Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Abatacept (rch)

Proprietary Product Name: Orencia

Sponsor: Bristol-Myers Squibb Australia Pty Ltd

April 2010

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

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

Contents

I. Introduction to Product Submission

Submission Details

Type of Submission	Extension of Indications
Decision:	Approved
Date of Decision:	4 March 2010
Active ingredient(s):	Abatacept (rch)
Product Name(s):	Orencia
Sponsor's Name and Address:	Bristol-Myers Squibb Australia Pty Ltd 556 Princes Highway Noble Park Vic 3174
Dose form(s):	Powder for IV infusion
Strength(s):	250 mg
Container(s):	Single-use vial with a silicone-free disposable syringe
Pack size(s):	Individually packaged
Approved Therapeutic use:	Orencia in combination with methotrexate is indicated for the treatment of moderate to severe active rheumatoid arthritis in adult patients who have had an insufficient response or intolerance to other disease modifying anti-rheumatic drugs (DMARDs), such as methotrexate or tumour necrosis factor (TNF) blocking agents. A reduction in the progression of joint damage and improvement in physical function have been demonstrated during combination treatment with Orencia and methotrexate. Orencia is indicated for reducing signs and symptoms in paediatric patients 6 years of age and older with moderately to severely active polyarticular juvenile idiopathic arthritis who had an inadequate response to one or more disease-modifying anti-rheumatic drugs (DMARDS). Orencia may be used as monotherapy or concomitantly with methotrexate (MTX). Orencia should not be administered concurrently with other biological DMARDs (eg, TNF inhibitors, rituximab, or anakinra).
Route(s) of administration:	IV infusion
Dosage:	Following the initial administration, Orencia should be given at 2 and 4 weeks after the first infusion, then every 4 weeks thereafter, 500 mg, 750 mg or 1 g, depending on body weight.

Product Background

Juvenile Rheumatoid Arthritis (JRA), also known as Juvenile Idiopathic Arthritis (JIA), represents a major clinical and societal problem with significant unmet needs. The common sequelae of failed medical therapy include chronic pain, diminution of quality-of-life, significant debility and economic hardship, which persist life-long. Recent adult trials of abatacept suggest it has a more favourable risk-benefit profile than other disease modifying

agents. The clinical efficacy of abatacept in RA suggests that the same approach may be successful in JRA/JIA. Hence, numerous reasons for extending the use of Orencia to paediatric patients with JRA/JIA were drawn from the fact that:

- JRA/JIA is the most prevalent paediatric rheumatic illness and one of the most common chronic diseases of childhood. Nearly 50% of children with JRA/JIA suffer from recurrent or persistent disease. This eventually leads to active arthritis and ongoing joint destruction in adulthood.
- Significantly increased mortality has been described especially when active synovitis persists into adulthood. Even during childhood, JRA/JIA is associated with increased mortality. Polyarticular JRA/JIA, accounting for about 40% of all JRA/JIA cases, has the poorest prognosis, with only a 15% probability of disease remission within 10 years. Over 60% of these children will have significant joint damage, often within the first 2 years of disease onset.
- Current medical treatments, including disease modifying anti-rheumatic drugs (DMARDs) and corticosteroids, particularly when used in combination, have been associated with unacceptable toxicity, often leading to discontinuation of treatment. In RA there is now compelling evidence that early treatment, during the 'window of opportunity', results in superior outcomes; a concept that has been tested in recent studies combining TNF-antagonists and methotrexate (MTX) started within the first 2 years of onset of the disease. Most rheumatologists believe there is a similar opportunity in JRA/JIA in which aggressive therapy could have a profound long term effect. The ultimate goal is to halt disease progression before permanent damage and debility have occurred.

The sponsor proposes an extension of indication for Orencia to allow treatment of paediatric patients with moderately to severely active polyarticular juvenile idiopathic arthritis. The active component of Orencia is the recombinant protein abatacept, which includes the extracellular domain of human CTLA4. Abatacept, a selective co-stimulation modulator and the first in this class of agents, inhibits T cell (T lymphocyte) activation by binding to CD80 and CD86, on antigen presenting cells, thereby blocking interaction with CD28 on T cells. This interaction provides a co-stimulatory signal necessary for full activation of T lymphocytes. Activated T lymphocytes are implicated in the pathogenesis of rheumatoid arthritis (RA) and are found in the synovium of patients with RA.

Orencia is proposed to be used as monotherapy or concomitantly with the DNA synthesis inhibitor methotrexate. Recommended dose for patients 6 to 17 years with juvenile idiopathic arthritis who weigh less than 75 kg is 10 mg/kg every 4 weeks. The dosing period is undefined but may be long-term.

The proposed indication for Orencia is as follows;

"reducing signs and symptoms in paediatric patients 6 years of age and older with moderately to severely active polyarticular juvenile idiopathic arthritis. Orencia may be used as monotherapy or concomitantly with methotrexate (MTX)."

The proposed dose determination is based on body weight. Table 1 below outlines the dosing regimen. The route of administration is a 30 minute intravenous infusion.

Table 1: Proposed Dosing Regimen for Orencia.

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

* Each vial provides 250 mg of abatacept for administration

Thus the proposed 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 at each administration. For paediatric patients weighing more than 75 kg the dosing regimen is the same as for adult patients, however the dose should not exceed the maximum dose of 1000 mg. Orencia may be given at 2 and 4 weeks after the initial infusion and at four weekly intervals thereafter.

Regulatory Status

Orencia was approved by the TGA for use in adults on 27 September 2007. The indication is for the treatment of moderate to severe rheumatoid arthritis (RA) in adult patients who have had an insufficient response to or intolerance of other DMARDs, such MTX or tumour necrosis factor (TNF) blocking agents.

Orencia is approved in the European Union (EU), USA and Canada and has been registered in New Zealand and Singapore but currently is not marketed in these two countries. The application in the EU for an extension of indications to JIA was filed in Dec 2008 and its evaluation is ongoing. Similar applications have been submitted in New Zealand (15 May 2009) and Switzerland (30 January 2009).

Paediatric use of Orencia is approved in the USA, Canada, India (13 April 2009) and Mexico (27 July 2009). The indication for use in the USA for paediatric patients approved on 7 April 2008 is:

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. Orencia may be used as monotherapy or concomitantly with methotrexate (MTX).

The US letter of approval for the paediatric indication stated that the sponsor was still required to study paediatric patients ages 2 – 5 years but that this requirement had been deferred until additional safety data had been collected from three animal safety studies described in the letter. The sponsor was also required to conduct the following post-approval observational study: *"A JIA patient safety registry comprised of at least 500 patients*".

The approved dosage regimen in the US label is as follows:

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.

In Canada the indication approved on July 11 2008 for the paediatric population is:

Orencia is indicated for reducing signs and symptoms of moderately to severely active polyarticular juvenile idiopathic arthritis/juvenile rheumatoid arthritis in paediatric patients 6 years of age and older who have had an inadequate response to one or more DMARDs, such as MTX. Orencia has not been studied in children less than 6 years of age.

Product Information

The approved product information current at the time this AusPAR was prepared is at Attachment 1.

II. Quality Findings

Drug Substance (active ingredient)

Orencia (abatacept) is composed of 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 portion of human immunoglobulin G1.

Drug Product

Orencia (abatacept) is a lyophilized powder for intravenous infusion which is supplied as an individually packaged, single-use vial with a silicone-free disposable syringe. Each 15-mL vial contains 250mg abatacept. The excipients include maltose, sodium dihydrogen phosphate monohydrate and sodium chloride. Following reconstitution, utilizing the silicone-free disposable syringe, with 10mL of Sterile Water for Injection, the solution of Orencia is clear, colourless to pale yellow with a pH range of 7.2 to 7.8..

Quality Summary and Conclusions

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

III. Nonclinical Findings

Introduction

The data presented were of an acceptable quality. The studies examining pharmacokinetics and repeat-dose toxicity were performed according to Good Laboratory Practice (GLP) standards.

The sponsor has previously submitted toxicological studies using adult mice and cynomolgus monkeys in support of the use of abatacept in adult humans. Consistent with European Medicines Agency (2005) guidelines indicating that applications for extensions of indication to paediatric patients should be supported by studies using juvenile animals, the sponsor has now submitted toxicological studies using juvenile and adult rats that were repetitively dosed with abatacept.[1] The dosing periods in these studies were approximately 13 weeks in length and started on either postnatal day (PND) 4 or 28, or 8 to 10 weeks of age in the adults. Two different dosing periods were used in the juveniles because of the difficulties in aligning immune system maturity in juvenile rodents and humans (Holsapple *et al*. 2003). Animals with short gestation periods (such as rodents) generally have relatively immature immune systems at birth that undergo considerable maturation during the early postnatal period. For example, 10-day old rat pups lack lymphocyte subsets and germinal centres in the spleen. However, 21-day old rats show both B- and T-cell subsets and can demonstrate an immune response (albeit at lower levels than are seen for an adult animal). By comparison, the immune system of humans is essentially fully developed at birth. Accordingly, it could be

[1] EMEA/CHMP/SWP/169215/2005 Guideline on the need for non-clinical testing in juvenile animals of pharmaceuticals for paediatric indications.

argued that 3-4 week old rats are a better model for the paediatric population targeted for abatacept treatment.

Pharmacology

An important feature of rheumatoid arthritis is the activation of T-cells leading to proliferation and secretion of cytokines that modulate the immune response. The recombinant protein abatacept (the active component of Orencia) includes the extracellular domain of human CTLA4 and is designed to inhibit the activation of T-cells via its ability to bind to CD80/86 on antigen-presenting cells.

Specific *in vitro* and *in vivo* pharmacodynamic studies were not performed, although expected drug-induced changes in immune functions were demonstrated in the toxicology studies.

Pharmacokinetics

The pharmacokinetics of abatacept were determined as part of toxicology studies in juvenile and adult rats. The maximal plasma concentration (C_{max}) and the area under the plasma concentration time curve [from zero to 72 hours] ($AUC_{0\text{-}72\ h}$) values increased less than dose-proportionally between 20 and 200 mg/kg for both adult and juvenile animals. Exposure values at the end of the repeat dosing period (for both adults and juveniles) were normally higher for males (around 1.2-1.7-times) than for females. Consistent with this difference, abatacept had a longer elimination half-life in males as compared with females. Higher area under the plasma concentration time curve (AUC) values were observed at the end of repeated dosing in juvenile rats (but not adult rats) suggesting accumulation of abatacept.

Toxicology

Relative exposure

Relative exposure was determined as the area under the plasma concentration time curve from time zero to 72 hours ($AUC_{0\text{-}72\ h}$) in rat serum divided by 3 (to convert to daily) and multiplied by 28 (to normalise to 28 days exposure). For the juvenile animal studies, this value was then divided by 35,927 µg.h/mL, the highest AUC in children and adolescents given the recommended dose of 10 mg/kg every 28 days. For the adult animal study, this value was divided by 50,102 µg.h/mL, the AUC in human adults given 10 mg/kg of abatacept every 28 days. It is important to note that, in the three studies detailed, No Adverse Effect Levels (NOAELs) were not determined as there were adverse toxicological findings at the lowest doses tested.

Table 2: Relative exposure to abatacept: repeat-dose toxicology studies of juvenile and adult rats

Study no.	Dosing duration[a]	Drug dose (mg/kg/3d)	PK analysis[b]	Sex	$AUC_{0\text{-}72h}$ (µg.h/mL)	Exposure ratio[c]
DN07013	PND 4-94	20	PND 28	M	10,300	2.7
				F	10,100	2.6
			PND 88	M	25,200	6.5
				F	20,100	5.2
		65	PND 28	M	26,800	7.0
				F	29,600	7.7
			PND 88	M	68,100	17.7
				F	52,900	13.7
		200	PND 28	M	67,000	17.4
				F	69,800	18.1
			PND 88	M	148,000	38.4
				F	117,000	30.4
DS07165	PND 4-97	65	PND 28	M	23,000	6.0
				F	22,500	5.8
			PND 88	M	49,700	12.9
				F	38,900	10.1
	PND 28-97	20	PND 88	M	20,200	5.2
				F	17,900	4.7
		65	PND 88	M	49,400	12.8
				F	41,100	10.7
DS07166	13 weeks (commencing at 8-10 weeks old)	65	day 31 of dosing	M	44,600	8.3
				F	27,500	5.1
			day 91 of dosing	M	39,000	7.3
				F	25,000	4.7
		200	day 31 of dosing	M	82,600	15.4
				F	60,900	11.3
			day 91 of dosing	M	92,700	17.3
				F	63,900	11.9

Abbreviation: PND = postnatal day; [a] times on which first and last drug dose was given; [b] day on which analysis of drug pharmacokinetics was performed); [c] $AUC_{0\text{-}72\,h}$ in rat serum divided by 3 and multiplied by 28, to normalise to 28 days exposure, and then divided by 35,927 µg.h/mL (the highest AUC in children and adolescents given the recommended dose of 10 mg/kg every 28 days) for juvenile animal studies or by 50,102 µg.h/mL for the adult animal study (DS07166).

Repeat-dose toxicity

Groups of juvenile or adult rats were necropsied following subcutaneous or intravenous doses of abatacept once every three days at 20, 65, or 200 mg/kg. Dosing continued for 13 weeks and commenced at postnatal day (PND) 4 or 28 (juvenile studies) or at 8-10 weeks (adult study). Additional groups of animals were analysed following a 2-3 month post-dose period. The studies were performed by established laboratories according to GLP procedures, and used both sexes and standard testing times and group numbers. As noted above, juvenile dosing studies were initiated at two different PNDs to explore the possibility that abatacept-induced toxicology might be influenced by the stage of immune system maturity at the time of commencement of dosing. However, the toxicological findings were similar for both dosing schedules.

Consistent with the immunomodulatory ability of abatacept, a variety of immunological and associated histopathological changes were seen in all drug-treated groups in both rats treated as juveniles or adults. These changes were seen in both sexes, although (consistent with the higher exposure values generally seen in males- see above) there was a tendency towards earlier occurrence and higher incidence in males. The most notable drug-induced changes in juvenile rats were:

- An increased incidence of opportunistic infections
- T-cell hyperplasia (predominantly T-helper cells) and contraction of B-cell areas in spleen and lymph nodes. T-helper cell levels also increased in peripheral blood. These changes were at least partially reversed during the post-dosing period.
- Decrease in serum immunoglobulin G (IgG) levels, which was partially reversed during the post-dosing period.
- Significant incidence of inflammation in pancreas and thyroid glands, which was associated with lymphocytic infiltration. The severity and incidence of this inflammation increased during the post-dosing period. The appearance of glands was consistent with autoimmune disease.

