjects weighing >100 kg 200 mg abatacept.

In subjects with active RA, the $AUC_{7\ days}$ in subjects <60 kg given 125 mg abatacept was higher, whereas $AUC_{7\ days}$ of subjects >100 kg administered 125 mg abatacept was lower, compared to subjects <60 kg given 75 mg, subjects 60 - 100 kg given 125 mg and subjects >100 kg given 200 mg abatacept. In addition, the C_{max} in subjects > 100 kg given 125 mg abatacept was lower compared to the other treatment groups described above.

Pharmacodynamics

Eleven of 40 healthy subjects (27.5%) developed antibodies to the CTLA4 binding portion of the abatacept molecule following SC injection of either the IV or SC formulation of abatacept.

The endpoint titres in healthy subjects who received the SC formulation ranged from 33 to 106 and from 62 to 872 in subjects who received the IV formulation given SC.

No dose dependent increases in immunogenicity were observed.

In 30 healthy subjects who had been administered a subcutaneous abatacept dose approximately 3 years previously, six of which who had initially demonstrated CTLA4 T specific antibody reactivity, none of the subjects were positive for anti abatacept antibodies. In addition, none of the subjects were positive for anti CTLA4 T specific antibody.

By contrast in subjects with active RA, none of the 51 abatacept treated subjects were positive for anti CTLA4 antibody through to Day 85.

In subjects with active RA, similar improvements were observed in the mean change from baseline in the DAS 28 (CRP) scores in subjects administered SC abatacept + MTX and in subjects administered SC abatacept alone. The proportion of subjects with a Clinically Significant Improvement, defined by a reduction from baseline in the DAS 28 (CRP) score of ≥1.2, was 62.5% and 66.7%, respectively.

Although transient and infrequent positive antibody responses were observed at earlier time points, generally before Day 85, at the end of a ST study period (Day 113), none of the subjects with RA were seropositive for anti abatacept or anti CTLA4 T antibodies.

During the ST treatment period, the overall immunogenicity rate at any time in the SC abatacept monotherapy and SC abatacept + MTX cohorts was 4.1% (2/49) and 3.9% (2/51), respectively, and only one seropositive response was observed following treatment discontinuation.

There did not appear to be any correlation between the development of antibodies with clinical safety or efficacy findings.

Clinical efficacy

The efficacy of SC abatacept was based on one pivotal trial (IM101174). This was a large (n=1457), double blind, randomised, controlled, non inferiority study comparing SC to IV abatacept. The design was in line with guidance documents[13] and the non inferiority approach was an appropriate way to compare efficacy of the two routes of administration.

The study had an issue with GCP non compliance with a site in South Korea that necessitated removal of subjects (n=8) from this site from the data analysis. A revised study report was submitted. This reanalysis did not, however, alter the study's results. Rate of protocol deviations leading to exclusion from the PP analysis was low and compliance high.

The primary outcome measure was ACR 20 response at six months – a well accepted and validated composite endpoint for assessing a patient's sign and symptom response. This measure was also used in the IV abatacept studies. The non inferiority margin was -7.5% for the treatment difference on ACR 20 response at Month 6. The sponsor states this margin was discussed and agreed on with the FDA. The aim was for the SC formulation to maintain at least 70 % of the treatment effect. The estimated effect of 25% was based on the comparison of IV abatacept to placebo in Study IM101100.

The study population was adults with moderate to severe RA and an inadequate response to MTX. This population was felt appropriate as this is the currently approved patient population for IV abatacept and it was the largest group studied with IV abatacept.

IM101174 met the primary objective as SC abatacept was found to be non-inferior to IV abatacept. The ACR 20 response at six months was 76.1% with SC abatacept compared to 75.8% with IV abatacept. Results in the PP population were confirmed on the ITT population. Similar responses were seen across other efficacy measures (ACR 50 ACR 70, HAQ response, HAQ-DI, DAS28-CRP and hsCRP). In the subgroups of gender, race, geographic region, duration of RA, baseline DAS-CRP, baseline RF status and prior anti-TNF use the efficacy (as measured by ACR 20 response and HAQ response) was similar. Importantly, given the flat dosing regimen proposed, in the weight subgroups (<60, 60-100, >100 kg) efficacy was also similar between the formulations.

There were three other Phase IIIb studies included in the current submission (IM101167, IM101185 and IM101173), though the primary objective of these studies was safety and

[13] European Medicines Agency, "Committee for proprietary medicinal products. Points to consider on the clinical investigation of medicinal products other than NSAIDs for treatment of rheumatoid arthritis", December 2003, Web, accessed 12 April 2012 <http://www.emea.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003439.pdf>. European Medicines Agency, "Committee for medicinal products for human use. Guideline on the choice of non-inferiority margin", July 2005, Web, accessed 12 April 2012 <http://www.emea.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003636.pdf>.

immunogenicity. IM101167 assessed treatment withdrawal and reintroduction over three 12 week periods. For subjects in whom treatment was withdrawn there was an increase in DAS28-CRP which returned to pre withdrawal levels on treatment reintroduction. Similar results were found with HAQ-DI scores and hsCRP.

Study IM101173 was a small, open label comparison of SC abatacept monotherapy with SC abatacept with MTX. This showed similar improvements in efficacy though the design and sample size make it not possible to draw definitive conclusions.

Switching from LT (at least four years) IV abatacept to SC abatacept treatment was assessed in the open label study IM101185. Efficacy was maintained after up to one year of treatment, as demonstrated by stable results on DAS28-CRP, and HAQ-DI scores as well as LDAS and remission rates based on DAS28 CRP.

Supportive, LT efficacy data was available from three open label trials. In IM101174 the cumulative exposure was 13.8 months and study retention rates were high. During this time the response on the efficacy parameters was maintained. In IM101173LT after 18 months of treatment (Day 533), efficacy was maintained as measured by DAS28-CRP and HAQ-DI. In IM101167, efficacy on DAS28-CRP was maintained at about 15 months (Day 449). Study IM10101063LT had small numbers and limited efficacy assessments.

The lack of an IV loading dose was assessed in a randomised, controlled and blinded fashion in IM101167 and did not affect efficacy as measured by DAS28-CRP. There was no loading dose in IM101173 and while efficacy response appeared similar to other studies, the design was open label and uncontrolled.

Clinical safety

There were five main studies that contributed safety data with a pooled population of 1879 subjects. The pivotal efficacy Study IM101174 provided a direct comparison between the safety of the SC and IV formulations over six months of treatment in 1460 subjects. The pooled data provided an assessment of longer term safety with a mean exposure duration of 12.6 months.

The safety profile of the SC formulation was similar to the IV formulation with no higher rates of AE (67.0% versus 65.2%), SAE (4.2% versus 4.9%) or discontinuation due to AE (2.0% versus 3.5%). For AEs of clinical interest, the rates were comparable for infection/infestation SOC (31.8% versus 30.7%), malignancies (0.4% versus 0.7%), autoimmune events (1.0% versus 0.8%), local injection reactions (2.6% versus 2.5% SC placebo), systemic injection reactions (7.6% versus 7.8%), and acute infusional events (2.7% versus 2.2%).

A summary of the cumulative SC data is presented below in Table 7.

Table 7: Summary of subjects with AEs: cumulative SC period (integrated population) for all treated subjects.

	Cumulative SC Period N = 1879		
	Number (%) of Subjects N = 1879	Incidence Rate (per 100 p-y)	Poisson 95% Confidence Interval
Deaths	9 (0.5%)	0.46	(0.24, 0.89)
SAEs	161 (8.6%)	8.63	(7.39, 10.07)
Related SAEs	37 (2.0%)	1.91	(1.39, 2.64)
Discontinued due to SAEs	24 (1.3%)	1.23	(0.83, 1.84)
AEs	1267 (67.4%)	144.36	(136.63, 152.53)
Related AEs	518 (27.6%)	33.97	(31.17, 37.03)
Discontinued due to AEs	46 (2.4%)	2.37	(1.78, 3.16)

Source: Table 2.1.3 and SCS-A - Appendices 3.1, 3.9, 3.18, 3.19, 5.1, 6.10, 6.11
Abbreviations: AE = adverse event; p-y = person-years; SAE = serious adverse event; SC = subcutaneous

From this cumulative data, the most frequent AE were URTI, naspharyngitis, UTIs, bronchitis, sinusitis and headaches. Infections remain a major risk of treatment, occurring in 40.2% of subjects with an incidence rate of 54.9 per 100 p-y. Overall, 2.4% of subjects discontinued treatment due to an AE, with the main ones being cellulitis, URTI, pneumonia, headache and myocardial infarction.

Severe infections remained one of the notable risks with abatacept with 2.1% of subjects having an infection/infestation SAE, the most frequent of which included pneumonia and herpes zoster. There were nine deaths in the cumulative SC data with an incidence of 0.46 per 100 p-y. Malignancies occurred in 1.1% of subjects with an incidence of 0.46 per 100 p-y when NMSC was excluded. Autoimmune disorders occurred in 0.9% of subjects with the most frequent being psoriasis and Sjogren's syndrome. Injection site reactions occurred in 3.1% of subjects but only led to 2 discontinuations.

Laboratory test results were comparable between the SC and IV formulation, with mild elevations of liver function tests (AST and ALT >3x ULN in 0.6% and 1.5%, respectively) and low leucocytes (<0.75x LLN in 1.1%) the main findings.

Due to the lower overall exposure using the fixed dose regimen, but the higher trough concentrations in the low body weight group (<60 kg), safety was examined across weight subgroups. AE rates were comparable in the <60 kg and 60-100 kg groups (approximately 66%), however in those >100kg the rate of AEs were higher (77.6% versus 77.4%, SC versus IV abatacept). This trend was also seen in the cumulative data. Subjects with low body weight did not have a higher AE rate, SAE rate or AE discontinuation rate compared to the those receiving the IV formulation, though there was a higher rate of injection site reactions (3.8% versus 0.6%).

The risk of safety events and discontinuation due to AE was noted to increase with increasing age. Most subjects were White with only small proportion Black (4%) or Asian (8%). Blacks had a slightly higher rate of AE and SAE though numbers were small making conclusions in this subgroup difficult.

Switching from IV to SC formulations of abatacept was assessed in the open label Study IM101185 as well as in the long term period of IM101174 when subjects who were randomised to IV abatacept switched to SC abatacept. In both studies there were no notable safety issues associated with the switch.

Unwanted immunological events were assessed through the clinical program. In Study IM101174, the immunogenicity rate at six months was 1.1% and 2.3% in the SC abatacept

and IV abatacept groups, respectively. Rates were comparable between formulations in the low body weight (<60 kg) group (1.6% versus 1.8%). From the cumulative data (1430 subjects with 4446 samples) the seropositive rate was 1.7%. In the 24 seropositive subjects in this population, there were no reported autoimmune disorders and 12.5% had systemic injection reactions (rash and headache). There was, however, one case of sarcoidosis in a seropositive subject in IM101185.

In the small sample with available data (n=71), there was an indication of an increase in seropositivity post treatment with a rate of 9.9% at Day 85, although titres were low. The small numbers (n=30) followed up in Study IM101128 about three years after a single dose of SC abatacept make it difficult to draw conclusions on the lack of seropositivity in this group.

In the controlled Study IM101167, the withdrawal for three months of SC abatacept resulted in an immunogenicity rate of 9.6% (95% CI: 0.8, 18.3) compared to 0% in those who continued on treatment, though the difference was not statistically significant. On reintroduction of therapy the rates were comparable (2.6% versus 2.7%). There were no safety events related to hypersensitivity on treatment reintroduction. In the Phase II open label Study IM101173, immunogenicity rates were comparable between subjects receiving add on MTX or on SC abatacept monotherapy. Rates were also comparable when switching from IV to SC therapy in Study IM101185.