While the clinical significance of the increased opportunistic infections in juvenile rats is not clear, such adverse events continue to be a risk with any prolonged immunosuppressive therapy and should be monitored in the postmarket setting.

In a previous submission, pups born to female rats treated at a dose of 200 mg/kg every three days with abatacept during early gestation and throughout the lactation period showed alterations of immune function: these included a 9-fold increase in the T-cell dependent antibody response in female pups and inflammation of the thyroid in one female out of 10 male and 10 female pups evaluated. Whether these findings indicate a risk for development of autoimmune diseases in humans exposed *in utero* and/or in lactation to abatacept has not been determined.

Whether these autoimmune findings in juvenile and adult rats are species-specific cannot be answered as no other species of juvenile animal has been tested with abatacept. Long-term treatment of both adult mice (6 to 20 months) and adult monkeys (1 year) showed no evidence of drug-related autoimmunity. Moreover, no autoimmune signals have been noted in human clinical trials of adults or juveniles.

Given the absence of abatacept data from other species of juvenile animals (or data from juvenile animals treated with other immunomodulatory drugs used in the treatment of JIA) it can only be concluded that autoimmunity is a potential adverse event of abatacept treatment that should be monitored carefully in the sponsor's Risk Management Plan. Furthermore, the

Australian Product Information (PI) should contain the same statement as the US PI, which outlines the major findings from the juvenile animal studies.

Genotoxicity

Studies of this type are considered unnecessary for biotechnology-derived pharmaceuticals (ICH S6, 1997).[2]

Carcinogenicity

The carcinogenicity of abatacept in rats was not specifically examined. Localised lymphomas were observed in 2 juvenile male rats treated at 20 mg/kg in the second 13 week juvenile rat study. However, this study was not specifically designed for the detection of carcinogenicity and the ability to draw conclusions from such data is limited. Nevertheless, it is reasonable to suggest that these lesions are likely to be spontaneous rather than treatment-related as there was no dose-response relation, lymphoma was found in one control animal in the same study, and Sprague Dawley (SD) rats are known to have a significant frequency of spontaneous lymphomas. Irrespective of such results, the possibility of increased tumour incidence in long-term, immunosuppressed, juvenile patients is an ongoing concern, particularly given that abatacept is commonly used in combination with methotrexate, a known inducer of chromosomal aberrations (Choudhury et al. 2000) and a potential carcinogen.

Reproductive and developmental toxicity

Possible effects on reproductive capability were studied using juvenile rats dosed with abatacept once every three days at 20, 65, or 200 mg/kg on postnatal days (PND) 4 through 94. At all doses there was no effect on oestrous cycling or on the timing of sexual maturation in both sexes. Reproductive capability was assessed by cohabitation of males or females that had just completed dosing with untreated animals. There were no drug-related effects on mating or fertility in males or females at any dose. Similarly, there were no drug-related effects on the litter parameters (corpora lutea, implantations, pre- and post-implantation losses, litter sizes etc.) of treated animals.

Antigenicity

Anti-abatacept antibodies were detected in rats during the post-dosing period. As antibody production was occurring at a time when abatacept levels had significantly declined, any effect on total exposure would have been trivial.

Nonclinical Summary and Conclusions

No evidence of abatacept-related toxicity was observed on the developing neurobehavioral or reproductive systems in juvenile rats.

GLP-compliant, 13-week repeat-dose studies with abatacept were performed in juvenile and adult rats. Toxicities in juvenile rats included an increased susceptibility to infection and the development of signs of autoimmunity (lymphocytic infiltration of pancreas and thyroid glands). A NOAEL could not be determined in these studies, with exposure ratios (AUC) ranging from 3 at the lowest doses to about 40 at the highest doses.

The clinical relevance of the nonclinical observations in juvenile rats is not entirely clear. No autoimmune signals have been noted in human clinical trials of adults or juveniles. Nevertheless, in the absence of any data from juvenile animals treated with other immunomodulatory drugs used in the treatment of JIA, it must be considered that increased

[2] CPMP/ICH/302/95: Note for guidance on preclinical safety evaluation of biotechnology-derived pharmaceuticals.

susceptibility to infection and autoimmunity are potential adverse consequences of abatacept treatment in a human paediatric population.

Overall, there are no nonclinical objections to the registration of Orencia provided that:

1) A suitable statement is included in the Australian Product Information (similar to the US label) outlining the adverse findings in juvenile animal studies, and

2) The company's Risk Management Plan (RMP) includes provisions for specific post-market monitoring of possible increases in infection rates and the development of autoimmunity symptoms in the intended paediatric population. Moreover, the RMP should include the monitoring of the potential increased tumour incidence that could conceivably occur in long-term, immunosuppressed, juvenile patients that are being treated with abatacept and methotrexate in combination.

IV. Clinical Findings

Introduction

The clinical application submitted to the TGA for evaluation consists of 11 volumes which refer to one clinical study, IM101033 (a phase 3, multicentre, multinational, randomised study) which is comprised of;

- 1 clinical efficacy and safety study which was made up of 3 parts; short term (Periods A and B), long term (Period C)
- 1 population pharmacokinetics (POPPK) report using data from IM101033
- an immunogenicity analysis

The POPPK analysis looked at the paediatric population (6-17 years) to examine the drug pharmacokinetic (PK) parameters and characteristics in the intended population of the study. In addition there was an immunogenicity analysis of abatacept in the paediatric population.

In addition, some supplementary data was provided which was evaluated by the Delegate.

Overall the dossier for submission was adequate. The investigators declared adherence to international guidelines in conducting a trial in JRA. In particular the principles of Good Clinical Practice and the European Medicines Agency (EMEA) "Guideline on Clinical Investigation of Medicinal Products for the Treatment of Juvenile Idiopathic Arthritis" were closely observed. The sponsor's Overview is a fair summary of the issues raised in IM101033. The evaluator supported the fact that the trial's investigators adhered closely to the guidelines set by EMEA for conducting trials of medicinal products for the treatment of JIA (CPMP/EWP/422/04). In regard to the safety profile, the documents submitted to the TGA were accurate in their reporting of the trial. There were no issues identified with the trial investigators.

There are three specific TGA adopted European guidelines relevant to this submission:

- CPMP/EWP/422/04 (pdf,117kb)
  Guideline on Clinical Investigation of Medicinal Products for the Treatment of Juvenile Idiopathic Arthritis
  Published: TGA Internet site
  Effective: 26 June 2009

- CHMP/EWP/147013/2004 (pdf,103kb)
  Guideline on the role of Pharmacokinetics in the Development of Medicinal Products in the Paediatric Population (corrigendum)

Published: TGA Internet site
Effective: 24 August 2009

- CPMP/ICH/2711/99 (pdf,119kb)
  Note for Guidance on Clinical Investigation of Medicinal Products in the Paediatric Population
  Published: TGA Internet site
  Effective: 19 April 2001

As well, there are two further adopted EU guidelines which may be of value in the consideration of this submission:

- CPMP/EWP/556/95 Rev 1 (pdf,176kb)
  Points to Consider on Clinical Investigation of Medicinal Products other than NSAIDS for Treatment of Rheumatoid Arthritis
  Replaces: CPMP/EWP/556/95 (Adopted by TGA February 2001)
  Published: TGA Internet site
  Effective: 29 January 2007

- pp. 127 - 132 of Rules 1998 (3C) - 3CC6a Clinical Investigation of Medicinal Products for Long-Term Use See also: pp. 121 - 125 of Rules 1998 (3C) - 3CC5a (Adopted by TGA with conditions)

Pharmacokinetics

The investigators' main objectives were:

- To characterise the population pharmacokinetics (POPPK) of abatacept in children and adolescents (6-17 years) with JRA/JIA.
- To quantify potential relationships between subject covariates and the PK parameters of abatacept in the JRA/JIA patient population.
- To compare the steady state exposure of abatacept (minimum plasma concentration (C_{min}), C_{max} and AUC) for subjects of this study and compare it to the adult POPPK.

The serum concentrations of abatacept were measured in children and adolescents with JIA/JRA (n=186) following the IV administration of 10mg/kg of abatacept on Days 1, 15 and 29 and every 28 days thereafter up to 40 weeks. Following from this the mean trough serum abatacept concentration was calculated to be approximately 11.9µg/mL.

The POPPK analysis used serum collected from all subjects in Periods A and B. In addition data that was used to develop the POPPK adult model with RA was also included in the analysis to help compare the steady state exposure between children and adolescents and adults. The following previously evaluated adult studies were used:

- 3 Phase II RA studies (IM103002, IM101100 and IM101101)
- 3 Phase III RA studies (IM101102, IM101029 and IM101031)

Subject specific co-variates (body weight, age, gender, race, duration of disease, prior medications, hepatic and renal status and disease state) were subsequently evaluated for clinical significance.

The mean clearance of abatacept in the JIA/JRA subjects was approximately 0.40 mL/h/kg. POPPK analyses of serum concentration showed increased abatacept clearance with an increased baseline body weight (bw). It was also shown that age, gender, concomitant MTX, corticosteroids and non-steroidal antiinflammatory drugs (NSAIDs) did not affect the

clearance rate. Thus body weight was the only clinically significant subject covariate identified.

The $C_{min,}$ C_{max} and AUC for JRA and JIA subjects were found to be 15-39% lower than those for adult RA subjects receiving the same abatacept dose of 10mg/kg. The investigators had anticipated this as the relationship between clearance (CL) and body weight is less proportional (CL α 1/bw) and the body weights of JIA/JRA subjects were generally lower than those of adults. Despite the lower exposure in JRA/JIA subjects the response rate was comparable to that in the adult population when assessed against the ACR 20 response rate criteria.

In addition the PK analysis showed that abatacept was not metabolised by the liver. Once administered, abatacept undergoes cellular, receptor-mediated clearance through Kupffer and sinus endothelial cells in the liver. The cells act to remove dead cells and other large proteins from the blood. Also abatacept is a protein that is too large to undergo renal filtration. The effects of abatacept are currently unknown for patients with significant renal and hepatic impairment.

Comment

The POPPK comparison using dataset from adult RA subjects and the JRA/JIA population needs to be cautiously interpreted. This is because it is not clearly based upon current evidence whether adult RA and JIA/JRA can be regarded as the same disease. Thus comparing PK in 2 different disease groups and 2 different age populations for the same drug is potentially flawed. In the 6-17 year old subjects specific drug clearance pathways may not have been fully established. For example, the onset of puberty is highly variable and occurs earlier in girls, in whom normal onset may occur as early as 9 years of age. It is known that puberty can affect the apparent activity of enzymes that metabolise drugs and so requirements for some medicinal products on a mg/kg basis may decrease dramatically (theophylline, for example). This is particularly relevant as approximately 71% of study subjects in Period B of this study were female with a median age of 13 years.

However, the clinical evaluator acknowledges that the adult RA and JIA/JRA populations do share similar characteristics. It may be that this is the best POPPK model for this point in time with the current understanding of these diseases.

The long terms effects of abatacept in patients with hepatic or renal impairment are unknown. Currently, there is no intention by the sponsor to study abatacept in adult or paediatric subjects with significant hepatic or renal impairment due to the PK characteristics of abatacept. This may limit the external validity of abatacept. The current approved PI in Australia for Orencia only mentions that no dose can be calculated for patients with hepatic and renal impairment.

PK Summary

A linear 2-compartment model was derived from the concentration-time data for abatacept in JRA/JIA subjects.

The clearance and distribution of abatacept (central and peripheral) increased with baseline body weight.

It appears that age, gender and race did not influence abatacept clearance.

Concomitant MTX, corticosteroid or NSAID therapy did not affect abatacept clearance.

It appeared that regardless of age, patients with the same body weight given the same dose of abatacept had similar abatacept exposure time.

Delegate's evaluation of Immunogenicity up-date from Clinical Study Report for Study IM101033 (open-label extension phase –Period C, case report form lock date 07 May 2008)

There was no observable effect of seropositivity on abatacept serum concentrations.

Pharmacodynamics

Mechanism of action

Abatacept is the first in a class of drugs designed to interfere with key co-stimulator signals that are required for antigen-specific T-cell activation and maintenance of memory T-cells. Abatacept prevents the interaction of the T-cells' CD28 with the antigen presenting cells' CD80/CD86 by binding avidly to the latter. In the absence of these signals, the T-cell is rendered anergic. This in turn inhibits multiple aspects of T-cell driven autoimmunity and inflammation.

Primary Pharmacology

There was no pharmacodynamic (PD) study performed or submitted for the purpose of this application. The investigators based their understanding of abatacept on previous PD studies in the adult population (the studies were IM101-102, IM101-100 and IM101-029). A summary including immunogenicity findings is as follows;

- Abatacept produced dose-dependent reductions in systemic levels of biomarkers associated with T-cell activation (soluble IL-2 receptor), accessory cell (macrophage) activation (IL-6 and TNF-α), B- cell auto-antibody production (RF), fibroblast activation (MMP-3) and systemic inflammation (CRP) in Phase II and III studies.
- Abatacept appeared to reduce the immune response to tetanus and pneumococcal vaccines when administered 2 weeks before the vaccines. It numerically decreased the titres response, however, the ability to mount a 2-fold increase in titres was not significantly affected.
- Abatacept was associated with a relatively low (2.8%) frequency of immunogenicity in RA subjects and immunogenicity was not increased in subjects with missed doses although subjects who discontinued abatacept treatment were more likely to be immunopositive. Development of anti-abatacept antibodies did not appear to affect abatacept PK; however the number of immunopositive subjects was too small to enable definitive conclusions regarding potential effects on safety and efficacy.

IM101033 analysed the levels of biomarkers as well as the immunosuppressive effects of abatacept. PD activity was assessed to look at changes in selected cytokines (CRP, ESR, IL-6, soluble IL-2receptor, TNF-α, E-selectin, MMP-3 and sICAM-1). As anticipated by the investigators there were reductions in cytokine levels observed in the children and adolescent subjects with JIA/JRA following treatment with abatacept. However, these changes from baseline in cytokine levels varied considerably and showed no consistent pattern across the two treatment groups. In addition when rheumatoid factor (RF) was assayed, there were only a small number of subjects who seroconverted, however this was not associated with any clinically significant findings.

Comment

Despite the reductions seen in the level of cytokines the importance of this finding is inconclusive, and further study is required to clarify its significance in clinical practice. It also is noted that the PD activities of abatacept in adults may differ from those in children, which will need to be clarified by future studies.

Delegate's evaluation of Immunogenicity up-date from Clinical Study Report for Study IM101033 (open-label extension phase –Period C, case report form lock date 07 May 2008)

The report presented immunogenicity data following abatacept (BMS-188667, cytotoxic T-lymphocyte antigen 4 immunoglobulin [CTLA4Ig] treatment in children and adolescents with active polyarticular JRA or JIA. The presence of antibodies directed against the entire molecule (anti-abatacept antibodies) or the CTLA4 portion (CTLA4-T) of abatacept (anti-CTLA4 antibodies) and their correlation with safety, efficacy and pharmacokinetics was evaluated. The case report cut-off date for this report was 07 May 2008.

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 and therefore withdrawn from therapy for up to 6 months, the rate of seropositivity was 40.7% (22/54).

There were 44 (23.3%) subjects who were seropositive at least once during the study. Of these, 40 had serum anti-CTLA4 antibodies. Two subjects (1.1%) were seropositive for both anti-abatacept (IgG portion of the molecule) and anti-CTLA4 antibodies. Four subjects were seropositive for anti-abatacept antibodies only.

There was a higher frequency of seropositivity (40.7%, 22/54) in subjects who were withdrawn from therapy for up to 6 months (randomized to placebo in period B) than for subjects who continued to receive abatacept in Period B (13.0%, 7/54).

The frequency of seropositivity in subjects who discontinued from the study and were followed up for up to 85 days post-dose was 13.0% (3/23 who discontinued in Period A) and 8.3% (2/24 who discontinued during Period C).

Anti-abatacept and anti-CTLA4 antibodies were generally transient. Most seropositive subjects had antibodies at only a single visit. Fourteen (14) of 44 seropositive subjects had persistent antibodies (defined as detectable serum antibodies at 2 or more consecutive visits). One of these 14 subjects had antibodies at 2 post-discontinuation visits in Period A. The rest had persistent antibodies while on the study. Only 2 subjects had elevated titres at the last recorded evaluation in the study. The presence of these persistent antibodies did not have any apparent effect on efficacy or safety.

Concomitant MTX treatment had no effect on antibody production in placebo-treated subjects in Period B, that is, the rate of seropositivity was not increased in Period B-placebo subjects who were not treated with concomitant MTX, compared to those treated with concomitant MTX.

Thirty seropositive samples from 25 subjects were evaluable for neutralizing antibody activity. Thirteen samples from 10 subjects contained antibodies with neutralizing activity. The presence of neutralizing antibodies had no apparent effect on pharmacokinetics or on the safety profile or maintenance of efficacy.

Efficacy

Pivotal study (IM101033)

IM101033 was a phase 3, multicentre, multinational randomised study with three parts. There were 190 patients between the ages of 6 and 17 years with moderate to severe polyarticular JIA who had failed disease modifying anti-rheumatic drugs who were recruited into the study. The clinical efficacy and safety of Orencia were assessed in three parts, designated Period A, Period B and Period C. In Period A, which was open-labelled and of 4 months duration, patients received Orencia at intervals according to protocol and were assessed for

response using the ACR Paediatric 30/50/70[3] definition of improvement. Patients who had an adequate response at the end of Period A were then entered into Period B, which was randomised and double-blind. Patients in this period received either placebo or Orencia for 6 months or until the subject experienced a disease flare. Period C comprised of patients who were re-introduced to Orencia after Period B had finished. These subjects were patients who had a disease flare in period B or an inadequate response in Period A. The duration of Period C was ongoing at the time of evaluation and is due to terminate in late July 2009. The dose of abatacept given to subjects during any part of the study was weight based at 10mg/kg.

Primary Objective

The primary objective was to compare the clinical efficacy of abatacept to that of placebo in children and adolescents with JIA/JRA in whom a response had been initially induced with abatacept in Period A.

Secondary Objectives

The secondary objectives were to be analysed after 6 months of double blind therapy (Period B). The particular interests for the investigators were:

1. Safety and tolerability of abatacept in children and adolescents
2. The changes to erythrocyte sedimentation rate (ESR) and C-Reactive Protein (CRP) in these patients (surrogate markers) from baseline
3. Functional changes as assessed using the Childhood Health Assessment Questionnaire (CHAQ)
4. Changes in the overall wellbeing of the patients as measured by the parent global assessment of overall wellbeing
5. The disease activity (change from baseline)
6. The number of joints that became affected (change in joint motion, determined by range of movement)
7. The number of joints that are involved compared to baseline (ACR guidelines used to determine active joints)
8. The number of patients that have disease flare by day 169 of Period B

Comment

Using components of the ACR Paediatric 30 score as secondary objectives was supported by the evaluator. The clinical evaluator acknowledged that the issue of multiplicity is not of concern as the secondary objectives were exploratory in nature. The ACR Paediatric 30 incorporates multiple dimensions of disease activity into a single measure which removes the need for adjustment of multiple comparisons and reduces the chance of finding statistically significant differences between outcomes.

Other Objectives

1. Changes to sleep quality
2. Change to pain experience

[3] ACR Paediatric 30 is now the accepted primary outcome measure in therapeutic trials in JIA/JRA. The American College of Rheumatology criteria comprises a core set of six outcome variables for the assessment of clinical improvement. ACR30/50/70 represents a 30/50/70% improvement in at least three of the response criteria (and with no more than one response variable worse by greater than 30%).

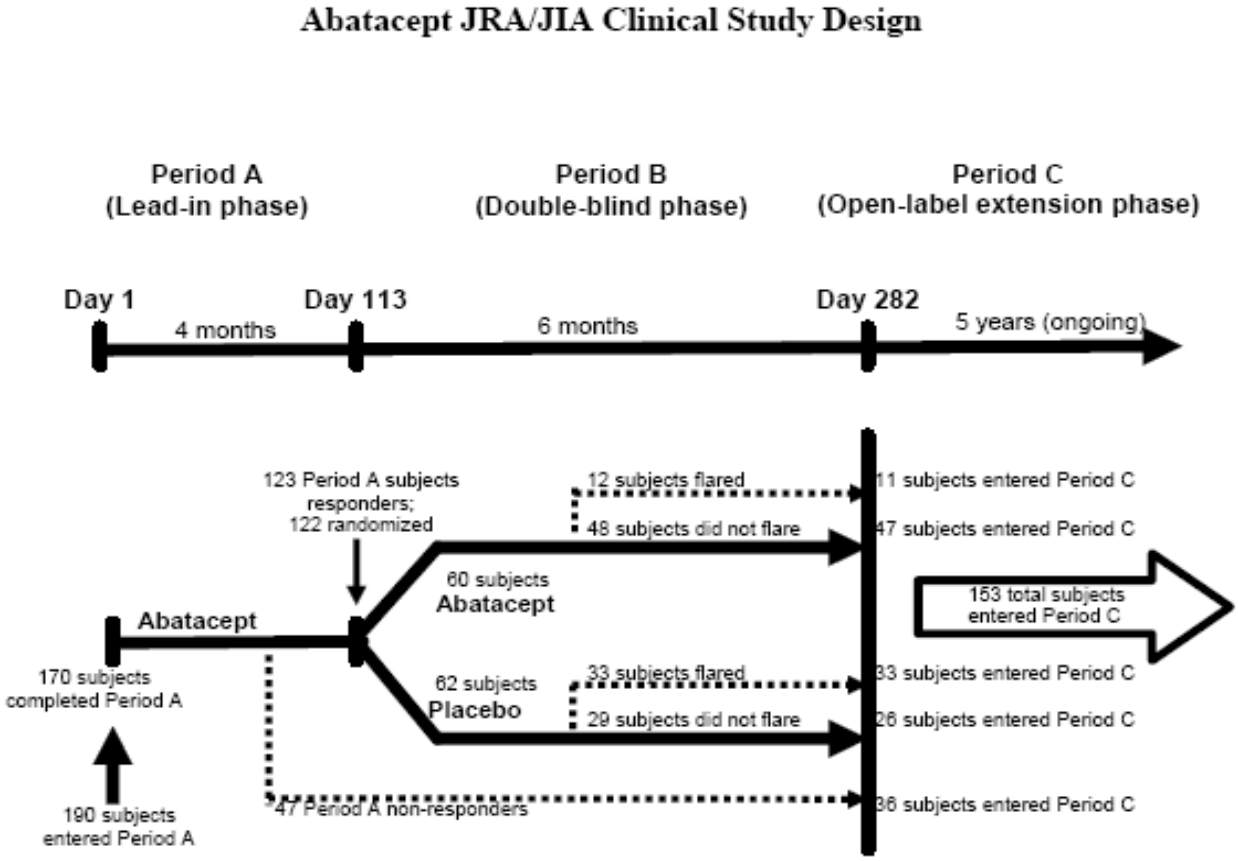
3. Change in socioeconomic status
4. Change to health-related quality of life
5. Changes in height, weight and Tanner stage

All the exploratory objectives were assessed using various patient questionnaires.

Study Design IM101033

This phase III study was conducted at 45 sites across the USA, Europe and South America. There were 3 periods as follows (Figure 1).

Figure 1: Overview of study flow



Lead-in Phase (Period A)

Subjects were treated with open-label abatacept for a period of 4 months and were then assessed for response to medication using the ACR Paediatric 30 definition of improvement. Response was defined as ≥ 30% improvement in at least 3 of the 6 JRA/JIA core set variables and ≥ 30% worsening in not more than 1 of the 6 JRA/JIA core set variables. The dose of abatacept was weight based at 10mg/kg with a maximum dose of 1000mg for subjects > 100kg.

The ACR Paediatric components (JRA/JIA) core set variables were as follows:

1. The number of active joints
2. The number of joints with limited range of motion
3. The physician global assessment of disease activity
4. The parent global assessment of overall wellbeing
5. The childhood health assessment questionnaire (CHAQ)
6. ESR (erythrocyte sedimentation rate)

Double-blind Phase (Period B)

Subjects who were responders at the end of Period A were randomised into a double-blind phase, with either IV abatacept or IV placebo. The dose of abatacept was weight based at 10mg/kg with a maximum dose of 1000mg for subjects > 100kg. Subjects were treated for 6 months or until they experienced a flare.

Disease flare was defined as:

- A worsening of 30% or more from baseline in more than three of the six ACR response variables.
- No fewer than two active joints.
- Improvement of greater than 30% in no more than one of six criteria.

Open-label Phase (Period C)

The following subjects were given the option to receive open-label therapy with abatacept in a follow-up treatment phase;

- Subjects who completed Period A without adequate response
- Subjects in Period B who did not experience a flare
- Subjects who discontinued in Period B due to a flare

The dose of abatacept was weight based at 10mg/kg with a maximum dose of 1000mg for subjects > 100kg. The duration of Period C was 5 years from 23 July 2004.

Comment

The clinical evaluator acknowledged the ACR Paediatric 30 as a recognised tool to measure efficacy outcomes in JIA/JRA therapeutic trials. However it has to be recognised that currently the ACR Paediatric 30 has some notable short-comings which limit both internal and external validity when used as a clinical trial measure.

The problems are;

1. It primarily assesses relative efficacy within the context of clinical trials. The ACR criteria were developed to distinguish between responders and non-responders in trials that compared patients taking active medication to those on placebo. It was not designed to distinguish between levels of disease activity, that is, low versus high[4]. In addition the ACR Paediatric 30 omits systemic features of JIA such as ocular disease which is a feature of disease activity in clinical practice.
2. A patient's age and developmental stage may limit that subject's ability to answer patient self-report such as the CHAQ. Therefore a different version of the same measure must be developed/used for each developmental stage that reflects the developmental ability of the child that is targeted.
3. The CHAQ, physician global assessment of disease activity and parent global assessment of overall wellbeing are susceptible to inadvertent placebo response. The reason is that in the child-family-physician relationship the desire to please has been shown to be strong.[5] This is important to highlight as these variables make up 50% of the ACR Paediatric 30 criteria. In addition the child is often anxious to please his or her parents who in turn are anxious to believe the child is improving.[6] Thus by only selecting children who responded at the end of Period A, the interpretation of abatacept and its role in JIA/JRA is made more difficult in terms of safety and efficacy. An alternative trial design that would help mitigate the placebo response is

[4] Alessandro Consolaro, Nicolino Ruperto et al. Development and validation of a composite disease activity score for juvenile idiopathic arthritis. Arthritis Rheum. 2009; 61: 658-66.
[5] Fernandes R, Ferreira JJ, Sampaio C. The placebo response in studies of acute migraine. J Pediatr 2008; 152: 527–33.

to randomly assign patients to abatacept or placebo at the start of treatment. However there may be difficulties conducting such a trial based on ethical objections.

The ESR is prone to confounders such as intercurrent infection not related to disease activity which may artificially cause it to rise. However the clinical evaluator notes that CRP is also measured in the efficacy analysis which is a better reflection of an acute phase reaction.

It would have been interesting to see the Disease Activity Score (DAS) also used as an alternative or adjunct to the ACR Paediatric 30 for response to therapy and effects on disease activity. Recent papers have shown good concordance of the DAS and the ACR Paediatric 30. The DAS was designed as a measure of disease activity albeit in adults with RA. An analysis by Lurati et al[7] comparing the tools concluded that the DAS can be an alternative to the ACR Paediatric 30 in both children and young adults with JIA. In addition the continuous scale of the DAS corresponds to the extent of underlying inflammation in RA which has the advantage of reflecting both a continuous measure of disease activity over time and an absolute measure of disease state unlike the ACR criteria.

Endpoints

The primary efficacy variable was the time to disease flare in Period B. This endpoint was the major focus for the investigators as they aimed to show;

- A longer time to disease flare for patients treated with abatacept.
- A higher proportion of abatacept treated subjects will have a greater reduction in the incidence of JIA/JRA flare compared to the placebo group.

The other endpoints are discussed below.

Period A: In this open-label period all patients received 4 months of abatacept therapy. Only patients with an adequate response (endpoint) to abatacept using the ACR Paediatric 30 response criteria entered into Period B.

Period B: The study was terminated for a patient when they experienced a flare up of their JRA/JIA or if they reached the end of the trial period. The definition of a flare up was based on the ACR Paediatric 30 core-response variables.

Period C: Any patients who were non-responders in Period A or who experienced a disease flare in Period B were given the option of entering into Period C. Endpoints will be the analysis of functional and laboratory parameters to determine the state of patients' JRA/JIA from baseline. The ACR Paediatric 30 response criteria will also be used to assess efficacy.

Statistical methods

Sample size and power were determined prior to the commencement of the study. The investigators estimated 220 patients were required to be recruited into Period A. This was based on the following assumptions;

- 64 % responder rate in Period A
- 10% drop out rate in Period B
- α=0.05

[6] Rothner AD, Wasiewski W, Winner P, Lewis D, Stankowski J. Zolmitriptan oral tablet in migraine treatment: high placebo responses in adolescents. Headache 2006; 46: 101–19.

[7] A. Lurati I. Pontikaki B. Et al. A comparison of response criteria to evaluate therapeutic response in patients with juvenile idiopathic arthritis treated with methotrexate and/or anti-tumour necrosis factor α agents. Arthritis Rheum 2006; 54: 1602-1607.