First round benefit risk assessment

First round assessment of benefits

The benefits of the subcutaneous formulation of abatacept in the proposed usage are:

- The injection may be self administered which allows the possibility for home use and will provide greater convenience to patients than an IV infusion.
- The flat dosing regimen, rather than a weight based one, provides prescribing ease for physicians and may result in less dosing errors.
- The efficacy and safety of the SC formulation are comparable to the registered IV formulation. The efficacy of the SC formulation was non-inferior to IV in direct comparison in a randomised controlled trial over 6 month treatment duration. The safety data was obtained from a pooled population of 1879 subjects with a mean exposure of 12.6 months and showed no new safety signals above what is known for IV abatacept.

First round assessment of risks

The risks of SC abatacept in the proposed usage are:

- The safety risk of infections, in particular serious infections such as sepsis and pneumonia, was present and comparable to what is seen with IV abatacept. Other safety risks such as malignancies, autoimmune disorders and systemic injection reactions were also present but at no greater frequency than with the IV formulation.
- The SC administration has the potential for inducing an increase in the immunogenicity of abatacept. The immunogenicity rates were, however, comparable between the SC and IV formulations. There was, however, an increase in immunogenicity following withdrawal of SC treatment.
- The SC injection may lead to local injection reactions and while this risk was not increased overall, it was increased in those weighing <60 kg.

- The fixed dosing schedule could result in increased exposure and therefore safety events in subjects with low body weight, and reduced exposure and therefore reduced efficacy in those with high body weight. Safety and efficacy were, however, comparable between the formulations across the weight groups.
- There are limited data on the use of SC abatacept with DMARDs other than MTX as this was not directly assessed in the ST studies and there were few subjects using this treatment in the LT open label extensions.

First round assessment of benefit-risk balance

The clinical development of SC abatacept included two clinical pharmacology and four Phase III efficacy, safety and immunogenicity studies which included 1963 subjects. The program was sufficiently large, well designed and conducted with adequate long term data for conclusions to be drawn.

The patient population in the pivotal efficacy study was adults with RA who had inadequate response to MTX. This population was the largest group in the IV abatacept program and so is an appropriate group for comparison of the formulations.

The non-inferiority margin in the pivotal efficacy study was 7.5%. The margin represented 70% preservation of the minimum expected benefit as measured by ACR 20. This was based on previous trials showing a treatment difference of 25% between IV abatacept and placebo in ACR 20 response. This margin was reportedly discussed with the FDA. The evaluator believes that 70% preservation of response would be the lower limit of clinical acceptability. The actual treatment difference was minimal (0.3%) and the lower bound of the 95% CI was -4.2% which was reassuring as the sponsor calculated this as preserving at least 83% of the effectiveness.

The SC formulation at a dose of 125 mg weekly resulted in systemic exposure (AUC and C_{max}) lower than the monthly IV formulation while the tough levels (C_{min}) were higher and these differences did not translate into any clinically relevant difference in safety or efficacy between the formulations. Steady state trough concentrations were a predictor of efficacy with IV abatacept and this was also shown with SC abatacept.

Unlike the IV formulation the proposed dosing schedule is not weight-based and there was a concern that this could lead to safety events in those with low weight and lack of efficacy in those with high weight. However, these concerns were not observed in the submitted data and so the flat dosing regimen is appropriate.

From PK data, it is seen that the lack of an IV loading dose leads to achievement of steady state concentrations in six to eight weeks, instead of four to five weeks. Nevertheless target C_{min} levels of at least 10 μg/mL were reached by two weeks. Assessment of a lack of loading dose on efficacy was undertaken in two studies, of which one was randomised and controlled (79 subjects), and efficacy was seen to be maintained. There is an obvious benefit for patients of avoiding the loading dose and while there is the potential for a slower onset of efficacy, the limited results indicate that this is an important treatment option for those patients who are unable to receive the IV infusion. As the clinical program was primarily conducted with an IV loading dose, and the efficacy data on its absence are limited, the evaluator recommends that the weight-based IV loading dose still be included in the dosage instructions. It is noted that this is the situation on the US label.

The safety of SC abatacept was in line with the IV formulation. The significant risk of infections is comparable to the IV formulation and is covered adequately in the draft PI and Risk management Plan (RMP). The risk of autoimmune disorders was present (0.9%, incidence 0.88 per 100p-y) although was no greater than with IV abatacept.

The SC administration has the potential for increased immunogenicity with possible consequences of hypersensitivity, injection reactions with treatment reintroduction, and antibodies directed at CTLA4 on endogenous T cells resulting in? autoimmune disease. There is also the possibility for altered drug concentrations or binding prevention thereby lowering efficacy. The concerns for increased immunogenicity were not borne out with a rate no higher than IV abatacept (1.1% versus 2.3%) and an overall rate from cumulative (ECL) data of 1.7%. Immunogenicity response was also comparable across the weight groups. Safety assessment in the small population (n= 24) of seropositive subjects (from this dataset) noted no autoimmune disorders, though there were two cases of moderate to severe rash. There was however an increase in immunogenicity on treatment withdrawal, albeit with low titres. The sponsor states the reason is not known and while it did not lead to significant safety events, the numbers were small. The evaluator therefore recommended this issue be monitored such as through specific follow up on ongoing extension studies.

The patient instructions for use of the two types of prefilled syringe are comprehensive. Despite this, it is recommended that patients be initially trained by a health professional and seen to competently self-administer prior to commencing home use. There was one case of angioedema and two cases of severe headache post injection in the cumulative SC abatacept data. The safety data do not appear to contraindicate home use of the product but, in the interest of caution, it was recommended that the first dose be done under medical supervision.

The pivotal efficacy trial with SC abatacept did not include patient taking DMARDs other than MTX. In the open label long term period, sulfasalazine, chloroquine, hydroxychloroquine, gold, or azathioprine could be used if clinically indicated however this subgroup was not assessed. Concomitant use was allowed in other LT studies and use was infrequent. As data on coadminstration of abatacept with these agents is limited, such use should remain listed under *Precautions* in the PI.

The SC formulation would provide obvious benefits in the paediatric population with JIA and so this development program should be pursued.

In summary, the clinical efficacy and safety data for SC abatacept result in a benefit-risk balance that is unfavourable given the proposed usage, but would become favourable if there is a satisfactory response to the question (see previous section) on post treatment increase in immunogenicity.

V. Pharmacovigilance Findings

Risk Management Plan

The sponsor submitted a Risk Management Plan which was reviewed by the TGA's Office of Product Review (OPR).

Safety Specification

Subject to the evaluation of the non clinical aspects of the Safety Specification (SS) by the Toxicology area of the Office of Scientific Evaluation (OSE) of the TGA and the clinical aspects of the SS by the Office of Medicines Authorisation (OMA) of the TGA, the summary of the Ongoing Safety Concerns as specified by the sponsor is shown in Table 8.

Table 8: Ongoing Safety Concerns for SC abatacept.

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

OPR reviewer comment:

The sponsor has stated that no new safety signals were identified for SC abatacept in the cumulative SC population and the safety profile observed in the SC abatacept group was similar to the IV abatacept group across safety parameters of death, SAEs, AEs/SAEs leading to early discontinuation, treatment related AEs/SAEs, and overall AEs. The sponsor also reported that there was no new safety signal identified in either treatment group relative to the known safety profile of IV abatacept in RA.

Pharmacovigilance Plan (PP)

The sponsor states that routine pharmacovigilance activities, consistent with the activities outlined,[14] are proposed to monitor all the specified ongoing safety concerns.

In regard to the conditions of registration for the IV current product, the updated RMP states that signal detection activities include:

> *Monthly frequency reviews of all serious and non serious cases for the current period, compared with the total cumulative case frequency, including AEs of special interest: Bristol-Myers Squibb's internal safety database (CARES) generates monthly frequency reviews of all serious, non serious and special interest AEs for the current period, compared with the total cumulative case frequency. These data will be reviewed by the safety physician in conjunction with the Medical Surveillance Team (MST) for absolute frequencies and trends in reporting over time, particularly for labelled events of special interest and unlabeled events of potential clinical importance. Spontaneous reporting rates and trends for special interest AEs will be monitored in a descriptive fashion and compared over time in the early post marketing period, taking subject exposure and product market penetration into consideration.*

The sponsor states that the following additional pharmacovigilance activities have also been proposed:

- The continuation of the open label periods of the five core RA studies (IM101102, IM101100, IM101029, IM101031, and IM101101) and the polyarticular JIA clinical trial (IM101033). Subjects in these studies will be followed for up to five years. The LT follow up will allow for better ascertainment of events with a long latency period such as lung and breast cancer, NMSC, and lymphoma; facilitate the assessment of cumulative effects of therapy; and mitigate the effects of any screening for malignancy that may have preceded entry into the ST portion of the studies. The data estimates

[14] European Medicines Agency, "ICH Topic E 2 E Pharmacovigilance Planning (Pvp) Step 5: Note for Guidance on Planning Pharmacovigilance Activities (CPMP/ICH/5716/03)", June 2005, Web, accessed 4 April 2012 <www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002818.pdf>

incidence rates and changes over time and provides the opportunity to make comparisons with data accruing in epidemiology studies. The clinical study setting permitted complete data collection on both non serious and serious AEs. The studies also provided additional data on infusion related reactions, safety in the elderly, the development of autoimmune diseases, the effectiveness of vaccination, and outcomes in subjects who become pregnant. These activities apply to the important identified risks: 'Infections' & 'Infusion related reactions'; the Important potential risks: 'Malignancies', 'Autoimmune symptoms and disorders' & 'Pregnancy'; and the Important missing information: 'Elderly subjects'.

- Specialised case report forms (CRF) will be utilised for the Important identified risks: 'Infections' & 'Infusion-related reactions'; and the Important potential risks: 'Malignancies', 'Autoimmune symptoms and disorders' & 'Progressive multifocal leukoencephalopathy'. The sponsor states 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, and have been provided.

- 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 reports 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 2013-2014.

- 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 hospitalised 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.

Incidence rates will be stratified by the abatacept route of administration (IV or SC), where this information is available. Where possible, information on switching between IV and SC abatacept will be examined.

The study numbers and protocol titles for each study in the core RA epidemiology program are listed below:

- IM101045A: Safety of DMARD and Biologic Treatment of Rheumatoid Arthritis
- IM101045B: An Observational Cohort to Assess Safety and Outcomes in Patients Treated with Abatacept and Other Anti Rheumatic Therapies
- IM101125: A Nation Wide Post Marketing Study on Safety and Effectiveness of Abatacept Treatment in Patients with Rheumatic Disease in Sweden
- IM101126: BSR Register of Abatacept Treated Patients and Prospective Surveillance Study for Adverse Events
- IM101127: LT Observation of Treatment with Biologics in Rheumatoid Arthritis
- IM101213: Post Marketing Observational Study Assessing the LT Safety of Abatacept Using a Population Based Cohort of Rheumatoid Arthritis Patients in the Province of British Columbia
- IM101212: Post Marketing Observational Study Assessing the LT Safety of Abatacept Using the DREAM Database in the Netherlands

  In addition to these studies, per the Committee for Medicinal Products for Human Use (CHMP) request to use all available data, the sponsor has proposed an active surveillance study titled, 'Multinational Safety Surveillance of Abatacept treated Patients Using Disease Registries' (Study IM101211).

  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 one year following delivery.

  Protocols for each of these ongoing studies have been provided.

- The sponsor is initiating a registry to evaluate the LT safety of abatacept use in patients with JIA. A final protocol for Study IM101240 has been provided. Approximately 900 patients who receive abatacept for JIA according to physicians'/families' decisions will be enrolled in the registry. The goal is to have approximately 750 patients with at least five years of follow up and 500 of these patients with ten years of follow up at the end of the study. The registry is being coordinated by the Paediatric Rheumatology Collaborative Study Group (PRCSG) and the Paediatric Rheumatology International Trials Organisation (PRINTO). Patients with JIA who are less than 18 years of age and treated with abatacept are being

recruited from PRCSG centres in North America and PRINTO centres in the EU and rest of world. This JIA registry will also examine the proportion of patients with autoimmune events who have antibodies to CTLA-4, the incidence of antibodies to CTLA-4 after discontinuation of abatacept, and the association between anti-CTLA-4 antibodies and autoimmune events.

- For the Important potential risk 'Immunogenicity', a new generation of immunogenicity assays employing Meso Scale Discovery (MSD) technology have been developed to improve the monitoring of anti abatacept antibodies in subjects under treatment. The method validation was completed in November 2007. Samples from the currently enrolling early RA Study IM101023 will be tested by both the new and present immunogenicity assay methods. This will allow for the comparison of the two test methods in a prospective RA study. Based on the results of this cross validation, the MSD assay will be implemented in new clinical studies. Immunogenicity samples will be obtained in the open label extensions of Studies IM101102, IM101029 and IM101031 at every six months. In addition, these protocols will be amended to request an additional immunogenicity sample when a pre specified event is reported or when a subject discontinues abatacept treatment. The sponsor states that results will be summarised annually and included the appropriate Periodic Safety Update Report (PSUR) for that period. The sponsor is currently amending ongoing protocols (Studies IM101063, IM101167, IM101173, IM101174 and IM101185) to extend the follow up post discontinuation for at least six months.

OPR reviewer's summary in regard to the PP and appropriateness of milestones:

In principle there is no objection to the sponsor implementing additional pharmacovigilance activities to further monitor all the specified ongoing safety concerns, except for the Important missing information 'Vaccinations' and 'Hepatic and renal impairment'. Nevertheless, the clinical aspects of the SS remain subject to the evaluation by the OMA.

The ongoing and initiated studies are 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 this study, as outlined in the updated RMP, will be expected in future PSURs

For the Important identified risk 'Infusion-related reactions', the 'Summary of Risk Management Plan' table should be amended to include 'Special CRFs for spontaneous ADRs of special interest' to be consistent with the 'Action Plan for Infusion-related reactions' table.

'Summary of Risk Management Plan' states that Study IM101064 is a proposed pharmacovigilance activity for the important missing information 'Vaccinations'. Study IM101064 was an open label study to evaluate the efficacy, tolerability and safety of abatacept in subjects with active RA on background non biologic DMARDs who have an inadequate response to anti TNF therapy and have limited therapeutic options. However, this study would appear to have been completed and is not referred to anywhere else in the PP. Consequently, the 'Summary of Risk Management Plan' should be amended by deleting reference to Study IM101064 to be consistent with 'Planned Pharmacovigilance Actions' for the important missing information 'Vaccinations'.

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 'Infections'.

OPR reviewer's comment:

The sponsor's conclusions would appear to be reasonable, except 'Risk Communication' of the updated RMP states:

> *Educational programs will be initiated for health care professionals. Such programs may be adjuncts to local or national medical meetings.*
>
> *A training program will be developed for sales field personnel. As needed, the educational program may include health care professional letters, and physician's/pharmacist's guides.*

Such communication would appear to be additional risk minimisation activities and contrary to the sponsor's previous conclusions. No further information concerning these activities has been provided in the updated RMP. The sponsor should clarify this situation and amend this section of the RMP accordingly.

Summary of Recommendations

The OPR provides these recommendations in the context that the submitted RMP is supportive to the application; the implementation of a RMP satisfactory to the TGA is imposed as a condition of registration; and the submitted European Union RMP is applicable without modification in Australia unless so qualified:

- The clinical aspects of the SS remain subject to the evaluation by the OMA.
- In principle there is no objection to the sponsor implementing additional pharmacovigilance activities to further monitor all the specified ongoing safety concerns, except for the important missing information: 'Vaccinations' and 'Hepatic and renal impairment'.
- The ongoing and initiated studies are not considered to be part of the planned clinical studies in the PP. Therefore the related study protocols have not been reviewed. Nevertheless, an update on the progress/results/analysis of this study, as outlined in the updated RMP, will be expected in future PSURs.
- For the Important identified risk – 'Infusion-related reactions' – the 'Summary of Risk Management Plan' table should be amended to include 'Special CRFs for spontaneous ADRs of special interest' to be consistent with the 'Action Plan for Infusion-related reactions' table.
- The 'Summary of Risk Management Plan' table states that Study IM101064 is a proposed pharmacovigilance activity for the important missing information: 'Vaccinations'. Study IM101064 was an open label study to evaluate the efficacy, tolerability and safety of abatacept in subjects with active RA on background non biologic DMARDs who have an inadequate response to anti TNF therapy and have limited therapeutic options. However this study would appear to have been completed and is not referred to anywhere else in the PP. Consequently, the 'Summary of Risk Management Plan' table should be amended by deleting reference to Study IM101064 to be consistent with the table 'Planned Pharmacovigilance Actions' for the important missing information: 'Vaccinations'.
- The sponsor's conclusion that routine risk minimisation activities are sufficient for all the specified ongoing safety concerns, except for the important identified risk: 'Infections' would appear to be reasonable, except 'Risk Communication' of the updated RMP states:

Educational programs will be initiated for health care professionals. Such programs may be adjuncts to local or national medical meetings.

A training program will be developed for sales field personnel. As needed, the educational program may include health care professional letters, and physician's/pharmacist's guides.

Such communication would appear to be additional risk minimisation activities and contrary to the sponsor's previous conclusions. No further information concerning these activities has been provided in the updated RMP. The sponsor should clarify this situation and amend this section of the RMP accordingly.

- In regard to the specific condition of registration for the current IV product, the sponsor has advised that only routine risk minimisation in the form of the following subsection in the 'Dosage and Administration' section of the Australian PI has been proposed:

Hypersensitivity Reactions

Hypersensitivity reactions are uncommon with the infusion of Orencia, however these may occur. To minimise 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.

Given that the IV presentation of this product has been registered in Australia since August 2007, such newly introduced routine risk minimisation may not be sufficient to ensure appropriate monitoring and management of patients being given Orencia. The sponsor should provide justification for why additional risk minimisation is not required to communicate the management of this important identified risk.

- In addition such proposed routine risk minimisation for the important identified risk: 'Infusion-related reactions' has not been captured in the updated RMP, as it is an Australian specific requirement. Consequently, the sponsor should consider appending an Australian specific annex to the RMP for completeness.

- In regard to the proposed routine risk minimisation activities, it is recommended to the Delegate that the draft product information document be revised to include all the TGA approved changes made to this document as a result of the approval of the previous application to extend the indications for the IV product. The sponsor has advised the draft PI was submitted before this previous application was approved and therefore did not capture these changes.

- In addition the non clinical and clinical aspects of the PI remain subject to the evaluation by the Toxicology area of the OSE and by the OMA, respectively.

- In regard to the proposed routine risk minimisation activities, it is recommended to the Delegate that the draft consumer medicine information document be revised to adequately reflect any changes made to the Australian PI as a result of the above recommendations.

VI. Overall Conclusion and Risk/Benefit Assessment

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

Quality

Approval of this submission has been recommended with respect to quality (Molecular biology/Biochemistry, Sterility, Viral/TSE safety, Endotoxin, Container safety and Device design/performance) and manufacturing control. The standard specific condition of registration relating to Batch Release Testing by OLSS has been recommended by the evaluator. The Delegate intends to impose this condition as recommended.

Nonclinical

Data contained within this submission consisted of local tolerance studies and a mechanistic study in rats. No major deficiencies were identified.

In rats, injection site reactions after SC administration of the clinical formulation were unremarkable.

As the anticipated systemic exposure of abatacept with the maximum clinical dose of the SC formulation would be approximately half the exposure with the maximum IV dose, there were no additional toxicological concerns with proposed SC dosage regimen.

A mechanistic study in rats indicated that the unique abatacept associated autoimmune reactions seen in this species were not associated with anti abatacept antibody production. This immunotoxicity study was conducted to investigate the potential relationship between the immunogenicity of abatacept (that is, development of an anti abatacept antibody response) and lymphocytic inflammation of the thyroid gland and pancreatic islets previously observed in rats. There were no drug related mortalities or clinical signs. There were no abatacept related effects on haematology or immunological parameters, suggesting that abatacept was not pharmacologically active at the administered dose. There were no abatacept related changes in spleen, thymus or thyroid gland weights and no histopathological findings in the kidney, lung, lymph node, pancreas, spleen, thymus or thyroid gland that could be attributed to abatacept treatment. All abatacept treated rats had an anti drug antibody response, detected using ELISA for abatacept specific and CTLA-4 specific antibodies. Four control rats had at least one sample with a positive anti abatacept response. As the titres were low compared with those in abatacept treated animals and only one of these rats had a corresponding positive anti CTLA-4 response, the positive results were attributed to a non specific response. As noted by the nonclinical evaluator, the clinical relevance of these reactions remains unknown. The sponsor is asked to comment on the results of this mechanistic study in rats and clarify any possible clinical relevance.

There were no non clinical objections to the proposed registration of the new dosage form for Orencia. The nonclinical evaluator has made a number of recommendations for amendments to the PI that are endorsed by the Delegate.

Clinical

Pharmacokinetics

Study IM101013

This was a double blind, randomised (within dose), placebo controlled, parallel group, single dose study which examined the PK of SC doses of abatacept (50, 75, 100 or 150 mg) in 48 healthy subjects weighing less than 100 kg and randomised to one of eight treatment

groups with six subjects each. The geometric means of C_{max} and AUC_{inf} of abatacept appeared to increase in a dose proportional manner in the dose range of 50 to 150 mg following administration of a single SC dose. Median T_{max} times ranged from 3 to 7 days and were not affected by dose. Differences in injection volume, osmolality of drug solution and the concentration of the drug solution had no impact on the PK of abatacept (for some of the groups, the IV formulation was injected SC). In subjects who did not exhibit abatacept-specific antibodies, $t_{1/2}$ ranged from 11.2 to 14.7 days and was independent of increasing dose, whereas $t_{1/2}$ values ranged from 3.2 to 7.5 days in subjects who were seropositive.

Study IM101063

This was a double blind, randomised, placebo controlled, parallel group, multiple dose study which assessed the steady state trough serum concentrations of abatcept following SC administration in 68 subjects with RA. Subjects were randomised in a 3:1 ratio, to receive either abatacept or placebo in 1 of 5 parallel groups based on body weight. Steady state trough serum concentrations of abatacept occurred approximately 4 to 5 weeks following the combined regimen of a single IV loading dose and weekly SC injections. The geometric mean steady state trough value of abatacept for subjects weighing >100 kg given 125 mg abatacept was lower than for subjects weighing ≤100 kg given 75 to 125 mg abatacept and subjects weighing >100 kg given 200 mg abatacept. The $AUC_{7\ days}$ in subjects <60 kg given 125 mg abatacept was higher, whereas $AUC_{7\ days}$ of subjects >100 kg administered 125 mg abatacept was lower, compared to subjects <60 kg given 75 mg, subjects 60 - 100 kg given 125 mg and subjects >100 kg given 200 mg abatacept. In addition, the C_{max} in subjects > 100 kg given 125 mg abatacept was lower compared to the other treatment groups.