- A 95% power to detect change in the time to disease flare between the active and placebo group in Period B. The change in treatment effect was set at 35% difference between active treatments and placebo. This assumed that in those receiving placebo, 65% of subjects will have a disease flare.

Thus it was expected 128 subjects would be entered into Period B with 64 patients in each arm of the randomised double blind phase of the study. All efficacy analyses used were based on the intention to treat group. The treatment groups were compared using a log-rank test (Table 3).

Table 3: Statistical Considerations – An Overview of the Primary and Secondary Efficacy Analyses Performed

Measure of Interest	**Analysis Method**
Time to JRA/JIA disease flare (primary)	Log-rank test, Kaplan-Meier curves, Cox proportional-hazards model
Proportion of subjects with disease flare	Continuity corrected Chi-square test
Change from baseline in: · Number of active joints · Number of joints with limited range of motion · Physician global assessment of disease severity · Parent global assessment of overall well being · CHAQ disability index (parent assessment of physical function) · CRP and other surrogate markers including ESR	Change from baseline by treatment, 95% confidence intervals (CI) for treatment difference in change from baseline

Comment

As abatacept is the first in a new class of medications, the benefits are unknown for patients with JIA/JRA taking abatacept. Thus, it was appropriate for placebo to be chosen as the active comparator.

Patient enrolment, characteristics and disposition

Approximately 220 subjects were planned to be enrolled into Period A and 128 subjects into Period B. However only 190 subjects met the study criteria and were treated and analysed in Period A. At the end of Period A, there were 122 subjects who were eligible to enter into Period B. For Period C a total of 152 subjects were enrolled and treated. This sample group was composed of 36 non-responders in Period A and 117 subjects who were initially randomised and treated in Period B. Inclusion criteria included:

- Subjects between the ages of 6 – 17 years.

- Formal diagnosis of JRA (with pauciarticular, polyarticular or systemic disease onset and polyarticular course) or
- Formal diagnosis of JIA (extended oligoarticular [RF+], polyarticular [RF-], or systemic disease onset and a polyarticular course).
- History of at least 5 joints with active disease, and currently have articular disease
- Insufficient therapeutic response or intolerance in the opinion of the examining physician to at least 1 DMARD

Exclusion criteria included:

- Females of child bearing potential unable or unwilling to use a method of contraception for the entire study period
- Systemic onset of JRA or JIA with intermittent fever due to their disease, rheumatoid rash, hepatosplenomegaly, pleuritis, pericarditis, or macrophage activation syndrome within 6 months prior to enrolment.
- A history of other rheumatic disease or major chronic infections/inflammatory/immunologic disease.
- Had received any live vaccines within 3 months of the first dose of study medication.

A total of 190 patients entered into Period A. At the end of this period 20 had dropped out, the main reason being lack of efficacy (n=17 or 8.9%). Baseline demographics for this period were as follows;

- Age (years) mean of 12.4, median of 13.0.
- Weight (kg) mean of 41.7, median of 41.0.
- Gender: female (137 or 72.1%) versus male (53 or 27.9%).
- The mean duration for JRA in subjects was 4.4 years with a median of 3 years. With regard to the actual duration of disease 41.6% of subjects had disease for less than 2 years, 22.1% had disease for 2 to 5 years, 26.3% had disease for 5 to 10 years and 10.0% had disease for greater than 10 years.
- The mean number of joints involved was 16.2, with a median of 12.0. The mean number of joints with limitation of passive motion (LOM) was 16.3, median 11.0.
- The ESR mean was 32mm/hr, with a median of 27.0mm/hr. The majority were RF negative (149, 78.4%).

As per protocol all subjects were required to stop any prior therapy except MTX. Thus 140 subjects entered into period B with concomitant MTX use.

A total of 123 subjects were classified as responders and thus were eligible to enter Period B. There was one drop out leaving 122 subjects to be randomised: 60 to abatacept and 62 to placebo. In the abatacept group 49 completed Period B. The main reason for dropping out was lack of efficacy of therapy. In the placebo group 31 out of the 62 completed this phase. All subjects who dropped out cited lack of efficacy.

Baseline demographics for this period were as follows;

- Age (years); abatacept group had a mean of 12.6 with a median of 13.0. The placebo group had a mean of 12.0 with a median of 12.5.
- Weight (kg); abatacept had a mean of 41.6 and median of 41.0. The placebo group had a mean of 39.0 and a median of 37.9.
- Gender: in the abatacept group the majority of subjects were female (43 or 71.7%), males accounted for 17 or 28.3%. The placebo group was similar, female 45 or 72.6%, male 17 or 27.4%.
- The mean duration for JRA in abatacept subjects was 3.8 years with a median of 3.0 years. With regard to the actual duration of disease 48.3% of subjects had less than 2 years of disease, 20.0% had disease for 2 to 5 years, 21.7% had disease for 5 to 10 years and 6.0% had disease for greater than 10 years.
- The mean duration for JRA in the placebo group was 3.9 years with a median of 3.0 years. In terms of the actual duration of disease 43.5% of subjects had less than 2

years of disease, 27.4% had disease for 2 to 5 years, 24.2% had disease for 5 to 10 years and 4.8% had disease for greater than 10 years.

- The mean number of joints involved in the abatacept group was 18.2 (median 17.0). The mean number of joints with LOM was 17.3 (median of 14.0).
- The mean number of joints involved in the placebo group was 14.7 (median 9.0). The mean number of joints with LOM was 14.3 (median of 9.0).
- The ESR means for the abatacept and placebo group were 30.8mm/hr and 31.4mm/hr respectively with medians of 26.0mm/hr and 23.5mm/hr respectively. In the abatacept group 68.3% of subjects were RF negative, while in the placebo group 80.6% had RF negative status.
- Concomitant MTX use in both groups during Period B occurred in 94 subjects. There were 48 in the abatacept group who took a mean dose of 13.5mg/m2/kg, and in the placebo group (46 subjects) the mean dose was 12.9mg/m2/kg

A total of 153 subjects were invited to enter Period C (start date was 23 July 2004), which included 117 subjects from period B (59 placebo and 58 abatacept subjects). In addition 36 subjects from Period A who were non-responders were also entered to this period. The lock date for the purpose of the clinical report was 8 December 2006. At this time 85.6% of all subjects were still participating in the study. So far 22 subjects have withdrawn from the study; the main reason identified was lack of efficacy.

Baseline demographics for this period were as follows;

- Mean age 12.3 years.
- Mean weight 40.5kg.
- Gender: females accounted for the majority (70%).
- The mean duration for JRA in subjects was 4.1 years with a median of 3 years. With regard to the actual duration of disease, 43.8% of subjects had experienced less than 2 years of illness, 23.5% had disease for 2 to 5 years, 24.2% had disease for 5 to 10 years, and 8.5% had disease for greater than 10 years.
- The mean number of joints involved was 16.0 (median of 11.0); the mean number of joints with LOM was 16.0, with a median of 10.0.
- The ESR mean was 31.2mm/hr with a median of 25.0mm/hr. The majority were RF negative (117, 76.5%).
- Concomitant MTX was taken by 117 subjects with a mean dose of 13.2 mg/m^2/wk.

Primary efficacy results

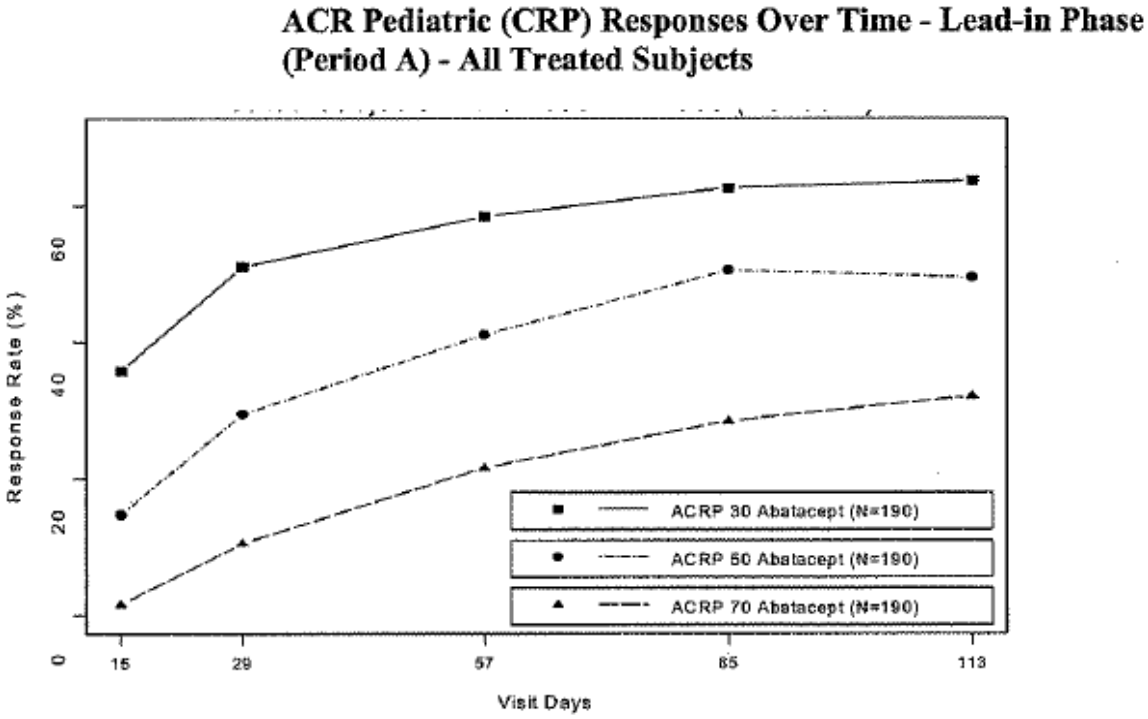
Overall for IM101033 the compliance rate was high. In Period A only 3.2% of subjects missed a single infusion. In Period B, 2 subjects in the abatacept group and 3 subjects in the placebo missed 1 infusion. No subjects in either group missed more than 1 infusion. A total of 132 (86.3%) treated subjects in period C did not miss an infusion of abatacept at any time during this period. No subjects missed more than 2 infusions of abatacept in Period C.

Key results were as follows:

Period A: n=190

- ACR responses at 4 months (Figure 2):
  - ACR30: 64.7% (123/190).
  - ACR50: 49.5%.
  - ACR70: 28.4%.
- Discontinuations: 10.5% (20/190); 17 due to lack of efficacy, 1 each due to adverse effects, withdrawal of consent and investigator decision.

Figure 2: ACR Paediatric Reponses over time Period A for CRP



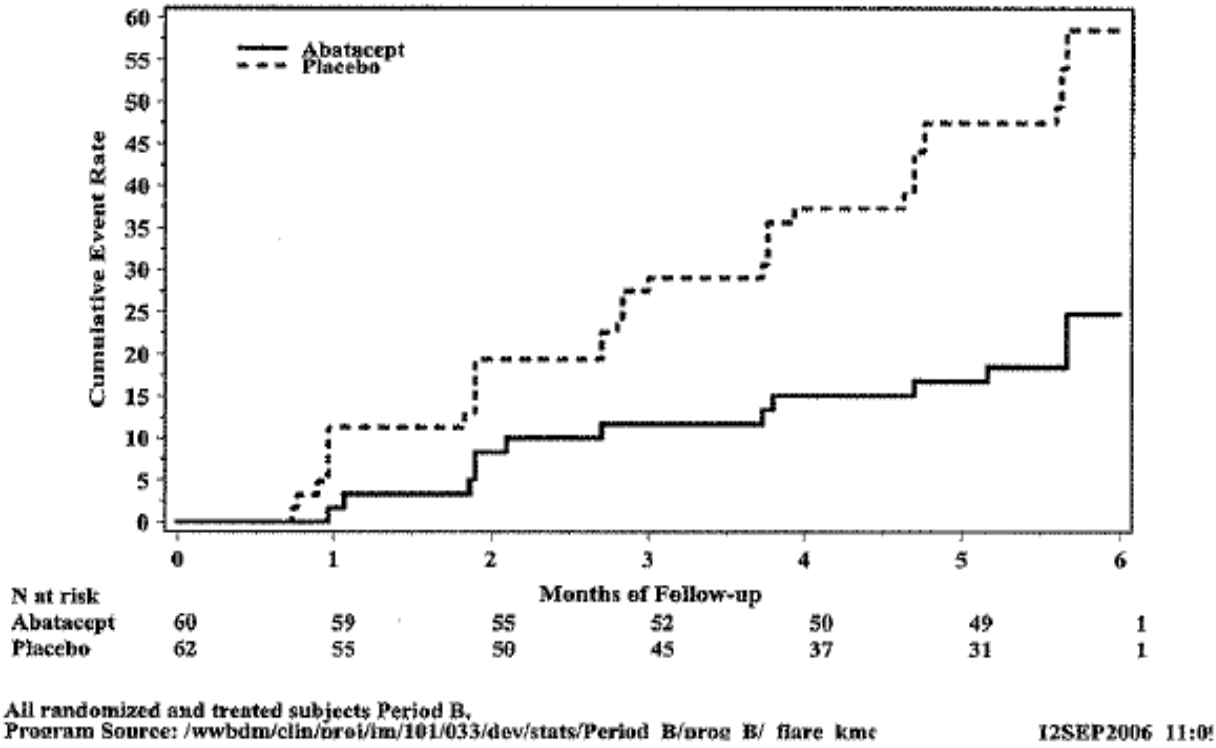
Comment

It is noted that the ACR Paediatric 30, 50 and 70 response rates were based on CRP instead of ESR, the latter not being available. The investigators stated that ESR was not collected at each visit. In the clinical protocol for IM101033 it is stated that CRP would be used to examine acute phase inflammation while ESR was to be used for "in-office" evaluation. ESR and CRP are two tests commonly performed in clinical practice to monitor disease activity as neither test is specific/diagnostic for disease activity. The ACR Paediatric 30 only lists ESR as a measure of inflammation in relation to measuring response rates.

Period B

- n=123 (ACR responders from Period A. Sixty (60) randomised to abatacept and 62 to placebo, 1 responder withdrew consent).
- The primary efficacy variable was time to disease flare (Figure 3), which was statistically significantly shorter for the placebo treated group than for the abatacept treated group (p=0.0002). There was a significant reduction in the risk of disease flare up in the abatacept group compared to the placebo group (HR=0.31, 95% CI 0.16-0.59). Disease flare: abatacept 20% (12/60); placebo 53% (33/62); p=0.0002.