Pharmacodynamics

Study IM101013

Eleven of 40 healthy subjects (27.5%) developed antibodies to the CTLA binding portion of the abatacept molecule following SC injection of either the IV or the SC formulations. The endpoint titres in healthy subjects who received the SC formulation ranged from 33 to 106 and from 62 to 872 in subjects who received the IV formulation given SC. No dose dependent increases in immunogenicity were observed.

Study IM101128

In 30 out of 48 healthy subjects who had been administered a SC dose of abatacept approximately 3 years previously in Study IM101013, there were six who had initially demonstrated CTLA-4 T specific antibody reactivity. None of these six subjects was positive for anti abatacept antibodies on follow up three years later and none was positive for anti CTLA-4 T specific antibody.

Study IM101063

This study assessed the immunogenicity of abatacept administered SC in 68 subjects with active RA. On Day 71, only one of the abatacept treated subjects was seropositive for anti abatacept antibody, the subject's blood sample having a titre of 758 with specificity towards the IgG portion of the abatacept molecule. This particular immune response was transient and by Day 85 the subject was negative for anti abatacept antibody. None of the 51 abatacept treated subjects was positive for anti-CTLA4 antibody through to Day 85 and so the cell based abatacept neutralising antibody assay was not undertaken. The low incidence of an immune response to abatacept in RA subjects is in contrast to the 27.5% incidence rate observed in healthy subjects in Study IM101013.

Study IM101173

This was a multicentre study which evaluated the immunogenic potential of SC abatacept with or without background methotrexate and in the absence of an initial IV loading dose in 100 subjects with active RA. The primary immunogenicity endpoint was the proportion of subjects with positive antibody (anti abatacept and anti CTLA-4 T) response at Day 113 (month 4) based on ELISA. At the end of the ST treatment period (Day 113), none of the 95 subjects with immunogenicity data (50 in SC abatacept + MTX, 45 in SC abatacept monotherapy cohort) was seropositive for anti abatacept or anti CTLA-4 T antibodies. Transient and infrequent positive antibody responses were observed at earlier time points, generally before Day 85, during the ST treatment period or during the follow-up and were associated with low titres. During the ST treatment period, the overall immunogenicity rate at any time in the SC abatacept monotherapy and SC abatacept + MTX cohorts was 4.1% (2/49) and 3.9% (2/51), respectively. Only one seropositive response was observed following treatment discontinuation. One subject in the SC abatacept monotherapy cohort was seropositive for anti CTLA-4 T antibodies at post treatment Day 85 and did not develop neutralising antibodies; this subject was withdrawn for lack of efficacy after receiving twelve SC injections. There did not appear to be any correlation between the development of antibodies with clinical safety or efficacy findings.

Efficacy

Dosage selection for the pivotal studies

C_{min} was the best predictor of clinical efficacy and concentrations of ~5 µg/mL were associated with lower efficacy. From these data, the aim with SC abatacept was to target a trough concentration in the range of 10 to 30 µg/mL. In Study IM101063, the steady state trough concentrations with 125 mg SC abatacept once weekly were within the target range and over 90% of subjects dosed with 125 mg had C_{min} ≥10 µg/mL. The findings were comparable across the weight groups of <60 kg and 60-100 kg. The steady state trough concentrations were lower in those weighing above 100 kg, although they were still within the target range. A fixed dose of SC abatacept was chosen for the Phase III program for simplicity. Sub group analyses by weight group were planned.

Pivotal study

Study IM1011174

This was Phase IIIb multicentre, randomised, double blind, double dummy study to compare the efficacy and safety of abatacept administered SC and IV in subjects with RA receiving background methotrexate and experiencing an inadequate response to methotrexate. It consisted of a six month (169 days) ST blinded and controlled period, followed by an open label, LT period in which all subjects received weekly 125 mg SC abatacept. The primary objective of the ST period was to demonstrate non inferiority of SC abatacept versus IV abatacept. There was a sub study which assessed immunogenicity, efficacy and safety in 18 subjects who had failed or had an inadequate prior response to anti TNF therapy.

The primary efficacy variable was the ACR 20 and the primary efficacy outcome was to demonstrate that SC abatacept was non inferior to IV abatacept in ACR 20 response after six months' treatment. There were a number of other efficacy outcomes including ACR 50, ACR70, HAQ-DI and DAS-28. A treatment difference of 25% between IV abatacept and placebo in ACR 20 response was the minimum expected benefit based on previous trials. The sponsor stated that for demonstrating non inferiority, SC abatacept would need to demonstrate at least 70% of the treatment effect of IV abatacept, that is, a non inferiority margin of 7.5% [(1-0.7) x 25%] and SC abatacept would be deemed non inferior to IV

abatacept if the lower bound of the 95% CI for the difference on ACR 20 was greater or equal to -7.5%. This equates to a point estimate of the difference of 2.1%. Assuming an equivalent ACR 20 response rate of 60%, a sample of 1370 (685 per group) would give the study an 80% power to detect non inferiority at a 0.025 significance level. A sample of 1440 randomised patients was chosen to allow for protocol deviations leading to exclusion from the PP analysis.

During the short term period, subjects received either abatacept 125 mg SC weekly, together with an IV abatacept loading dose on Day 1 based on weight, or abatacept IV infusion on Days 1, 15 and 29, and then every 28 days. The IV dose was 500 mg for subjects weighing <60 kg, 750 mg for subjects weighing 60 to 100 kg, and 1 gram for subjects weighing >100 kg. Subjects were randomised to SC or IV abatacept in a 1:1 ratio stratified by body weight (<60 kg, 60 to 100 kg and >100 kg).

There were 2472 subjects enrolled, 1464 randomised and 1457 treated. There were seven subjects randomised and not treated. There were 736 SC abatacept and 721 IV abatacept subjects, with 693 (94.2%) and 676 (93.8%), respectively, completing the six month ST treatment period. Premature discontinuation from the ST period occurred in 43 (5.8%) and 45 (6.2%) of the SC abatacept and IV abatacept groups, respectively. Adverse events were the most common reason for premature termination (2.3% versus 3.5%).

The treatment groups were comparable on demographics and baseline disease characteristics. Study subjects were mainly female (82.3%), had a mean age of 49.9 years and a mean weight of 71.8 kg. About half were from South America with the rest from the range of other countries and 74% were White. The subjects had moderate to severe arthritis with a mean disease duration of 7.6 and 7.7 years in the SC abatacept and IV abatacept groups, respectively. In the PP population, other disease characteristics were similar between groups such as the mean number of tender joints (30.0 versus 29.2), swollen joints (20.5 versus 19.6), mean HAQ-DI score (1.73 versus 1.69), mean DAS28-CRP score (6.25 versus 6.22) and mean hsCRP (2.65 versus 2.72 mg/dL). About 85% of subjects were RF positive and the mean baseline MTX dose was 16.4 mg/week.

In the PP population at Day 169, the proportion of subjects with an ACR 20 response was 76.0% (527/693) and 75.8% (514/678) in the SC abatacept and IV abatacept groups, respectively. The treatment difference was 0.3% (95% CI: -4.2%, 4.8%). As the lower bound of the 95% CI was greater than the non-inferiority margin of -7.5% the primary objective was met. The response was similar on the ITT population analysis with a treatment difference of 0.5% (95% CI: -4.0%, 4.9%). The ACR 20 response improved similarly over time in both groups.

Responses as measured by the secondary parameters ACR 50, ACR 70, HAQ-DI and DAS28-CRP were also comparable between the SC and IV groups. It was noted for both the SC and IV formulations that there was a trend for increasing efficacy with decreasing body weight. Responses as measured by the primary and secondary parameters ACR 20, ACR 50, ACR 70, HAQ-DI and DAS28-CRP were maintained throughout the long-term period to Day 449.

Other efficacy studies

Study IM101167

This was a Phase IIIb, multicentre, randomised, withdrawal study to evaluate the immunogenicity and safety of subcutaneously administered abatacept in 120 adults with active rheumatoid arthritis on MTX. Withdrawal of abatacept treatment for 12 weeks led to a small increase in disease activity which improved on treatment reintroduction. Efficacy was maintained to Day 449.

Study IM101185

This was a Phase IIIb, multicentre, open label, single arm study evaluating the safety of abatacept in 123 subjects who switched from IV to SC therapy after a minimum of four years treatment with IV abatacept. Efficacy was maintained after up to one year of open label treatment, as demonstrated by stable results on DAS28-CRP and HAQ-DI scores as well as the proportion with low disease activity and remission (as based on the DAS28-CRP).

Study IM101063LT

This was an open label, LT extension study of IM101063, a PK study assessing dosing regimens for SC abatacept in RA subjects receiving DMARDs. The primary objectives were safety, immunogenicity and LT tolerability. As noted by the clinical evaluator, efficacy assessments were minimal and limited to tender and swollen joint counts. On Day 1 of the fixed dose phase, the mean (SD) number of tender and swollen joints were 8.5 (9.5) and 7.0 (6.1), respectively. At Day 365, the mean (SD) number of tender and swollen joints were 6.0 (8.2) and 5.1 (5.3), respectively. The Delegate would agree with the clinical evaluator that this study does not provide robust clinical efficacy data due to the small subject numbers with large response variability, the open label nature of the study and its limited efficacy assessments.

Study IM101173LT

This was an open label, LT extension study of IM101173 which evaluated the immunogenicity and PK of SC abatacept in RA subjects with or without MTX. This small open label study provided some supportive evidence for maintenance of efficacy over an 18 month treatment period as measured by DAS28-CRP and HAQ-DI.

There were no pooled efficacy analyses. However, there was a comparative analysis of the efficacy of the SC regime with and without an IV loading dose. In Studies IM101174 and IM101167, all subjects received an IV loading dose prior to SC administration while in Study IM101173 no loading dose was given. In patients receiving SC abatacept, at Day 85, the mean change from baseline in DAS28-CRP was 31.6%, 33.1% and 27.8% in Studies IM101167, IM101174 and IM101173, respectively, and in HAQ-DI was 44.6%, 31.4% and 32.2% indicating that the lack of loading dose in IM101173 did not greatly impact on clinical response. In Study IM101167 after 12 weeks treatment in Period III, the mean change from baseline in DAS28-CRP was similar between groups (-0.93 and -0.89 in the IV abatacept and IV placebo groups, respectively).

Safety

Evaluable safety data was available from five Phase II and III studies, that is, all studies except Study IM101013, the study in healthy volunteers.

Pivotal studies which assessed safety as a primary outcome

Study IM101167

This was a Phase IIIb, multicentre, randomised, withdrawal study to evaluate the immunogenicity and safety of subcutaneously administered abatacept in adults with active rheumatoid arthritis on MTX. The primary objective was the assessment of safety and immunogenicity in subjects where, after clinical response, SC abatacept was withdrawn for 12 weeks or maintained for 12 weeks.

There was a ST period consisting of three 12 week periods. In Period I, subjects received weekly open label SC abatacept 125 mg after a single IV loading dose of abatacept. In Period II, subjects who were responders at the end of Period I (decrease from baseline in DAS28-CRP of ≥ 0.6), were randomised 2:1 to double blind, weekly SC placebo or SC

abatacept. In Period III, all subjects received weekly open label SC abatacept with a single IV loading dose of abatacept or placebo. After completing Period III, subjects could enter the open label, LT extension of weekly SC abatacept.

There were 167 subjects treated with open label abatacept in Period I. At its end there were 120 responders who were randomised to SC abatacept or SC placebo. There were 119 subjects treated in Period III and 150 entered the LT extension (37 after Period I and 113 after Period III).