Figure 3: Kaplan Meier curves for Time to Disease Flare (Abatacept vs. Placebo)



Discontinuations: None due to adverse effects from either the abatacept or placebo groups. Fifty percent (50%) of the placebo group and 17% of the abatacept discontinued due to flare or lack of efficacy. 1 patient from the abatacept group withdrew consent.

In the period of the study 30.0% of subjects had received prior biologic therapy, and 2 of 8 (25.0%) abatacept-treated subjects and 8 of 13 (61.5%) placebo-treated subjects experienced disease flare. The proportion of patients who had received prior biologic therapy in the abatacept group was similar to that in the placebo group. Of those who did not receive biologic therapy, the disease flare rate was 19.2% in the abatacept-treated group and 51.0% in the placebo-treated group.

Comment

Some aspects of the study design may have affected efficacy results. The trial design preselects responders to the placebo effect who might retain their response throughout the course of the trial regardless of subsequent randomisation. This is because in Period A all subjects initially received abatacept, but only those who responded entered Period B. This leaves the possibility of an equal number of patients in the abatacept and placebo group who achieved a response due to the placebo effect rather than from active treatment. Thus despite statistical significance, if we assume an equal placebo response in both groups the difference in response may actually be far smaller than the results given. In addition there was no washout period which raises the concern of a carryover effect. It is estimated the half life of abatacept is 16.7 days in healthy controls and 13.1 days for adults with RA[8] who received

8 Bristol-Myers Squibb Company. Orencia (abatacept). http://www.fda.gov/cder/foi/label/2005/125118lbl.pdf

multiple doses of abatacept. Thus the combined effects of these factors can overestimate any potential benefits in clinical practice and underestimate side-effects.

The proportion of patients experiencing disease flare is also important to note. It was reported that 20% of the abatacept group had a flare of their disease compared to 53% in the placebo group. The evaluator assumed that 47% of the placebo group did not have a flare by the end of the 6 months of treatment. The interpretation of this is either abatacept had continued efficacy for 6 months after treatment had stopped or that there was a continued placebo response or both. Again because of the trial design it was difficult to come to a conclusion.

Period C

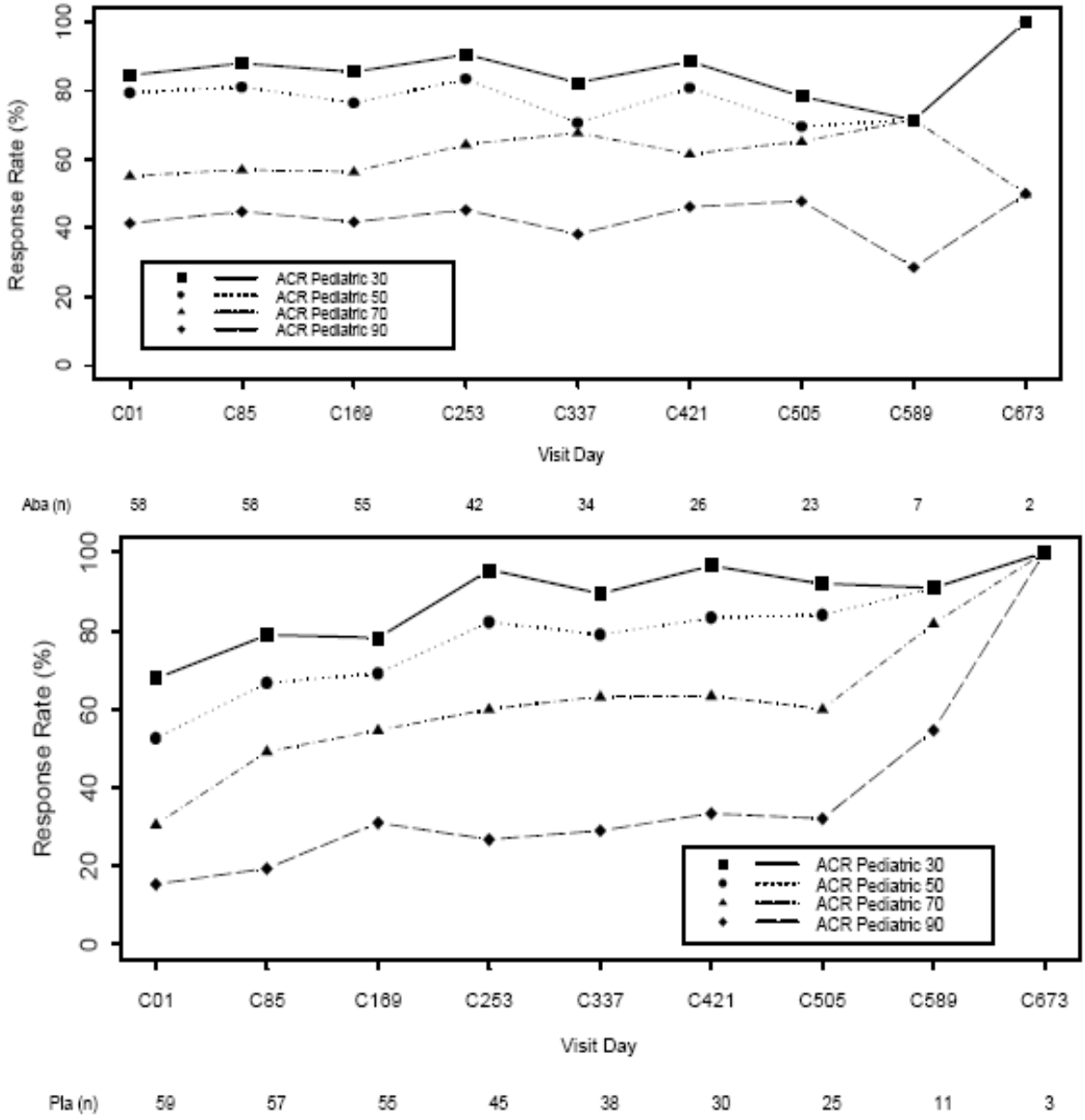
The ACR Paediatric 30, 50, 70 and 90 response rates were maintained from the end of Period B for the cohort of subjects who received abatacept during Period B and Period C. It would appear that there was an early treatment effect for patients who received placebo in Period B who were then treated with abatacept in Period C. These improvements in the ACR response rate were maintained through to day 589 of Period C.

Comment

The maintenance effect of abatacept was not fully substantiated in this study as this period has not come to its conclusion and thus only partial data is presented in this submission. Figure 4 is of limited value as it only represents an ACR responder at some visit days and not at the other visit days. For example, referring to the abatacept group in Figure 4 at visit C01 and the ACR Paediatric 30 response rate it shows i) 58 subjects were recorded at visit C01 and ii) approximately 83% of the 58 subjects achieved the ACR Paediatric 30 response rate for ESR. At visit C253 it is not possible to ascertain whether all of these 42 subjects attended visit C01. It is therefore difficult to determine whether the ACR response is clinically meaningful over that time. This may be the way the investigators chose to represent the data and that individually each patient may have had appropriate follow up as per trial protocol to track their response. However, it may have been clearer if the responders at the beginning of Period B and their ACR scores were tracked together to see how many of them maintained the effect over an extended period of time.

Figure 4: Period C efficacy results (incomplete)

ACR Pediatric Response Rates (ESR) over Time for Abatacept-treated (top graph) and Placebo-treated (bottom graph) Subjects Who Entered the Open-label Extension Phase (Period C)



Population: All Treated Subjects in Period C.
All subjects received a fixed dose of abatacept in Period C.
Response information for Period C is derived from observed data.
Classification of response based on value observed at Day A1.
Visit Number C01 = Period B Day 169 LOCF.

Secondary efficacy results

JRA/JIA Core Set Variables

The ACR Paediatric component variables continued to improve slightly or remained stable during Period B in the abatacept group whereas most of the variables worsened in the placebo group in Period B (Table 4).

Table 4: JRA Core Set Variables (ACR Paediatric Components) Efficacy Results Period B – Median Percent Change from Baseline (B1) to Day 169 (all randomised and treated subjects in the double-blind phase)

		Abatacept N=60	**Placebo N = 62**
	N	60	62
Active joints	Baseline median	3.00	2.00
	Post-baseline median	1.50	4.50
	Median % change from baseline	-20.9	50.00
	% change percentile (25th, 75th)	(-92.00, 17.86)	(0.00, 100.00)
Joints with LOM	Baseline median	4.00	3.00
	Post-baseline median	3.00	5.00
	Median % change from baseline	0.00	50.00
	% change percentile (25th, 75th)	(-45.5, 0.00)	(0.00, 100.00)
Phys Global Assessment	Baseline median	17.50	9.00
	Post-baseline median	6.50	21.00
	Median % change from baseline	-29.8	55.96
	% change percentile (25th, 75th)	(-86.3, 22.48)	(-31.3, 250.0)
Parent Global Assessment	Baseline median	15.00	12.50
	Post-baseline median	10.00	16.50
	Median % change from baseline	-11.2	8.39
	% change percentile (25th, 75th)	(-56.8, 28.41)	(-31.8, 100.00)
CHAQ Disability Index	Baseline median	0.50	0.50
	Post-baseline median	0.50	0.56
	Median % change from baseline	0.00	0.00
	% change percentile (25th, 75th)	(-38.9, 2.17)	(-13.3, 55.56)
ESR (mm/hr)	Baseline median	16.00	15.50
	Post-baseline median	15.00	20.50
	Median % change from baseline	0.00	20.50
	% change percentile (25th, 75th)	(-20.7, 50.00)	(-14.3, 92.00)
CRP (mg/dL)	Baseline median	0.50	0.40
	Post-baseline median	0.30	0.85
	Median % change from baseline	0.00	6.25
	% change percentile (25th, 75th)	(-46.6, 67.00)	(-33.3, 150.0)

Comment

The clinical evaluator noted that the JRA core set variables were recorded as a change from baseline for both Period A and Period B. However, it may have also have been useful to see data that looked at the number of patients who improved by ≥ 30% in 3 of the 6 JRA core set variables and to see how many achieved the JRA Paediatric 30 criteria for flare by worsening of ≥ 30% in no more than 1 of the 6 core set variables. The data as it is presented in the dossier allows for a positive response to be achieved, but the same patient may actually be worse off in one of the other criteria from baseline. It is of clinical interest to see which variable(s) is more likely to improve or worsen in those patients that achieved a positive response.

Currently, the JRA Paediatric 30 only reflects the signs and symptoms accepted for evaluation of JIA/JRA; it does not incorporate a single component for pain. It is of clinical interest to see whether abatacept is also able to provide pain relief which is an important component of treatment response in all categories of JIA[9].Thus, it would have been useful to know the proportions of subjects achieving an improvement of≥ 30% in the individual criteria that make up the JRA Paediatric 30 to see whether abatacept is also suitable as a symptom-relieving therapy.

Other efficacy results

By MTX use

Similar response rate were seen with and without concomitant MTX therapy. Thus the MTX and abatacept response rates using the ACR Paediatric 30, 50, 70 and 90 response rates at the end of Period A were 68.8, 50.7, 27.5 and 12.3% respectively; while the response rates in those who did not receive MTX concomitantly with abatacept were 53.8, 46.2, 30.8 and 13.5% respectively.

Physical Function and Subject-reported Outcomes

The increase in (worsening) pain scores as measured by the visual log analogue scale from 0-100mm was statistically less for abatacept subjects compared with the placebo group. The mean difference in pain scores was -7.2 with a 95% CI -14.4 to -0.10. Overall, there were no statistically significant differences in the physical and psychosocial summary of the CHQ between the abatacept and placebo groups. It is noted that the disability index scores for the CHAQ worsened in the placebo group compared to the abatacept group, however the clinical significance of this is uncertain.

Disease Subtype

ACR Paediatric 30 response rates at the end of Period A were 59.3, 68.4, 64.3 and 64.9% for oligoarticular extended, polyarticular RF positive, and polyarticular RF negative and systemic JIA/JRA subtype populations respectively.

Conclusions regarding efficacy

It has been demonstrated from study IM101033 that the children who received abatacept were more likely to have a longer time to disease flare compared with children randomised to placebo (p=0.0002). In this study it was shown the median time to flare was much shorter in the placebo group compared to the active treatment group as less than half of those subjects who were assigned to abatacept actually experienced a disease flare during Period B. Also important were the actual numbers of patients who had a disease flare, again the abatacept

[9] EMEA "Guideline on Clinical Investigation of Medicinal Products for the Treatment of Juvenile Idiopathic Arthritis"

group had a much lower proportion who had a flare up of their JIA/JRA from those given placebo (p=0.0002). However due to the withdrawal design of the study, the high rate of attrition of subjects in the placebo group, the use of last observation carried forward data and the carry-over effects of treatment, the efficacy endpoints were subject to bias.

In regard to whether abatacept is efficacious with or without MTX needs further clarification. At the start of Period A, 73.7% of patients were taking MTX with abatacept. The response rates according to the ACR 30, 50, 70 and 90 were similar with or without concomitant MTX use by the end of the 4 month open-label period. In period B, 78.7% of patients were also taking MTX regardless of randomisation. There were roughly equal distributions of MTX takers in each group for Period B (49/56 or 81.7% vs. 47/61 or 75.8%, abatacept versus placebo respectively). There appears to be no subgroup analysis comparing the concomitant use of MTX with abatacept and abatacept alone. This makes it difficult to comment on the true efficacy of abatacept as monotherapy. In turn this leads to the issue of whether the efficacy result is partly contributed by the combined therapy of abatacept and MTX. Thus, it may be argued a condition of registration for abatacept is its use as adjuvant therapy with MTX only. Monotherapy is only given when a patient fails MTX during concomitant use with abatacept. Trials looking at abatacept in the future needs to compare efficacy between abatacept monotherapy versus MTX monotherapy and abatacept versus placebo to mitigate the confounder in the efficacy results presented in this submission.

The investigators acknowledged the flaws in trial design and the deliberate exclusion of patients with systemic manifestations of their disease. It was stated by the investigators that IM101033 was similar in methodology to other trials of anti-TNF agents (for example, etanercept and adalimumab) but had the advantage that it offered subjects immediate treatment and minimised the time of treatment with placebo. Overall the trial investigators were responsive to the guidelines set out by the EMEA in conducting IM101033. In particular the patient selection was well defined and typical of the types of patients with JIA/JRA one might see in clinical practice. The primary efficacy endpoint used is well supported by experts in the field of rheumatology and regulatory agencies world-wide. At present “time to remission” or “time in remission” is not incorporated as an efficacy endpoint in most trials of medicinal products for JIA/JRA. This is due to a lack of clear consensus on how to define remission.

Delegate’s evaluation of Efficacy up-date from Clinical Study Report for Study IM101033 (open-label extension phase –Period C, case report form lock date 07 May 2008)

There were 153 subjects enrolled and treated in Period C, including 36 non-responders in Period A and 117 randomized and treated in Period B (58 in abatacept-treated group and 59 in placebo-treated group). All of the 153 subjects entering Period C received treatment with open-label abatacept. The mean total duration of exposure to abatacept in Period C was 832.6 days (median = 898.0 days or ~ 32 months). By cohort, the mean total duration of exposure to abatacept in Period C was: 720.2 days (Period A non-responder), 875.3 days (Period B-abatacept) and 859.2 days (Period B-Placebo). At the time of database lock, all subjects that remained in Period C had received at least 589 days (~ 21 months) of treatment.

ACR Paediatric response rates (based on ESR) over time, beginning with day B169 LOCF (visit day 169 in period B) and continuing through to the day C589 (visit day 589, month 21 of open-label extension phase, Period C) are shown in Figures 5, 6 and 7, for the Period B-abatacept, Period B-placebo and Period A-non-responders, respectively. When one compares the graphs in these figures with those in Figure 3, one can see that there are now many more subjects for whom data is available up to visit day 589 of Period C. In the Period B-abatacept cohort, ACR Paediatric 30 and ACR Paediatric 50 response rates were maintained from the

end of Period B (day B169 LOCF) to day C589 (~ month 21) and additional increases were seen in the % of children attaining ACR Paediatric 70, ACR Paediatric 90 and inactive disease status. The Period B-placebo cohort improved following re-introduction of abatacept during Period C. By day C253 (~ month 9 of Period C), ACR Paediatric 30, 50 and 70 response rates were similar to those achieved by the Period B-abatacept cohort (92.5% and 96.2% for Period B-abatacept and Period B-placebo cohorts, respectively, for ACR Paediatric 30). The Period A-non-responder cohort improved by all response measures with additional abatacept therapy in Period C, although response rates in this cohort were consistently lower than those in the Period B-abatacept or Period B-placebo cohorts at each visit of open-label extension phase Period C.

Figure 5: ACR Paediatric Response Rates over time in Period C for Period B-abatacept cohort

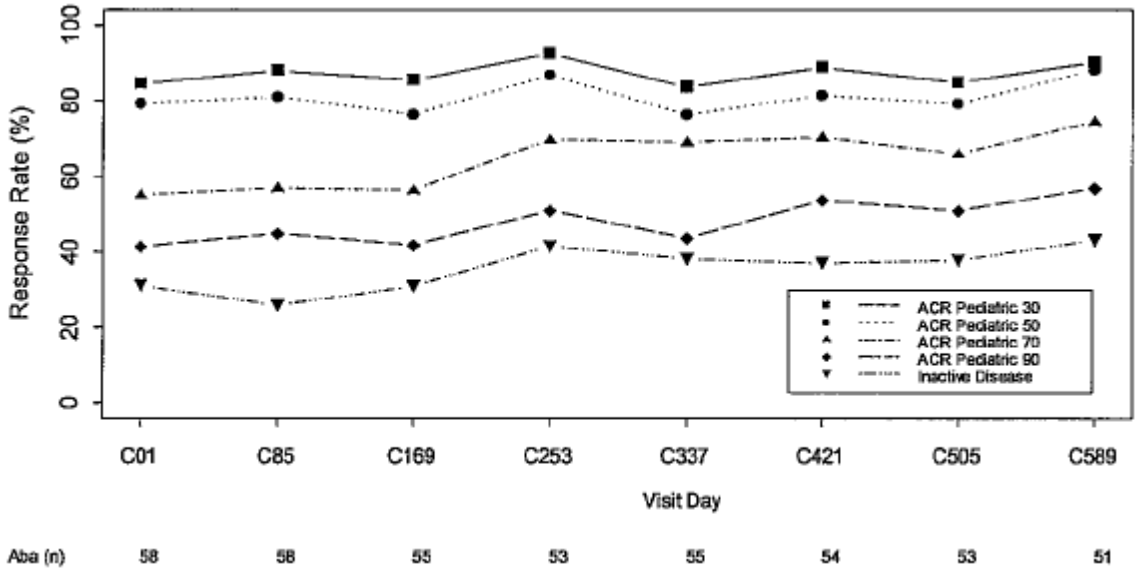


Figure 6: ACR Paediatric Response Rates over time in Period C for Period B-placebo cohort

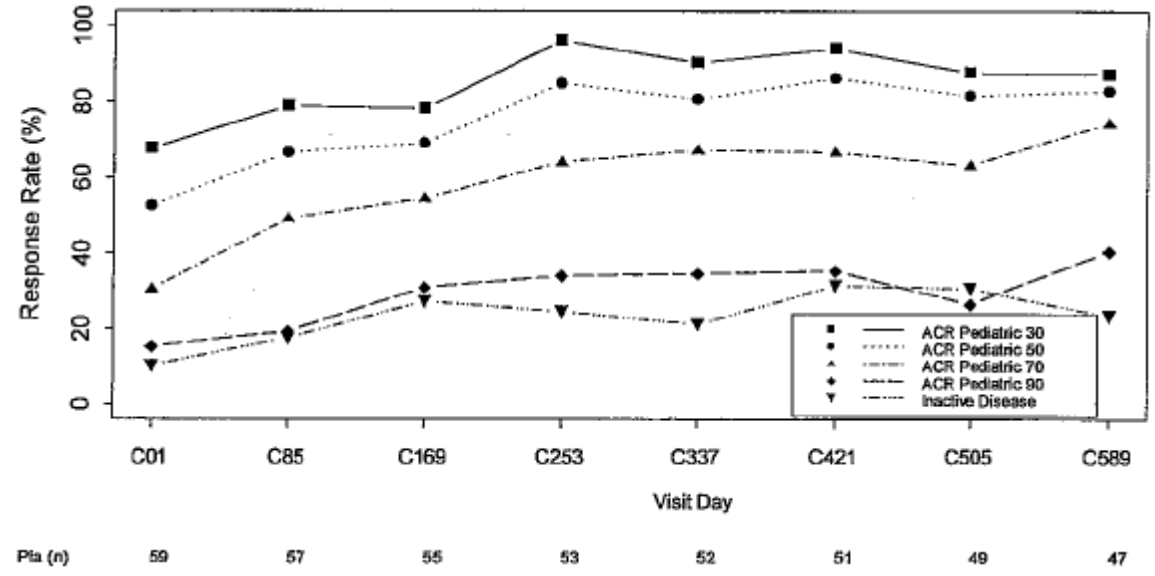
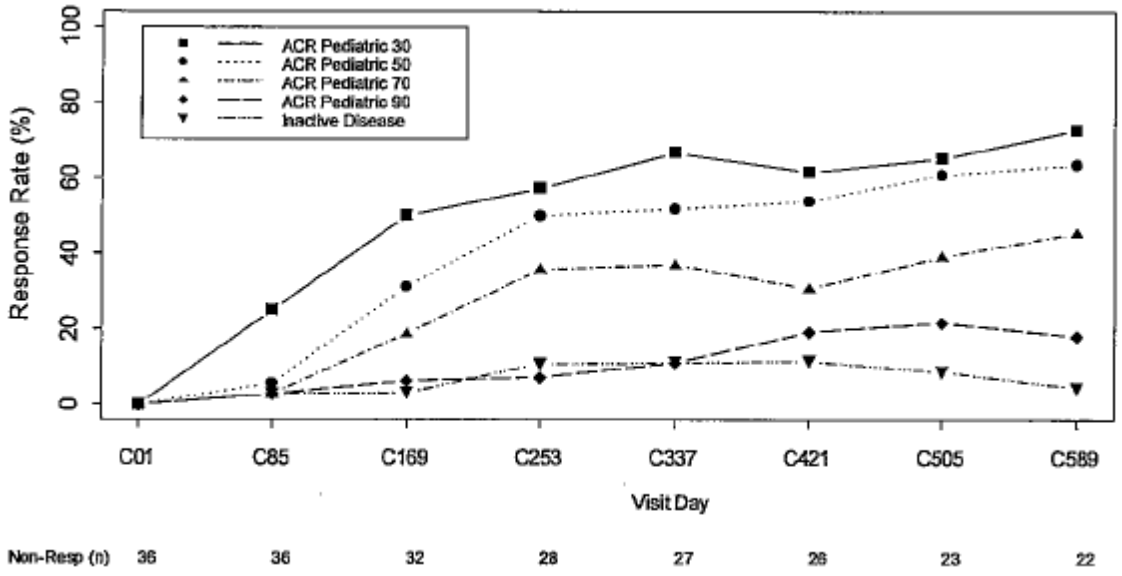


Figure 7: ACR Paediatric Response Rates over time in Period C for Period A-non-responder cohort



Analysis by Flare Status in Period B: Subjects who were randomized to double-blind treatment in Period B could enter the open-label extension phase Period C, either after they had completed the 6-month double-blind period without experiencing a flare or after they discontinued from the double-blind period due to a flare. At the day C589 (~ month 21), ACR Paediatric 30 (ESR) response rates among subjects who experienced a flare in Period B vs. those who did not, were 81.8% and 92.5%, respectively, for the Period B-abatacept cohort and 85.2% and 90.0%, respectively, for the Period B-placebo cohort.

Analysis by Age: Approximately 2/3 of subjects in each of the Period C cohorts were aged 12 to 18 years of age at study entry. At all time points analysed, there were no discernible differences in the ACR Paediatric 30, 50, 70, 90 or inactive disease status response rates among subjects aged 6 to < 12 years and those aged from 12 to 18 years for each of the 3 cohorts, Period B-abatacept, Period B-placebo or Period A-non-responder.

Analysis by JIA disease sub-type at diagnosis: There were no differences in ACR Paediatric (ESR) response rates as a function of JIA disease sub-type at initial diagnosis in the Period B-abatacept or Period B-placebo cohorts.

Delegate's evaluation of Immunogenicity up-date from Clinical Study Report for Study IM101033 (open-label extension phase –Period C, case report form lock date 07 May 2008)

There was no relationship between seropositivity and disease flare in Period B (flare was not evaluated in Periods A or C) nor between seropositivity and ACR Paediatric response during Periods A, B or C.

To further assess if seropositivity had an effect on efficacy, the addition of DMARDs during Period C in seropositive subjects was evaluated by seroconversion status at any time during the study. The addition of DMARDs was prohibited per protocol during Periods A and B. This analysis was done in order to ensure that persistence of efficacy in these seropositive patients was due to abatacept and not due to a disproportionate use of added DMARDs. The proportion of seropositive subjects who took DMARDs during Period C was 15%, comparable to the proportion in the seronegative population (13%).

Safety

Pivotal study (IM101033)

All subjects who received at least one dose of the study medication during Periods A or B were entered into the safety analysis. Infections, neoplasms, autoimmune disorders, infusion-related adverse events (AEs), any AEs associated with the use of immunomodulator drugs and classified AEs of special interest were examined.

Patient exposure

Period A

There were 190 subjects treated with abatacept for 4 months. The mean duration of exposure to abatacept was 118.2 days. The median was 112 days.

Period B

Abatacept group (60 subjects): Mean duration of exposure to abatacept was 153.4 days. The median was 168 days.

Placebo group (62 subjects): Mean duration of exposure to placebo was 127.0 days. The median was 158.5 days.

Period C

A total of 153 subjects were enrolled and treated with abatacept at the start of Period C. This phase is not expected to terminate until 5 years from the date of initiation of Period C. Thus patients potentially are exposed to abatacept until 23 July 2009.

Comment

Overall Periods A and B were relatively short time-wise to allow for insidious serious adverse events (SAEs) such as cancers to be discovered. Period C is to address the safety and tolerability of long term use of abatacept, thus data will be requested from the trial investigators as soon as this phase of IM10133 terminates.

Period A

The System Organ Class (SOC) associated with the highest number of AEs was *infections and infestations* (35.8%) (Table 5). Overall AEs were reported in 133 of 190 (70.0%) subjects. The most frequently reported AE was headache (13.2%). The majority of AEs during the lead-in phase were of mild or moderate intensity. Four of 190 (2.11%) subjects had an infection of interest. These were herpes simplex and varicella infections each in 2 subjects. All but one of the infections was considered to be of mild or moderate intensity by the investigators.

Table 5: Summary of AEs for Period A and B[10]

	4-month open-label period	6-month double-blind period		
	Abatacept (N=190)	Abatacept (N=60)	Placebo (N=62)	p-value*
Total serious adverse events	6 (3%)	0	2 (3%)	0.50
Total adverse events#	133 (70%)	37 (62%)	34 (55%)	0.47
Infections and infestations	68 (36%)	27 (45%)	27 (44%)	1.00
Influenza	7 (4%)	5 (8%)	4 (7%)	0.74
Bacteriuria	3 (2%)	4 (7%)	0	0.06
Nasopharyngitis	11 (6%)	4 (7%)	3 (5%)	0.72
Upper respiratory tract infection	14 (7%)	4 (7%)	5 (8%)	1.00
Gastroenteritis	1 (0.5%)	3 (5%)	1 (2%)	0.36
Sinusitis	6 (3%)	3 (5%)	2 (3%)	0.68
Rhinitis	8 (4%)	1 (2%)	4 (7%)	0.36
Gastrointestinal disorders	66 (35%)	10 (17%)	9 (15%)	0.81
Abdominal pain	9 (5%)	3 (5%)	1 (2%)	0.36
Nausea	19 (10%)	2 (3%)	4 (7%)	0.68
Diarrhoea	17 (9%)	1 (2%)	1 (2%)	1.00
Upper abdominal pain	10 (5%)	1 (2%)	0	0.49
General disorders and administrative site conditions	26 (14%)	4 (7%)	9 (15%)	0.24
Pyrexia	12 (6%)	4 (7%)	5 (8%)	1.00
Nervous system disorders	30 (16%)	3 (5%)	2 (3%)	0.68
Headache	25 (13%)	3 (5%)	1 (2%)	0.36
Respiratory, thoracic and mediastinal disorders	32 (17%)	6 (10%)	3 (5%)	0.32
Cough	17 (9%)	0	2 (3%)	0.50

*Fischer's test used to test the difference between groups given abatacept and placebo in the double-blind phase

Adverse events that occurred in at least 5% of patients in the open-label and double blind phases

The investigators considered the relationship to the study drug was 'unlikely' or 'unrelated' except for one infection that was considered 'possible'. All infections resolved with treatment and did not result in study drug discontinuation. Clinically, these infections were of typical presentation. The one event of severe infection (herpes simplex) was observed in a 14-year old female subject on Day 51. The event resolved in 13 days with treatment and did not result in study discontinuation. The relationship to the study drug was 'unlikely' according to the investigator.