At Day 169, none of the SC abatacept group had a positive antibody response. There were 7/73 (9.6%) of the SC placebo group who were positive, one (1.4%) to abatacept and six (8.2%) to CTLA-4 T. The difference of 9.6% (95% CI: 0.8, 18.3) was not significant (p=0.119). At Day 252, there were 1/38 (2.6%) and 2/73 (2.7%) of the SC abatacept and SC placebo groups, respectively, with a positive antibody response. The treatment difference was 0.11% (95% CI: -8.21, 8.43). All three had anti CTLA-4 T antibodies.

There was one death from a pulmonary thromboembolism (Period I) in a subject with cellulitis. This was deemed unrelated to study treatment. In Period I, there were three subjects with SAEs (1.8%); cholelithiasis, fatigue and the PE/cellulitis. In Period II, there were two (2.5%) subjects with SAEs in the placebo group and none in the abatacept group. The AE rates were 32.5% and 36.3% and the rates of infections were 12.5% and 8.8% in the SC abatacept and SC placebo groups, respectively. In Period III, the AE rates were 37.5% and 41.8% in the SC abatacept and SC placebo groups, respectively, and there were no local injection site reactions or acute infusional events when SC abatacept was reintroduced, although there was one peri infusional event and one systemic injection reaction in the SC placebo group. There were no safety issues identified from laboratory data, no malignancies and no autoimmune disorders.

Study IM101185

This was a Phase IIIb, multicentre, open label, single arm study evaluating the safety of abatacept in 123 subjects who switched from IV to SC therapy. The primary objective was safety assessment at Day 85 (3 months) after switching to SC abatacept. There were 126 subjects screened and 123 enrolled, all of whom received at least one dose of SC abatacept and 120 (97.6%) who completed three months of SC treatment.

During the first three months (Day 85), there were no deaths, malignancies or autoimmune disorders. There was one SAE (worsening RA). AEs were reported in 39.8% with 8.9% assessed as treatment related. Infections were reported in 16.3% of subjects, with none regarded as severe or resulting in treatment withdrawal. Local injection site reactions or systemic reactions within 24 hours occurred in 1.6% (n=2) of subjects.

After the cumulative treatment period of up to 20 months, 3.6% of subjects withdrew. There were no deaths and 13 (10.6%) subjects with SAEs of which two were deemed treatment related (sarcoidosis and pneumonia). The subject with sarcoidosis discontinued treatment. There were 2 (1.6%) malignancies (breast and uterine cancer). There were no notable laboratory findings.

Overall safety evaluation

Safety data in the dossier was analysed in three ways. First, there was a comparison of SC to IV abatacept in the ST period of Study IM101174 (739 SC abatacept and 721 IV abatacept). Second, the cumulative SC population based on pooled data from the five Phase II and III studies that provide LT data. Third, there was data from special groups from individual studies. The comparator for the cumulative SC population was the LT cumulative IV safety population that includes 12,132 person years of exposure with 1165 subjects with at least five years of exposure. In the comparative SC/IV populations

(IM101174), the mean exposure to SC and IV abatacept was 166.5 days and 165.6 days, respectively. In the Phase II/III program there were 1915 subjects in the ST and 1783 in the LT periods, with a cumulative total of 1879 subjects exposed to SC abatacept for 1945 patient years. The mean duration of exposure was 12.6 months with a range of 2 to 47 months. Thus, the pivotal efficacy Study IM101174 provided a direct comparison of the safety of the SC and IV formulations over 6 months of treatment in 1460 subjects, while the pooled data provided an assessment of LT safety with a mean exposure duration of 12.6 months.

The safety profile of the SC formulation was similar to that of the IV formulation with no higher rates of AEs (67.0% versus 65.2%), SAEs (4.2% versus 4.9%) or discontinuation due to AEs (2.0% versus 3.5%). For AEs of clinical interest, the rates were comparable for the infection/infestation SOC (31.8% versus 30.7%), malignancies (0.4% versus 0.7%), autoimmune events (1.0% versus 0.8%), local injection reactions (2.6% versus 2.5% SC placebo), systemic injection reactions (7.6% versus 7.8%) and acute infusional events (2.7% versus 2.2%). From the cumulative data, the most frequent AEs were URTI, naspharyngitis, UTIs, bronchitis, sinusitis and headaches. Infections remain a major risk of treatment, occurring in 40.2% of subjects with an incidence rate of 54.9 per 100 p-y. Overall, 2.4% of subjects discontinued treatment due to an AE, with the main ones being cellulitis, URTI, pneumonia, headache and myocardial infarction. Severe infections remained one of the notable risks with abatacept with 2.1% of subjects having an Infection/Infestation SAE, the most frequent of which included pneumonia and herpes zoster.

Laboratory test results were comparable between the SC and IV formulation, with mild elevations of liver function tests (AST and ALT >3x ULN in 0.6% and 1.5%, respectively) and low leucocytes (<0.75x LLN in 1.1%) the main findings.

Due to the lower overall exposure using the fixed dose regimen, but the higher trough concentrations in the low body weight group (<60 kg), safety was examined across weight subgroups. AE rates were comparable in the <60 kg and 60-100 kg groups (~66%), however in those >100kg the rates of AEs, although comparable between the SC and IV formulations (77.6% versus 77.4%, SC versus IV abatacept) were higher than in the lower weight sub groups. This trend was also seen in the cumulative data. Subjects with low body weight did not have a higher AE rate, SAE rate or AE discontinuation rate compared to the those receiving the IV formulation, though there was a higher rate of injection site reactions (3.8% versus 0.6%).

The risks of AEs and of discontinuation due to AEs were noted to increase with increasing age.

In the open label Study IM101185 as well as in the LT period of IM101174 when subjects who were randomised to IV abatacept switched to SC abatacept, no notable safety issues were associated with the switch.

Unwanted immunological events were assessed through the clinical program. In Study IM101174, the immunogenicity rates at six months were 1.1% and 2.3% in the SC abatacept and IV abatacept groups, respectively. Rates were comparable between formulations in the low body weight (<60 kg) group (1.6% versus 1.8%). From the cumulative data (1430 subjects with 4446 samples), the seropositive rate was 1.7%. In the 24 seropositive subjects in this population, there were no reported autoimmune disorders and 12.5% had systemic injection reactions (rash and headache). There was, however, one case of sarcoidosis in a seropositive subject in Study IM101185.

In the controlled Study IM101167, the withdrawal for three months of SC abatacept resulted in an immunogenicity rate of 9.6% (95% CI: 0.8, 18.3) compared to 0% in those

who continued on treatment, though the difference was not statistically significant. On reintroduction of therapy, the rates were comparable (2.6% versus 2.7%). There were no safety events related to hypersensitivity on treatment reintroduction. In the Phase II open label Study IM101173, immunogenicity rates were comparable between subjects receiving add on MTX or on SC abatacept monotherapy. Rates were also comparable when switching from IV to SC therapy in Study IM101185.

Risk Management Plan

The OPR at the TGA has evaluated the RMP for Orencia abatacept (rch) 125 mg single dose syringe subcutaneous injection, version 10, dated 14 February 2011. A number of questions were asked of the sponsor in relation to this RMP and the responses assessed by the OPR.

There are two outstanding matters that require resolution. The first concerns the treatment setting of the IV infusion of abatacept, that is, hospital versus other, given the Important identified risk of 'infusion-related reactions'; the second is a consequence of the first, namely the need for an Australian specific annex to the RMP to capture the approved routine risk minimisation activity for this identified risk of 'infusion related reactions'.

With regard to the first outstanding matter, the OPR evaluator has noted that if the administration of Orencia by IV infusion was limited only to the hospital setting, then routine risk minimisation for the Important identified risk of 'infusion related reactions' may be acceptable, as it would be expected that the necessary equipment, treatments and procedures sufficient to initiate management of acute infusion reactions would be in place. However, it is anticipated that the administration of Orencia may well occur in infusion centres where no medical back up is available to nursing staff. Therefore, in relation to the specific conditions of registration, the OPR will formally request that the sponsor provide details of the procotols it has in place concerning the administration of Orencia by IV infusion to patients and concerning the appropriate monitoring and management of patients being given Orencia by IV infusion. In addition the sponsor must describe in detail how these new protocols will be communicated to health care professionals, for example, whether by Dear Healthcare Professional Letter (DHCPL), or by other means and how they will be maintained to be consistent with:

- current clinical practice
- the currently approved PI and RMP documents, and
- the safe use of the product.

The Delegate intends to recommend a specific condition of registration which will enforce compliance with the foregoing.

Following on from the above, the Delegate requests the sponsor to provide, in its pre ACPM response, precise, detailed and comprehensive information about the advice it intends to provide to practitioners concerning the transitioning of patients currently on the IV formulation to the SC formulation. The Delegate is aware that the sponsor has provided some guidance under Dosage and Administration in the PI, namely the sentence:

> "*Patients transitioning from Orencia® intravenous therapy to subcutaneous administration should administer the first subcutaneous dose instead of the next scheduled intravenous dose*".

However, this advice merely relates to the relative timing of consecutive doses, first IV then SC. What advice does the sponsor intend to provide to practitioners about which patients, currently on IV infusion treatment, are the most or more appropriate to be

transitioned? Are there any particular groups of patients currently on the IV infusion who should be transitioned before others or is there any particular order in which such patients should be transitioned? Should patients be on the IV infusion for a minimum or certain length of time before being transitioned? The Delegate is sure that practitioners will want to know the answers to these or similar questions.

The Delegate requests the sponsor to append an Australian specific annex to the RMP, the purpose of this annex being to capture any proposed routine risk minimisation activities for the Important identified risk of 'Infusion related reaction'. The latter was requested of the sponsor by the OPR but the sponsor deemed the creation of such an Australian specific annex to be unnecessary. The Delegate disagrees with the sponsor and if necessary will impose this request as a specific condition of registration.

Risk-Benefit Analysis

Delegate Considerations

In the pivotal efficacy Study IM101174, the actual treatment difference for the primary efficacy endpoint between the IV and SC formulations was 0.3%, 95% CI [-4.2%, 4.8%]. As the lower bound of the 95% CI was well within the non inferiority margin of -7.5%, the primary efficacy endpoint was achieved. The results for the secondary efficacy endpoints were all consistent with the primary outcome.

The SC formulation at a dose of 125 mg weekly resulted in a systemic exposure (AUC and C_{max}) lower than that of the monthly IV formulation while the trough levels (C_{min}) were higher. These differences did not translate into any clinically relevant difference in safety or efficacy between the formulations. Steady state trough concentrations were a predictor of efficacy with IV abatacept and this was also shown with SC abatacept.

The flat dosing regimen for the SC injection, that is, independent of weight, was found to be appropriate.

Assessment of the lack of an IV loading dose on efficacy was undertaken in two studies and efficacy was observed to be maintained, although with the expected slightly slower onset. The Delegate endorses the recommendation of the clinical evaluator that the instructions for the weight based IV loading dose still be included under Dosage and Administration. As noted by the clinical evaluator, the clinical program was mainly conducted with an IV loading dose, and as such efficacy data without an IV loading dose are limited.

The safety of the SC abatacept was comparable with that of the IV infusion. The significant risk of infections is similar with each route of administration.