10 Table from original article published in *The Lancet* Vol 372 August 2, 2008 383-391

Period B

The SOC associated with the highest number of AEs was *infections and infestations* for both the abatacept (45.0%) and placebo groups (43.5%). AEs were reported by 61.7% of subjects in the abatacept group and 54.8% of subjects in the placebo group. The most frequently reported AE (≥ 5%) was influenza (8.3%) for the abatacept group; this event occurred at a frequency of 6.5% in the placebo group. The most frequently reported AEs (≥ 5%) for the placebo group were upper respiratory tract infection and pyrexia (8.1% for both); these events occurred at a frequency of 6.7% (for both) in the abatacept group. The proportion of placebo group subjects with AEs of severe intensity was 6.5% and very severe intensity was 1.6%; no subject in the abatacept group had an event that was considered of severe or very severe intensity according to the investigator.

Only one of 60 abatacept-treated and three of 62 placebo-treated subjects had infections of interest. The single infection reported in the abatacept cohort was herpes simplex of mild intensity which resolved without any treatment; the subject continued in the study. The investigator considered this infection 'unlikely' to be related to the study drug. Importantly, no opportunistic infections or atypical presentations of infections were reported in any subjects receiving abatacept. A total of five events of infections (2 cases of herpes simplex, 1 cellulitis, and 1 varicella with encephalitis) were reported for three placebo-treated subjects. These infection events for the placebo group subjects were mostly of moderate to severe intensity; one infection (varicella) also required treatment interruption.

Period C (clinical lock date 8 Dec 2006)

The SOC associated with the highest number of AEs was *infections and infestations* (54.2%). AEs were reported for 111 (72.5%) subjects. Upper respiratory tract infection (12.4%) and vomiting (10.5%) were the most frequently reported AEs (≥ 5%). Eleven subjects' AEs (7.2%, 16 AEs) were severe in intensity. Severe AEs in Period C were primarily related to gastrointestinal disorders (2 reports each of vomiting and nausea) and musculoskeletal and connective tissue disorders (1 report each of arthralgia, joint swelling, arthritis, and RA). Two subjects (1.3%) had a total of 3 AEs that were very severe in intensity; these included 1 report each of vomiting, diarrhoea, and depression.

Additionally the types of AEs were consistent with those observed in Period B and in the adult program. Specifically, during this period, 11 pre-specified infections (6 viral infections [3 varicella, 2 Herpes simplex, and 1 viral infection] and 5 bacterial infections [2 tooth abscesses, 1 cellulitis, 1 pneumonia, and 1 *Staphylococcal* infection]) were reported in a total of 10 (6.5%) subjects. Most of the pre-specified infections were mild or moderate in intensity and had a duration ranging from 3 to 15 days. One (1) of the pre-specified infections was considered severe in intensity (varicella) and resolved after 15 days. One (1) infection was continuing at the time of the case report form (CRF) lock date (*Staphylococcal* infection, verbatim term: "right upper left leg lesion with methicillin-resistant *S. aureus*"); additional data after this date indicated that the infection resolved following antibiotic treatment.

Related AEs were relatively uncommon in the abatacept-treated subjects and were usually mild to moderate and did not lead to treatment interruption. The frequency of related AEs was 27.4, 15.0, and 30.1% for abatacept-treated subjects during Periods A, B, and C respectively. The frequency for placebo-treated subjects during Period B was 21.0%. Most of the events during abatacept treatment were mild or moderate in intensity except 1 (chest pain) in Period A and 2 (eczema and hypersensitivity) in Period C. The chest pain event occurred on Day 1 and resolved in 2 days without any treatment or interruption of study medication;

eczema was continuing at the time of CRF lock; and hypersensitivity resolved in 1 day. A total of 3.2% of the events in the placebo group (Period B) were severe in intensity.

Most of the reported infections of interest were mild or moderate in intensity, "unlikely" or "unrelated" to the study drug according to the investigator, resolved with treatment without significant clinical sequelae, did not result in study drug discontinuation, and were consistent with those commonly seen in outpatient children and adolescent populations. Importantly, no opportunistic infections, fungal or protozoal infections, or atypical presentations of infections were reported in any subjects receiving abatacept.

None of the reported infections resulted in hospitalization or were serious. There was no evidence that any infection followed a course that differed in duration or severity compared to infections of a similar nature in a non-immunocompromised host.

Adverse reactions (drug-related adverse events)

The numbers and percentages of subjects experiencing AEs following abatacept administration were small (range across 3 periods: 1.7 to 4.2%). Most of the events were isolated and mild/moderate in intensity, and did not re-occur at subsequent infusions or result in discontinuation.

Period A

During Period A acute infusion-related AEs (reported within 1 hour of the start of the infusion) were infrequent (4.2%). All but 1 (headache) of the acute infusion-related AEs were mild in intensity and none were serious. The majority of different types of acute infusion-related AEs occurred in only 1 subject each except for headache and dizziness that occurred in 4 and 2 subjects respectively.

Period B

During Period B the rate of acute infusion-related AEs was 1.7% for the abatacept group and 3.2% for the placebo group. The single acute infusion-related AE for the abatacept group was mild in intensity whereas those for the placebo group were mild or moderate in intensity. For subjects who were withdrawn from abatacept during the 6-month, double-blind phase (Period B) and randomised to the placebo group, no serious acute infusion-related events were observed upon re-initiation of abatacept therapy in Period C. There were no cases of anaphylaxis reported following abatacept treatment in the paediatric/adolescent JRA/JIA population.

Period C

During Period C acute infusion-related AEs were reported in 4 (2.6%) subjects. Three of the 4 subjects with acute infusion-related AEs in Period C had received abatacept in double-blind phase Period B. None of the acute infusion-related AEs reported were serious or resulted in treatment discontinuation. One of the acute infusion-related AEs was severe in intensity (Verbatim term: 'palpebral oedema, pruritus, and rash due to allergic reaction', MedDRA Preferred Term: hypersensitivity).

Overdosage, Discontinuations, SAEs and Deaths

Since abatacept is administered as an IV infusion under medically controlled conditions, it is unlikely that a subject would receive notably more than the recommended dosage. Knowledge is limited regarding effects of an overdose. One subject (a 17-year-old female weighing 53.7 kg) inadvertently received an infusion of 750 mg abatacept instead of 540 mg on Day C421 of Study IM101033; the subject reported no AEs associated with this event. Past studies where subject have been administered abatacept of doses up to 50mg/kg showed

no dose-related toxicities. Doses of abatacept up to 100mg/kg have been given to non-primates with a similar absence of any dose related toxic effects. Based on this information, it is unlikely that a large infusion of abatacept would be harmful.

Only one subject discontinued due to a SAE during the lead-in (Period A), double-blind (Period B), or open-label extension (Period C) phases of the JRA/JIA study (IM101033). The one discontinuation was due to acute lymphocytic leukaemia (ALL). A bone marrow biopsy at Day 89 of Period A in the 7 year old male subject showed a marked decrease in haemoglobin count from baseline from 10.5 g/dL to 5.1g/dL (Day 83 of Period A). This case would appear to be unlikely due to abatacept as the patient was anaemic prior to treatment. The subject received treatment; no further information for this case is available despite the sponsor's continued efforts.

Also at this stage the effects of abatacept and the genetic mutations thought to be involved in the development of ALL appear to be unrelated.

There were no deaths reported during the study. Overall, SAEs were reported for a small number of subjects during each treatment period of the study. No unique SAEs relative to the adult RA program were noted. The following is a summary of SAEs of interest.

Period A

SAEs were reported for 6 subjects. Three of the 6 SAEs were representative of the underlying disease (disease flare or joint wear).The other 3 SAEs included 1 event each of varicella infection, ovarian cyst, and acute lymphocytic leukaemia; the relationship to the study drug for all of the 6 SAEs was either "unlikely" or "unrelated" according to the investigators. The varicella infection was clinically typical (not of unusual intensity, duration, or response to therapy) and resolved without sequelae despite continued abatacept treatment. The only SAE that resulted in discontinuation was the case of acute lymphocytic leukaemia discussed above.

Period B

SAEs were not reported for any of the abatacept-treated subjects. Three SAEs were reported for 2 placebo-treated subjects during this period (haematoma, varicella, and encephalitis). These SAEs were: arthritis, RA, synovial cyst, torticollis (condition aggravated), pyrexia, erysipelas, gastroenteritis, nausea, vomiting, food allergy, and overdose. None of these SAEs were considered to be related to the study drug by the investigator or led to treatment discontinuation.

Period C

During the open-label extension phase 13 SAEs were reported by 9 subjects (5.9%); all were considered to be unrelated to study treatment. None of the infections of interest were serious and only one case of varicella was considered severe in intensity. There was one case of vitiligo; the subject had a history of the disease prior to study entry.

Neoplasms: Benign, Malignant, and Unspecified

Neoplasms were reported in six abatacept-treated subjects during any period of the JRA/JIA study. Five of these 6 neoplasms were skin papilloma (all considered to be benign and of mild/moderate intensity) which did not result in study drug discontinuation. Specifically, skin papilloma was reported in 4, 0, and 1 abatacept-treated subjects during Periods A, B, and C, respectively, and in 1 placebo-treated subject during Period B. One (1) event of acute lymphocytic leukaemia during Period A resulted in treatment discontinuation.

Autoimmune Disorders

Abatacept did not appear to initiate or exacerbate pre-existing autoimmune disorders in the paediatric/adolescent JRA/JIA population. Autoimmune disorders were reported only in 2 subjects (erythema nodosum during Period A and increased vitiligo during Periods A and C) during the entire duration of the IM101033 study. Both events were moderate in intensity and were not considered serious. Neither of the potentially autoimmune-related symptoms or disorders reported resulted in discontinuation of study medication. The subject with the increased vitiligo event had a history of vitiligo prior to study entry; the subject remained on abatacept treatment. The proportion of subjects who seroconverted from the negative to positive status for either antinuclear antibodies (ANA) or antibodies to double-stranded DNA (dsDNA) was small (ANA: 10.6%, 5.9%, and 14.3% during Periods A, B, and C, respectively; dsDNA; 6.2%, 2.3%, and 7.1% during Periods A, B, and C, respectively).

Growth

From the start of Period A on the 5 February 2004 to the clinical lock date of 8 December 2006 (Period C, ongoing) all subjects treated with abatacept were observed for growth delay. Analysis showed that there were normal increases in height and body weight. Any effect of abatacept on the Tanner stages will be analysed at the conclusion of Period C to further evaluate the subjects' growth potential.

Comment

It is important to acknowledge that IM101033 was not a safety study, thus the power is limited in detecting rare but possibly serious AEs. As previously mentioned the long term data for period C is not yet available so a final assessment cannot be made about growth and development. It is recognised the time from 12-17 years of age is one of rapid sexual maturation, growth and neuro-cognitive development. It is a sensitive time when drugs may interfere with the actions of sex hormones and impede development. These factors need to be acknowledged when looking at long term safety issues.

Drug interactions

Formal drug interaction studies have not been conducted with abatacept. However, population pharmacokinetic analysis showed MTX, NSAIDs, corticosteroids, and TNF blocking agents did not influence abatacept clearance.

Comment

The issue of concomitant use of abatacept with anti-TNF medicines needs to be clarified in children. However a specific interaction study would not be ethical and thus our understanding is limited to looking at AEs and post-marketing experience. However, it has been shown in adult patients that taking abatacept and anti-TNF medicines together results in significant immune suppression. In clinical practice children/adolescents with JIA/JRA are commonly on anti- TNF therapy and in the proposed Australian PI this has been satisfactorily addressed under Indications, Precautions and Contraindications.

Laboratory abnormalities

Biochemistry and Haematology

ALT, AST, creatinine, and neutrophil levels remained stable with abatacept treatment during Periods A, B, and C. No consistent trends or safety concerns were identified in this study for either the abatacept or placebo groups. This finding is consistent with the abatacept experience in adult subjects with RA. Small changes from baseline in hematologic and blood chemistry parameters were noted with considerable variation but there was no consistent pattern.

Delegate's evaluation of Safety up-date from Clinical Study Report for Study IM101033 (open-label extension phase –Period C, case report form lock date 07 May 2008)

No deaths were reported in subjects treated with abatacept in open-label extension phase Period C.

SAEs were reported for 23 (15.0%) subjects during Period C, most of which were considered unrelated to study treatment. The proportions of subjects with SAEs were similar for each of the 3 cohorts of Period C. Four (2.6%) subjects had SAEs during Period C which were considered related to abatacept treatment (herpes zoster; hypersensitivity to abatacept; fibroadenoma of the breast; temporal lobe epilepsy (TLE) and multiple sclerosis (MS)[both of latter in 1 subject, see below]).

Three subjects (2.0%) discontinued treatment in open-label extension phase Period C due to an AE, including one subject who was withdrawn for SAEs (TLE and MS).

Infections: A total of 111 (72.5%) reported at least one AE in the SOC, Infections and Infestations, during Period C. The infections were bacterial, viral and fungal, with most bacterial. Many of the individual infections or infestations were reported in only 1 or 2 subjects each. Nasopharyngitis (17.6%), upper respiratory tract infection [URTI] (16.3%) and pharyngitis (12.4%) were the most common. Infections that were viral and reported in more than 2 subjects during Period C included influenza (15 subjects, 9.8%), varicella (5 subjects, 3.3%), viral infection (5 subjects, 3.3%), gastroenteritis viral (3 subjects, 2.0%), viral pharyngitis (3 subjects, 2.0%) and herpes zoster (3 subject, 2.0%). None of the viral infections was severe in intensity. Fifteen infections appeared fungal with most cutaneous and non-invasive. The one exception was a case of mucocutaneous candidiasis, mild in intensity and resolving with nystatin treatment. There were 2 reports of atypical pneumonia, both mild and both resolving with azithromycin treatment. There were 6 reports of parasitic infestations, all in subjects enrolled at South American sites. Five subjects had infections classed as serious, of which only one was considered possibly related to abatacept (herpes zoster). The remaining serious infections (bacterial meningitis, erysipelas, dengue fever, gastroenteritis and pyelonephritis) were assessed as unlikely related or unrelated to abatacept. All resolved with treatment.

Neoplasms: The fibroadenoma of the breast was serious and assessed as possibly related to abatacept. No malignant neoplasms were reported during Period C.

Autoimmune disorders: Three subjects (2.6%) had pre-specified autoimmune disorders reported during Period C (vitiligo; cutaneous vasculitis – resolved with treatment after 20 days and multiple sclerosis). The multiple sclerosis was diagnosed in a 12 year old boy, reported to have had a seizure on day C593 (4 days after the 12th infusion of abatacept in Period C). Brain magnetic resonance imaging (MRI) showed lesions consistent with demyelination. Electroencephalogram showed TLE, successfully treated with carbamazepine. Abatacept was discontinued. MS was diagnosed after cerebrospinal fluid analysis showed IgG oligoclonal bands and visual evoked potentials suggested anterior optic pathway dysfunction. There was no known personal or family history of MS and the MS is continuing.