Concerns for increased immunogenicity with the SC formulation were not borne out with a rate no higher than that for IV abatacept (1.1% SC versus 2.3% IV) and an overall rate from cumulative (ECL) data of 1.7%. Immunogenicity response was also comparable across the weight groups. Safety assessment in the small population (n=24) of seropositive subjects noted no autoimmune disorders, though there were two cases of moderate to severe rash. There was however an increase in immunogenicity on treatment withdrawal, albeit with low titres. As noted by the clinical evaluator, the sponsor states the reason is not known and while it did not lead to significant safety events, the numbers were small. The clinical evaluator therefore recommended this issue be monitored through specific follow up, that is, in ongoing extension studies. The clinical evaluator also noted that this potential risk of post treatment immunogenicity had not been addressed satisfactorily either in the draft PI or in the RMP.

The Delegate endorsed these concerns and refers the sponsor to the question asked by the clinical evaluator in the clinical evaluation report. In the sponsor's pre-ACPM response, this issue of post treatment immunogenicity must be comprehensively addressed,

beginning with a detailed summary of what is currently known about it. As well, the sponsor is requested to provide up to date information on the issue in the draft PI and is also requested to provide appropriate amendments to the RMP so that the issue receives the appropriate degree of ongoing monitoring and follow up. The clinical evaluator has cited the wording in the approved US PI as being more comprehensive and detailed. The requirements for appropriate amendments to the RMP will be made part of the specific condition of registration relating to the RMP.

The Delegate strongly endorsed the recommendation of the clinical evaluator that the first dose of the SC injection should be done under medical supervision and that injections should continue to be done under medical supervision until the treating doctor is completely assured that the patient's and/or carer's injection technique is satisfactory and that the SC injection is safely tolerated. There must be an explicit precaution in this regard in the PI.

There was no clinical trial data of the use of the SC formulation in children. This fact – and a statement recommending against its use in children – must be prominently and explicitly stated in the Clinical Trials section, in the Indications, in the relevant sub section of the Precautions section, and under Dosage and Administration in the PI. That is, wherever in these sections of the PI just mentioned there is information given regarding the use of Orencia in children, this information must now be qualified by the appending of a statement that there is no clinical trial data of the use of the SC formulation in children and therefore that its use in children cannot be recommended. There are four locations in the PI where this information **must** be included. The Delegate referred the sponsor to the information headed 'Paediatric and Adolescent (Juvenile Idiopathic Arthritis)' under Clinical Trials, to the Indication to reduce the signs and symptoms in paediatric patients six years of age and older with moderately to severely active polyarticular juvenile idiopathic arthritis, to the information headed 'Paediatric Use' under Precautions and to the information headed 'Paediatric and Adolescent' under Dosage And Administration.

Product Information and Consumer Medicine Information

The Delegate strongly endorses all recommendations for amendments to the PI made by all of the evaluators, that is, non clinical, biochemistry, clinical and RMP. These recommendations should be implemented along with the additional requests made specifically by the Delegate.

Delegate's Proposed Action

The Delegate proposed to approve this submission by Bristol-Myers Squibb Australia Pty Ltd to register Orencia [abatacept (rch)] based on the quality, safety and efficacy of the product having been satisfactorily established for the indications below and for the reasons stated above in the Risk/Benefit Discussion:

> *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® should not be administered concurrently with other biological DMARDs (for example, TNF inhibitors, rituximab, or anakinra).

Please note that the above indication recommended for approval in relation to the SC injection DOES NOT include the existing paediatric indication. The SC injection is recommended for approval ONLY for those elements of the current indication which refer to the treatment of rheumatoid arthritis in adults.

The Delegate proposed to recommend the imposition of the following specific conditions of registration:

- The standard condition relating to the requirements for Batch Release Testing by OLSS.
- The full implementation of the Risk Management Plan version 10, dated 14 February 2011, revised as specified in the sponsor's correspondence to the OPR of 13 July 2011, revised as requested by the OPR to append an Australian specific annex in relation to the identified risk of 'infusion related reactions' and as may be revised in the future following consultation with the OPR.
- The sponsor is required to consult with the OPR within one (1) calendar month of the date of this approval regarding appropriate amendments to the RMP in relation to the issue of post treatment immunogenicity
- The sponsor must provide to the OPR, within one (1) calendar month of the date of this approval, all protocols it has in place concerning the administration of Orencia® by IV infusion to patients and concerning the appropriate monitoring and management of patients being given Orencia by IV infusion. In addition, the sponsor must provide to the OPR full details of how these protocols will be communicated to health care professionals, for example, whether by DHCPL or by other means and how they will be maintained to be consistent with current best clinical practice, the relevant approved PI and RMP documents and finally safe use of the product.

The sponsor should address the following issues in the pre ACPM response:

- An update to the registration status (with dates) for this submission of abatacept (rch) in the USA, Europe/UK, Canada, Switzerland and New Zealand including any withdrawals, rejections or deferrals.
- The sponsor is asked to comment on the results of the mechanistic study in rats and clarify any possible clinical relevance .
- Please respond to the question asked by the clinical evaluator in the clinical evaluation report, the question about the rate of abatacept induced immunogenicity post treatment.
- Please provide precise, detailed and comprehensive information about the advice the sponsor intends to provide to practitioners, **by any means whatsoever** (whether in the PI, RMP, a DHCPL, proposed educational material or in any other medium or method of communication), concerning the transitioning of patients currently on the IV formulation to the SC formulation. Please refer to all the Delegate's comments. Please also be sure to provide the evidence base for any information which the sponsor intends to convey to practitioners, by any means, on this particular issue.

Response from Sponsor

The Delegate has requested the company to address the following issues in the pre ACPM response.

(a) An update to the registration status (with dates) for this submission of abatacept (rch) in the USA, Europe/UK, Canada, Switzerland and New Zealand, including any withdrawals, rejections or deferrals.

Response:

The updated registration status (with dates) for this submission of abatacept (rch) in the USA, Europe/UK, Canada, Switzerland and New Zealand, including any withdrawals, rejections or deferrals is shown in Table 9.

Table 9: Updated registration status for abatacept (rch).

Country	Submitted Date	Approval
US*	4 October 2010	29 July 2011
Switzerland	11 November 2010	27 February 2012
Canada	13 October 2010	Currently under evaluation
EU	27 July 2011	Currently under evaluation
New Zealand	25 October 2010	Currently under evaluation
Brazil	3 December 2010	Currently under evaluation

***US Indication**:

ORENCIA is indicated for reducing signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function in adult patients with moderately to severely active rheumatoid arthritis. ORENCIA may be used as monotherapy or concomitantly with disease-modifying antirheumatic drugs (DMARDs) other than tumor necrosis factor (TNF) antagonists.

There have not been any withdrawals deferrals or rejections for Orencia® (abatacept) Subcutaneous Dose Form Presentation

(b) Discussion on the mechanistic study in rats in relation to any possible clinical relevance.

Response:

This investigative GLP study was conducted to investigative the potential relationship between immunogenicity of abatacept (development of an anti-drug antibody response) and lymphocytic

inflammation of the thyroid and pancreatic islets previously observed in juvenile and adult rats when administered at pharmacologically active doses. As expected, exposure to abatacept a fully human protein administered at subpharmacologic doses was sufficient to induce robust and sustained anti-abatacept and anti-CTLA4 antibody responses in all 40 treated animals. This was in contrast to controls in which 4/40 rats in the control group showed a positive response. The control positive responses had low titers that were <220 as compared to the high titers in the abatacept-treated group that ranged from 15,000 to 130,000, and thus had no impact on the study. Importantly, there was no evidence of lymphocytic inflammation of the thyroid or pancreatic islets in any rat. Therefore, the suspected autoimmune-like inflammation observed in these non-lymphoid organs in previous rat studies is likely not a consequence of immunogenicity but related to the pharmacologic activity of abatacept in this species. As these autoimmune-like findings were determined to be rat specific, they were not considered clinically relevant.

(c) Discussion in relation to abatacept induced immunogenicity post treatment.

Response

Data provided in the dossier established that the immunogenicity profile of SC abatacept therapy by ELISA assay was comparable to that of IV abatacept, both when directly comparing both formulations in IM101174 and when comparing the SC abatacept immunogenicity data with historical data from IV abatacept. Though a second assay (ECL assay) showed better sensitivity and drug tolerance than the ELISA assay during method validation testing, results of this assay were similar to the ELISA results and confirmed the low immunogenicity profile of SC abatacept. Similar to IV abatacept, SC abatacept was associated with relatively low frequency of immunogenicity, and when antibodies against abatacept were detected, immunogenicity was transient and with low titers that did not persist nor increase upon continued dosing. The assumption that the transient seropositivity seen with SC abatacept does not represent a typical immunogenic reaction (i.e., persisting high antibody concentrations capable of biologic activity) is further supported by the fact that the clinical program with SC abatacept showed no impact of immunogenicity on PK, safety or efficacy.

While the number of post-treatment follow-up samples was limited due to the high retention rates, post-treatment immunogenicity results observed in all ongoing studies, as well as the immunogenicity rate established at the end of the 3 month withdrawal period in study IM101167 indicated that the frequency of immunogenicity slightly increased after therapy was discontinued. The increase in immunogenicity rate observed following withdrawal of SC abatacept therapy was consistent with the increase in immunogenicity rate historically seen after discontinuation of IV abatacept for 8 to 12 weeks, showing that immunogenicity of SC and IV abatacept formulations are comparable not only when treatment is continuous, but also upon treatment withdrawal, when abatacept serum concentrations approached levels below 1 μg/mL. The reason for the greater incidence of immunogenicity in subjects who withdraw treatment is unknown, but may be mechanistic (during active treatment and in presence of higher serum concentration of abatacept, the drug may prevent the development of an antibody response to itself) or may be due to an increase in assay sensitivity when drug is not present. Importantly, while the proportion of patients with a seropositive sample increased after drug withdrawal, antibody titers remained low. The lack of meaningful immunogenic response following withdrawal of SC abatacept treatment was further supported by the formal SC abatacept withdrawal/reintroduction study IM101167. The reintroduction period of this study showed that immunogenicity was not persistent upon reintroduction of SC abatacept therapy and that no safety events were associated when drug was reintroduced, even in subjects who were seropositive at the time of SC abatacept therapy

reintroduction. No hypersensitivity reactions (including systemic injection reactions, infusional reactions, or local injection site reactions), autoimmune AEs, SAEs or other important medical events were reported upon reintroduction of SC abatacept therapy. Furthermore, results of this study showed that efficacy or PK of SC abatacept therapy was not impacted by the presence of anti-abatacept or anti-CTLA4-T antibodies at the time of reintroduction. The fact that reintroduction of SC abatacept treatment did not create a booster effect leading to higher immunogenicity rates and higher antibody titers (associated with clinical implications) further underscores the non-immunogenic profile of SC abatacept. Of note, these results were again consistent with the IV abatacept experience, where it was previously demonstrated there were no clinical consequences to interruption and reinitiation of IV abatacept therapy.

Additionally, results of immunogenicity testing > 1 year after withdrawal of treatment indicated that anti-CTLA4-T antibodies did not persist. None of the subjects who received a single dose of SC abatacept in IM101013 and who subsequently participated in the follow-up study, IM101128, were found to be seropositive. Similar results have previously been presented for IV abatacept: immunogenicity testing 1 year after withdrawal of IV abatacept treatment indicated that anti-CTLA4-T antibodies did not persist as none of the subjects who completed IM101034 and had abatacept therapy withdrawn for approximately 1 year before enrolling in IM101129 were found to be seropositive at the start of that study.

While the immunogenicity profile of SC abatacept established in the clinical program was reassuring in that it confirmed the low immunogenic potential of abatacept previously established with the IV presentation, all ongoing SC abatacept studies will continue evaluation of immunogenicity during the long-term extension periods. Additionally, the protocols were amended to extend the follow-up period following treatment discontinuation to 168 days (6 months) from the previous 85 days (3 months) to allow longer term evaluation of post- treatment immunogenicity in a larger number of patients.

(d) Discussion on the information that will be provided to practitioners concerning the transitioning of patients from the current IV formulation the SC formulation.

Response

The delegate has requested information concerning advice to practitioners on the transitioning of patients from the current IV formulation to the SC formulation the company's response on this are described below:

All patients receiving Orencia® intravenous (IV) are able to be transitioned to Orencia® Subcutaneous (SC) formulation. The treating practitioners will have the choice of either using IV or SC for patients. For patients switching from Orencia® (IV) to Orencia® SC the PI has been updated to include guidance on when to administer the first dose subcutaneous dose.

The decision regarding the route of administration of Orencia® has to be the clinical judgement of the treating practitioner, a rheumatologist or a clinical immunologist, with expertise in the management of rheumatoid arthritis. Factors[1] that a practitioner may need to consider when individualising treatment for a patient may include: suitability of the route of administration, patient compliance, patient characteristics and co-morbidity. For example, a practitioner may continue to prescribe Orencia® (IV) to a patient who is unable to inject Orencia® SC or may use Orencia® SC in a patient where an IV line is difficult to use.

If a patient is deemed to be suitable to receive Orencia® SC, the following materials and support will be made available by BMS:

- Medical support to answer enquiries for HCP regarding all formulations of Orencia®
- Patient starter materials to aid patients in initiating or transitioning to Orencia® SC including:
    - in-home nurse training of patients (following practitioner consent)
    - patient information
    - Orencia 1800 support hotline
    - Developing how-to-switch card for practitioner/patient discussions
    - How to inject guide including video

In addition, BMS will:

- Issue DHCP letter to notify of the availability of Orencia® SC including new product information
- Conduct training of specialist representatives
- Conduct direct customer interactions and educational meetings on an ongoing basis

As Bristol-Myers Squibb has amended the PI and answered the issues raised by the delegate in his proposed action report, the Company looks forward to a satisfactory resolution to this application, and approval of the new subcutaneous formulation for Orencia®, as recommended by the evaluators and the Delegate.

Advisory Committee Considerations

The Advisory Committee on Prescription Medicines (ACPM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

Efficacy

The ACPM agreed with the Delegate that the submission demonstrated adequate clinically relevant efficacy.

Safety

The safety profile of the subcutaneous (SC) injection formulation closely follows the acceptable profile of the intravenous formulation. Both nonclinical and clinical trials with the SC formulation demonstrated adequate safety in regards to injection site reactions, which generally occurred on the first treatment. The ACPM advised that following first dose medical supervision, it is appropriate for the SC injection regimen to be administered in the home context.

Indication

The ACPM considered this product to have a positive benefit-risk profile for the indication of:

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 should not be administered concurrently with other biological DMARDs (for example, TNF inhibitors, rituximab, or anakinra).

PI/ CMI

The ACPM advised additional changes to the draft PI and CMI to those proposed by the Delegate

The ACPM advised that the implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided for Orencia would support the safe and effective use of this product.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Orencia single dose syringe for subcutaneous injection containing abatacept (rch) 125 mg/1 mL. The approved indication reads 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 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). (There is no clinical trial data for the use of Orencia subcutaneous formulation in children, therefore its use in children cannot be recommended.)*

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

Specific Conditions of Registration Applying to these Therapeutic Goods:

1. Implementation of the Risk Management Plan (RMP) version 10 dated 14 February 2011 revised as specified in the sponsor's correspondence to the Office of Product Review of the TGA of 13 July 2011 and with the Australian Specific Annex (Orencia ASA versus 1.0 to RMP versus 10 dated 14 February 2011) as agreed with the Office of Product Review and as may be amended in the future in agreement with the Office of Product Review.
2. The sponsor is required to consult with the Office of Product Review of the TGA within one (1) calendar month of the date of this approval regarding appropriate amendments to the RMP in relation to the issue of post treatment immunogenicity.
3. The sponsor must provide to the Office of Product Review, within one (1) calendar month of the date of this approval, all protocols it has in place concerning the administration of Orencia® by IV infusion to patients and concerning the appropriate monitoring and management of patients being given Orencia® by IV infusion. In addition, the sponsor must provide to the OPR full details of how these protocols will be communicated to health care professionals, for example, whether by Dear Healthcare Professional Letter or by other means and how they will be maintained to be consistent with current best clinical practice, the relevant approved PI and RMP documents and finally safe use of the product.
4. It is a condition of registration that the first five independent batches of Orencia® (abatacept) (rch) 125 mg/syringe, solution for subcuteneous injection (AUSTR 177174, 177176) imported into Australia are not released for sale until samples and/or the manufacturer's release data have been assessed and endorsed for release by the TGA Office of Laboratories and Scientific Services (OLSS).

   The sponsor should supply:

   1. Certificates of Analysis of all active ingredient (drug substance) and final product.
   2. Information on the number of doses to be released in Australia with accompanying expiry dates for the product and diluents (if included).
   3. Evidence of the maintenance of registered storage conditions during transport to Australia.
   4. 3 syringes of each batch for testing by the TGA OLSS together with any necessary standards, impurities and active pharmaceutical ingredients (with their Certificates of Analysis) required for method development and validation.

These batch release conditions will be reviewed and may be modified on the basis of actual batch quality and consistency. The conditions remain in place until the sponsor is notified in writing of any variation.

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.

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605
www.tga.gov.au
Reference/Publication #

PRODUCT INFORMATION

ORENCIA®
(abatacept)

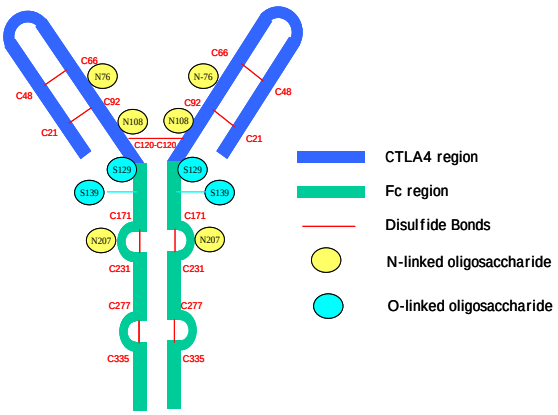
(LYOPHILIZED POWDER FOR IV INFUSION)
(SOLUTION FOR SUBCUTANEOUS ADMINISTRATION)

NAME OF THE MEDICINE

ORENCIA® (abatacept (rch))

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.

Abatacept structure:



CAS number 3 332348-12-6

DESCRIPTION

ORENCIA® powder for intravenous infusion is supplied as a sterile, white, preservative-free, lyophilized powder for parenteral administration. Following reconstitution of the lyophilized powder 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.

ORENCIA®, solution for injection, pre-filled syringe is supplied as a sterile, single-dose, preservative-free, ready-to-use solution for subcutaneous injection. The subcutaneous solution is clear, colorless to pale yellow with a pH of 6.8 to 7.4. Each single dose of subcutaneous injection

provides 125 mg abatacept, 170 mg sucrose, 8 mg poloxamer 188, 0.286 mg sodium phosphate monobasic, 0.838 mg sodium phosphate dibasic anhydrous, and up to 1 mL water for injection. ORENCIA® solution for subcutaneous administration contains no maltose.

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 – Intravenous Infusion

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.

Adult RA - Subcutaneous Administration

Abatacept exhibited linear pharmacokinetics following subcutaneous administration. The mean (range) for C_{min} and C_{max} at steady state observed after 85 days of treatment was 32.5 mcg/mL (6.6 to 113.8 mcg/mL) and 48.1 mcg/mL (9.8 to 132.4 mcg/mL), respectively. The bioavailability of abatacept following subcutaneous administration relative to intravenous administration is 78.6%. Mean estimates for systemic clearance (0.28 mL/h/kg), volume of distribution (0.11 L/kg), and terminal half-life (14.3 days) were comparable between SC and IV administration.

A single study was conducted to determine the effect of monotherapy use of abatacept on immunogenicity following subcutaneous administration without an IV load. When the IV loading dose was not administered, a mean trough concentration of 12.6 mcg/mL was achieved after 2 weeks of dosing. The efficacy response over time in this study appeared consistent with studies that included an IV loading dose, however, the effect of no IV load on the onset of efficacy has not been formally studied.

Consistent with the IV data, population pharmacokinetic analyses for SC abatacept 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 apparent clearance. Concomitant MTX, NSAIDs, corticosteroids, and TNF blocking agents did not influence abatacept apparent 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 patients. 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 in Patients treated with intravenous ORENCIA ®

Clinical trials

The efficacy and safety of ORENCIA® for intravenous administration 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), and 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 abatacept

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 IV and VI, 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 and 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							
	Intravenous Administration						Subcutaneous Administration	
	Inadequate Response to MTX		**Inadequate Response to TNF Blocking Agent**		**MTX-Naive**		**Inadequate Response to MTX**	
	Study III		**Study IV**		**Study VI**		**Study SC-I'**	
Response Rate	Abatacept[a] +MTX n=424	Placebo +MTX n=214	Abatacept[a]+ DMARDs[b] n=256	Placebo + DMARDs[b] n=133	Abatacept[a] +MTX n=256	Placebo +MTX n=253	Abatacept[e] SC +MTX n=693	Abatacept[e] IV +MTX n=678
ACR 20								
Month 3	62%***	37%	46%***	18%	64%*	53%	68%	69%
Month 6	68%***	40%	50%***	20%	75%**	62%	76%§	76%
Month 12	73%***	40%	NA	NA	76%***	62%	NA	NA
ACR 50								
Month 3	32%***	8%	18%**	6%	40%***	23%	33%	39%
Month 6	40%***	17%	20%***	4%	53%***	38%	52%	50%
Month 12	48%***	18%	NA	NA	57%***	42%	NA	NA
ACR 70								
Month 3	13%***	3%	6%*	1%	19%**	10%	13%	16%
Month 6	20%***	7%	10%**	2%	32%**	20%	26%	25%
Month 12	29%***	6%	NA	NA	43%***	27%	NA	NA
Major Clinical Response[c]	14%***	2%	NA	NA	27%***	12%	NA	NA
DAS28-CRP Remission <2.6[d]								
Month 12	NA	NA	NA	NA	41%***	23%	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).

§ 95% CI: −4.2, 4.8 (based on prespecified margin for non-inferiority of −7.5%)

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

e Per protocol data is presented in table. For ITT; n=736, 721 for SC and IV Orencia®, respectively

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 II, 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. 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 (see section 3.1).

[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. 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.

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
Mean Decrease			
Month 6	2.5 ***	2.3 ***	1.5
Month 12	2.9	2.3	NA[a]
Low Disease Activity			
Month 6	21%	26%	11%
Month 12	35%	22%	NA[a]
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.

Study SC-I (IM101-174)

Study SC-I (IM101-174) was a randomized, double-blind, double-dummy non-inferiority study that compared the efficacy and safety of abatacept administered subcutaneously and intravenously in subjects with rheumatoid arthritis (RA), receiving background methotrexate (MTX) as the only DMARD, and experiencing an inadequate response to MTX (MTX-IR). The primary endpoint was ACR 20 at 6 months. The pre-specified non-inferiority margin of -7.5% allows for a maximum difference in point estimate of -2.1% in the ACR20 response of the SC ORENCIA® compared with IV ORENCIA® at month 6, which is not considered a clinically significant difference**.** As shown in Table 2, the study demonstrated non-inferiority of ORENCIA® administered subcutaneously vs intravenously with respect to ACR20 responses up to 6 months of treatment. The estimated difference between the 2 treatment groups (SC - IV) in the proportion of ACR 20 responders at Day 169 was 0.3% (95% CI: -4.2%, 4.8%). The proportion of subjects with an ACR 20 response at Day 169 was 76.0% in the SC abatacept group and 75.8% in the IV abatacept group (PP analysis).

In Study SC-1, patients were randomized with stratification by body weight (<60 kg, 60 to 100 kg, > 100 kg) to receive ORENCIA® 125mg subcutaneous injections weekly, after a single loading dose

of ORENCIA® based on body weight or ORENCIA® intravenously on Days 1, 15, 29 and every four weeks thereafter. A total of 2472 subjects were enrolled in Study SC-I; 1457 were treated, 736 of subjects with SC abatacept and 721 were with IV abatacept. Subjects continued taking their current dose of MTX from the day of randomization.

ACR response

In Study SC-I, ORENCIA® administered subcutaneously (SC) was non-inferior relative to intravenous (IV) infusions of ORENCIA® with respect to ACR 20 responses up to 6 months of treatment. Patients treated with ORENCIA® subcutaneously also achieved similar ACR 50 and 70 responses as those patients receiving ORENCIA® intravenously at 6 months. No major differences in ACR responses were observed between intravenous and subcutaneous treatment groups in subgroups based on weight categories (less than 60 kg, 60 to 100 kg, and more than 100 kg; data not shown). 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 Study SC-I are shown in Table 2.

Health-related outcomes and quality of life

In Study SC-I, improvement from baseline as measured by HAQ-DI at 6 months and over time was similar between subcutaneous and intravenous administration.

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 paediatric ACR 30/50/70 responders has remained consistent for 31 months.

There is no clinical trial data for the use of Orencia® subcutaneous formulation in children, therefore its use in children cannot be recommended.

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). (There is no clinical trial data for the use of Orencia® subcutaneous formulation in children, therefore its use in children cannot be recommended.)

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 intravenous 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® intravenous 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. 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® for intravenous administration, resulting in falsely elevated blood glucose readings on the day of infusion. When receiving ORENCIA® for intravenous administration, 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.

Orencia® for subcutaneous administration does not contain maltose; therefore, patients do not need to alter their glucose monitoring.

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 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.

There is no clinical trial data for the use of Orencia® subcutaneous formulation in children, therefore its use in children cannot be recommended.

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

Subcutaneous Injections

The first dose should be done under medical supervision. Patients can self inject after the treating physician/healthcare practitioner is assured that the patient's and/or carer's injection technique is satisfactory, and while providing medical follow-up as necessary. (see PREPARATION AND ADMINISTRATION INSTRUCTIONS FOR SUBCUTANEOUS INJECTION.)

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

Clinical trial experience in adult RA patients treated with intravenous ORENCIA®

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 (≥ 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 Table7.

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.

AEs reported in patients treated by abatacept intravenous or subcutaneous which did not occur with an excess incidence (i.e. the difference was not > 0.2%) over placebo but were considered to be medically relevant based on the overall clinical experience included sinusitis (common), Pelvic Inflammatory Disease (uncommon) and urosepsis (uncommon)

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 1.41 per 100 patient-years, and the annualised incidence rate remained stable. The incidence rates per 100 patient-years were 0.74 for non-melanomatous skin cancer, 0.57 for solid malignancies and 0.13 for hematologic malignancies. The most frequently reported solid organ cancer was lung cancer (0.15 per 100 patient-years), and the most common hematologic malignancy was lymphoma (0.07 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 (upto 24hrs 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%]).

Autoimmune processes

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

The incidence rate of autoimmune disorders remained stable during open-label experience (1.63 per 100 patient-years) compared to the double-blind experience (2.07 per 100 patient-years). The most frequently reported autoimmune-related disorder during the open-label experience was psoriasis.

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.

Clinical trial experience in adult RA patients treated with subcutaneous Orencia®

In general, the adverse reactions in adult RA patients treated with subcutaneous abatacept were similar in type to those seen in patients treated with abatacept administered intravenously.

Study SC-I was a randomized, double-blind, double-dummy, non-inferiority study that compared the efficacy and safety of abatacept administered subcutaneously (SC) and intravenously (IV) in 1457 subjects with rheumatoid arthritis, receiving background methotrexate, and experiencing an inadequate response to MTX (MTX-IR). The safety experience and immunogenicity for Orencia® administered subcutaneously was consistent with intravenous Studies I-VI. Due to the route of administration, injection site reactions and immunogenicity were evaluated and are discussed in the sections below.

A subgroup analysis, although limited by assessments involving small numbers and the lack of a comparator, did not reveal any unexpected safety concerns. The finding that more AEs were reported subjects >100 kg both for IV and SC abatacept may reflect small numbers of subjects in some subgroups and differences in exposure**.**

Injection Site Reactions in Adult RA Patients Treated with SC Abatacept

Study SC-I compared the safety of abatacept including injection site reactions following subcutaneous or intravenous administration. The overall frequency of injection site reactions was 2.6% (19/736) and 2.5% (18/721) for the SC abatacept group and the IV abatacept group (SC placebo), respectively. All injection site reactions were described as mild to moderate (hematoma, pruritus, or erythema) and generally did not necessitate drug discontinuation.

Immunogenicity in Adult RA Patients Treated with SC Abatacept

Study SC-I compared the immunogenicity to abatacept following subcutaneous or intravenous administration. The overall immunogenicity frequency to abatacept was 1.1% (8/725) and 2.3% (16/710) for the subcutaneous and intravenous groups, respectively. The rate is consistent with previous experience, and there was no effect of immunogenicity on pharmacokinetics, safety, or efficacy.

Immunogenicity and Safety of SC Abatacept Administration as Monotherapy without an IV Loading Dose

Study SC-II was conducted to determine the effect of monotherapy use of ORENCIA® on immunogenicity following subcutaneous administration without an intravenous load in 100 RA patients, who had not previously received abatacept or other CTLA4Ig, who received either subcutaneous ORENCIA® plus methotrexate (n=51) or subcutaneous ORENCIA® monotherapy (n=49). No patients in either group developed anti-product antibodies after 4 months of treatment. The safety observed in this study was consistent with that observed in the other subcutaneous studies.

Immunogenicity and Safety of SC Orencia® upon Withdrawal (Three Months) and Restart of Treatment

Study SC-III in the subcutaneous program was conducted to investigate the effect of withdrawal (three months) and restart of ORENCIA® subcutaneous treatment on immunogenicity in RA patients treated concomitantly with methotrexate. One hundred sixty-seven patients were enrolled in the first 3-month treatment period and responders (n=120) were randomized to either subcutaneous ORENCIA® or placebo for the second 3-month period (withdrawal period). Patients from this period then received open-label ORENCIA® treatment in the final 3-month period of the study (period 3). At the end of the withdrawal period, 0/38 patients who continued to receive subcutaneous ORENCIA® developed anti-product antibodies compared to 7/73 (9.6%) of patients who had subcutaneous ORENCIA® withdrawn during this period. Half of the patients receiving subcutaneous placebo during the withdrawal period received a single intravenous infusion of ORENCIA® at the start of period 3 and half received intravenous placebo prior to reinitiating subcutaneous ORENCIA® in Period 3. At the end of period 3, when all patients again received subcutaneous ORENCIA®, the immunogenicity rates were 1/38 (2.6%) in the group receiving subcutaneous ORENCIA® throughout, and 2/73 (2.7%) in the group that had received placebo during the withdrawal period. Upon reinitiating therapy, there were no injection reactions and no differences in response to therapy in patients who were withdrawn from subcutaneous therapy for up to 3 months relative to those who remained on subcutaneous therapy, whether therapy was reintroduced with or without an intravenous loading dose. The safety observed in this study was consistent with that observed in the other studies.

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.

Clinical Trial experience in Paediatric and Adolescent patients treated with intravenous ORENCIA®

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 in Table 11 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® may be administered as an intravenous (IV) infusion or a subcutaneous (SC) injection. Methotrexate, other non-biologic DMARDs, corticosteroids, salicylates, nonsteroidal anti-inflammatory drugs (NSAIDs), or analgesics may be used during treatment with ORENCIA®.

IV dosing regimen

Orencia® IV should be administered as a 30-minute intravenous infusion utilizing the weight range-based dosing specified in Table 12. Following the initial IV administration, an intravenous infusion should be given at 2 and 4 weeks after the first infusion and every 4 weeks thereafter.

Table 12: Dose of ORENCIA® for Intravenous Infusion 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).

SC dosing regimen

Following a single intravenous loading dose (as per body weight categories listed in Table 12), the first 125 mg subcutaneous injection of ORENCIA should be given within a day, followed by 125 mg subcutaneous injections once weekly.

Patients who are unable to receive an infusion may initiate weekly injections of subcutaneous ORENCIA without an intravenous loading dose.

Patients transitioning from ORENCIA intravenous therapy to subcutaneous administration should administer the first subcutaneous dose instead of the next scheduled monthly intravenous dose.

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.

There is no clinical trial data for the use of Orencia® subcutaneous formulation in children, therefore its use in children cannot be recommended.

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 FOR INTRAVENOUS INFUSION

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.

PREPARATION AND ADMINISTRATION INSTRUCTIONS FOR SUBCUTANEOUS INJECTION

ORENCIA® Injection, 125 mg/syringe is not intended for IV infusion.

ORENCIA® Injection is intended for use under the guidance of a physician or healthcare practitioner. The first dose should be done under medical supervision. Patients can self inject after the treating physician/healthcare practitioner is assured that the patient's and/or carer's injection technique is satisfactory, and while providing medical follow-up as necessary.

After training in subcutaneous injection technique, the patient may self-inject ORENCIA® Patients should be instructed to follow the directions provided in the Patient/Caregiver Instructions for Use section for additional details on medication administration.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not use ORENCIA® prefilled syringes exhibiting particulate matter or discoloration. ORENCIA® should be clear and colorless to pale yellow. EACH PRE-FILLED SYRINGE OF ORENCIA® IS FOR SINGLE USE IN ONE PATIENT ONLY. DISCARD ANY RESIDUE.

Patients using ORENCIA® for subcutaneous administration should be instructed to inject the full amount in the syringe (1.0 mL), which provides 125 mg of ORENCIA®, according to the directions provided in the Patient/Caregiver Instructions for Use section.

Injection sites should be rotated and injections should never be given into areas where the skin is tender, bruised, red, or hard.

OVERDOSE

Doses up to 50 mg/kg have been administered intravenously 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

For Intravenous Infusion

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.

For Subcutaneous Injection

ORENCIA® (abatacept) injection solution for subcutaneous administration is supplied either in a 1mL single-dose disposable prefilled glass syringe (with a passive needle safety guard) or as a 1mL single-dose disposable prefilled glass syringe with flange extender. The product is available in the strength of 125 mg of abatacept and is provided in a pack of 4 1mL single-dose prefilled syringes.

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**)

ORENCIA® (abatacept) injection solution for subcutaneous administration must be refrigerated at 2°C to 8°C. DO NOT FREEZE.

Do not use beyond the expiration date.

Protect the vials and prefilled syringes 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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AUSTRALIAN REGISTRATION NUMBERS:

ORENCIA® lyophilized powder for intravenous infusion: AUST R 130100
ORENCIA® injection solution for subcutaneous administration with needle guard: AUST R 177174
ORENCIA® injection solution for subcutaneous administration: AUST R 177176
SYRINGE: AUST R 12743

Date of first Inclusion in the ARTG: 27 September 2007

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