Infusion-related adverse events: Acute infusion-related AEs (reported within 1 hour after the start of the abatacept infusion) were reported in a total of 5 (3.3%) subjects treated in Period C. There were three hypersensitivity-like events. Peri-infusion-related AEs (occurring within 24 hours of the infusion) were reported for 16 (10.5%) subjects treated with abatacept in Period C. Dizziness (n = 4, 2.6%) and nausea (n = 3, 2.0%) were the most common peri-infusion-related AEs. There was no increase in the frequency of infusion-related AEs

following the re-introduction of abatacept treatment in Period C in the Period B-placebo cohort.

Nasopharyngitis (17.6%), URTI (16.3%) and vomiting (15.0%) were the most frequent AEs reported during Period C. AEs were reported for 86.3% of subjects in Period C, with the majority mild or moderate in intensity. There was no difference in safety profile between males and females or between subjects aged < 12 years and those 12 years and above. AEs in Period C were similar to those seen in adult subjects.

No safety issues emerged from the evaluation of laboratory or vital sign data.

Increases in body weight and height were evident in Period C. At day C589, these changes averaged 7.39 kg for body weight and 8.04 cm for height.

Delegate's evaluation of Immunogenicity up-date from Clinical Study Report for Study IM101033 (open-label extension phase –Period C, case report form lock date 07 May 2008)

There was no observable correlation of seropositivity with the occurrence of SAEs, acute infusion-related AEs, peri-infusion-related AEs or autoimmune disorders.

Seropositive subjects in the Period B-placebo cohort were not at increased risk of experiencing SAEs, acute or peri-infusion-related AEs or autoimmune disorders when abatacept treatment was re-initiated in Period C, relative to subjects in the Period B-abatacept cohort or Period A-non-responders cohort, who continued on abatacept in Period C. Of the 22 placebo-treated subjects who became seropositive following withdrawal of abatacept in Period B, 21 re-initiated abatacept treatment in Period C. SAEs (gastroenteritis, synovial cyst and erysipelas, recurring nausea, vomiting and pyrexia as well as temporal lobe epilepsy and multiple sclerosis) were reported for four of these subjects in Period C. The events of TLE and MS were assessed as possibly related to abatacept and did not resolve. All other SAEs during Period C in Period B-placebo subjects were judged to be unlikely to be related or not related to abatacept. Furthermore, all these other SAEs resolved with treatment, did not lead to discontinuation and were not recurrent with further therapy.

During Period C, 3 (6.5%) seronegative subjects (all in the Period B-abatacept cohort) had acute infusion-related AEs (hypersensitivity, nausea and infusion-related reaction). Two seropositive subjects, including 1 Period B-placebo subject had non-serious acute infusion-related AEs. Neither of these events occurred with the first Period C dose. One of these subjects discontinued due to an autoimmune event. With the exception of urticaria the events did not recur with subsequent infusions.

During Period A, 1 subject had an autoimmune disorder (moderate erythema nodosum). The subject was seronegative for more than 4 months after the event but was seropositive (anti-CTLA4 antibodies) at day 85 after the last-dose visit in Period C. There were no pre-specified autoimmune disorders reported during the double-blind phase (Period B). During Period C, 3 (2.6%) subjects had pre-specified autoimmune disorders (vitiligo, cutaneous vasculitis and MS). Only one of these subjects was seropositive, the subject with MS and this was the only one considered possibly related to abatacept. The subject discontinued after diagnosis of moderate/grade II right TLE**.** The sponsor is requested to provide an up-date on the commentary on this case.

Post-marketing experience

The cumulative exposure since abatacept was first approved for use (23 December 2005 in the US) has been recorded by the sponsor as 337 968 511 mg which equates to approximately 32 187 patient years. The latest Periodic Safety Update Report (PSUR) was the sixth compiled and it was for the period from 23 June 2008 to 22 December 2008. During this

PSUR period approximately 11 621 500 mg of abatacept was sold between 1 April and 30 September 2008. The estimated number of patient-years treated for the same period was 11 068. Over 8000 subjects have participated in clinical trials worldwide. The longest exposure by a subject in a clinical trial to abatacept was approximately 96 months. No regulatory actions were taken against the sponsor in relation to safety issues.

Changes to the Company Core Data Sheet (CCDS) included the following:[11]

- Under the 'Warnings and Precautions for Use" section of the CCDS, a new statement for *Infections* that reflects the risk of sepsis, pneumonia and serious infections for patients already on immunosuppressive therapy.
- Another statement that warns about hypersensitivity was amended to also include hypotension, urticaria and dyspnoea occurring within 24 hours after infusion with Orencia.
- Under the 'Undesirable effects" section of the CCDS, a new statement for *Malignancies* which is explicit in stating the incidence rates for various malignancies that were reported in a double blind and open label clinical trial with 4149 patients treated with Orencia. It also mentions that the overall incidence rate was similar between the two trials when matched for age and gender in a rheumatoid arthritis population.

Conclusions regarding safety

As reported the overall safety profile for abatacept is acceptable clinically. The data shows that 62% (37/60) of abatacept patients and 55% (34/62) of placebo recipients had an AE. The long term effects of abatacept and the associated risk of harm are still unknown. The placebo-controlled withdrawal trial methodology and short trial duration do not allow harm to be adequately assessed especially in key safety areas such as growth and neurocognitive changes as well as the development of neoplasia. Despite the minimal difference in the incidence of SAEs from the lead-in phase, in which all children received abatacept, it has to be acknowledged this may have been the result of the carry-over effect (discussed in "Comments" of the Primary Efficacy results) leading to an underestimation of harm associated with abatacept use. As well, despite the limitations of post marketing monitoring by the sponsor, it would also appear that no new areas of concern have emerged from these reports.

Clinical Summary and Conclusions

Study IM101033 was a randomised, double blind, placebo-controlled withdrawal trial conducted in children and adolescents with active polyarticular juvenile rheumatoid arthritis. The study demonstrated:

- A greater effect of abatacept compared to placebo in treating signs and symptoms of JRA/JIA. This effect was measured by time to occurrence of disease flare based on the ACR Paediatric 30.
- A greater number of subjects **not** experiencing a disease flare for patients receiving abatacept vs. placebo.

[11] A Company Core Data Sheet (CCDS) is an internal company global reference document containing, in addition to safety information, material relating to indications, dosing, pharmacology and other information concerning the product. It is used to direct the content of local (affiliate) labeling.

- There is evidence of a possible greater efficacy effect for abatacept in patients taking concomitant MTX therapy vs. MTX alone, however the design of the trial makes it difficult to assess the magnitude of this effect.
- A satisfactory safety profile.

Thus, the evaluator recommended the approval of abatacept 250mg IV powder for infusion by Bristol-Myers Squibb for;

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

The evaluator also recommended the establishment of a patient registry which would include Australian patients and the provision of the final study report from Period C. The reason for this recommendation is to monitor AEs in patients with long term abatacept use. As previously discussed, the long term outcome for patients with renal and hepatic impairment treated with abatacept is not yet fully understood. The registry may help clarify this issue in the future.

V. Pharmacovigilance Findings

There was no Risk Management Plan submitted with this application as it was not a requirement at the time of submission.

VI. Overall Conclusion and Risk/Benefit Assessment

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

Quality

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

Nonclinical

No evidence of abatacept-related toxicity was observed on the developing neurobehavioural or reproductive systems in juvenile rats.

GLP-compliant, 13-week repeat-dose studies with abatacept were performed in juvenile and adult rats. Toxicities in juvenile rats included an increased susceptibility to infection and the development of signs of autoimmunity (lymphocytic infiltration of pancreas and thyroid glands). A No Adverse Effect Level could not be determined in these studies, with exposure ratios (AUC) ranging from 3 at the lowest doses to approximately 40 at the highest doses.

The clinical relevance of the nonclinical observations in juvenile rats was not entirely clear. No autoimmune signals have been noted in human clinical trials of adults or juveniles. Nevertheless, in the absence of any data from juvenile animals treated with other immunomodulatory drugs used in the treatment of JIA, it must be considered that increased susceptibility to infection and autoimmunity are potential adverse consequences of abatacept treatment in a human paediatric population.

Overall, there were no nonclinical objections to the registration of Orencia provided that:

- a suitable statement is included in the Australian PI (similar to that in the US label) outlining the adverse findings in juvenile animal studies, and
- the company's Risk Management Plan (RMP) includes provisions for specific post-market monitoring of possible increases in infection rates and the development of

autoimmunity symptoms in the intended paediatric population. Moreover, the RMP should include the monitoring of the potential increased tumour incidence that could conceivably occur in long-term immunosuppressed, juvenile patients that are being treated with abatacept and methotrexate in combination.

The Delegate supported the above recommendations of the nonclinical evaluator.

Clinical

The clinical evaluator has recommended approval of the application for the following revised indication: "Reducing signs and symptoms in paediatric patients 6 years of age and older with moderate to severe active polyarticular juvenile idiopathic arthritis who have had an inadequate response to one or more disease modifying anti-rheumatic drugs (DMARDs). Orencia may then be used as monotherapy or concomitantly with methotrexate (MTX)".

Pharmacodynamics

The study IM101033 analysed the levels of biomarkers as well as the immunosuppressive effects of abatacept. PD activity was assessed to look at changes in selected cytokines (CRP, ESR, IL-6, soluble IL-2 receptor, TNF-α, E-selectin, MMP-3 and sICAM-1). There were reductions in cytokine levels in paediatric subjects with JIA following treatment with abatacept but the changes from baseline in these levels showed no consistent pattern across the two treatment groups. Only a small number of patients were RF positive and no consistent clinical correlates could be made with the latter.

Pharmacokinetics

The POPPK analysis used serum collected from all subjects in Periods A and B as well as data from 6 adult RA studies (3 Phase II and 3 Phase III).

The mean clearance of abatacept in the JIA subjects was approximately 0.40 mL/h/kg with body weight the only clinically significant subject covariate identified. Abatacept clearance was shown to increase with baseline body weight. [In adults with RA, mean half-life was approx. 13 days, systemic clearance was 0.22 mL/kg and mean Vss ranged from 0.02 to 0.13 L/kg consistent with distribution in the extracellular volume].

The Cmin, Cmax and AUC for JIA subjects were found to be 15-39% lower than those for adult RA subjects receiving the same dose of 10 mg/kg. However, the ACR 20 response rates were comparable.

The effects of abatacept are currently unknown for patients with significant renal and hepatic impairment.

Primary efficacy results

Period A: overall ACR30 response at 4 months = 64.7% (123/190. ACR30 response in subjects with prior biologic therapy = 38.6% (22/57) and ACR response in subjects with no prior biologic therapy = 75.9% (101/133).

Period B: time to disease flare in responders from Period A statistically significantly shorter for placebo-treated group compared with abatacept-treated group. Placebo flares 33/62 (53.2%) vs. abatacept flares 12/60 (20.0%) with HR = 0.31, 95% CI [0.16, 0.59], p = 0.0002. The clinical evaluator made a comment that there was a possibility of an equal number of patients in the two groups who achieved a response to the placebo effect (or more accurately would have achieved a placebo response if they had been treated with placebo – Delegate). The clinical evaluator expressed a concern that this may mean that the difference in response would have been much smaller than reported. The study was akin to a withdrawal study. In the view of the Delegate, randomization at the beginning of Period B would have taken

account of those who would have responded anyway to placebo (if they had been given placebo). As the clinical evaluator says, both groups would have been balanced in terms of such people.

Period C: The ACR Paediatric 30, 50, 70 and 90 response rates were maintained through to day 589 of Period C (Figure 4). This shows the numbers in the abatacept-treated group at the corresponding visit day in Period C. Thus there were 58 subjects recorded as having attained Day 1, 58 for Day 85, dropping to 7 subjects for visit Day 589. This is clearly because at the data lock point of 08 December 2006, not a great number of subjects had been in Period C for a long time (Study Period B had only ended on 21 June 2006). In the top graph one can observe a maintenance of treatment effect in the abatacept group. Similarly, below the bottom graph in Figure 4, that showing response rates in the placebo-treated group, it can be seen that there were 59 subjects recorded as having attained Day 1, 57 for Day 85, dropping to 11 subjects for visit Day 589. In the bottom graph, one can see an initial rise in response rates as subjects, having been exposed to placebo in Period B, are now exposed to abatacept once again and gain a treatment effect. When the up-dated results (up to data lock point 07 May 2008) were considered, greater numbers of subjects had attained visit Day 589 in Period C.

Secondary efficacy results

The ACR Paediatric component variables continued to improve slightly or remained stable during period B in the abatacept group whereas most of the variables worsened in the placebo group in Period B.

Similar response rates at the end of Period A were seen with and without concomitant MTX therapy. In Period B there were roughly equal proportions of subjects taking concomitant MTX in the abatacept and placebo groups but the clinical evaluator makes the comment that there is no sub-group analysis of the efficacy of the combination of abatacept and MTX vs. that of abatacept alone. In Period B, there were four possible treatment regimens, namely abatacept + MTX, abatacept alone, placebo + MTX and placebo alone.

The Delegate also noted that the mean and median ages for the treatment groups in Period B are around 12-13 years. The comparison of efficacy in children below the age of 12 years with that for children aged 12 years and above was provided by the sponsor as extra data. The Delegate has evaluated this data.

Overall, the Delegate agreed with the clinical evaluator that efficacy of abatacept compared with placebo has been demonstrated in JIA (significantly longer time to disease flare in the abatacept group compared with placebo and a significantly lower proportion of subjects in the abatacept group with a disease flare compared with placebo).

Safety

Adverse events: The system organ class (SOC) associated with the highest number of AEs was *infections and infestations* for each of the three Periods A, B and C with the percentage accounted for by that SOC rising from Period A to Period C (35.8% in Period A; 45% in Period B in abatacept group, 43.5% in Period B in placebo group; 54.2% in Period C). No opportunistic infections or atypical presentations of infections were reported in any subjects receiving abatacept in Period B. The types of AEs in Period C were consistent with those observed in Period B and in the adult programme. Again, there were no opportunistic, fungal or protozoal infections or atypical presentations of infections in Period C.

Adverse Reactions: The percentages of subjects experiencing acute infusion-related AEs ranged from 1.7% to 4.2% across the 3 periods (Period A 4.2%, Period B 1.7% and Period C

2.6%). Most of the events were isolated and mild/moderate in intensity and did not re-occur at subsequent infusions or result in discontinuation.

Withdrawals due to adverse events: The one discontinuation due to an AE in the whole study was a case of acute lymphocytic leukaemia in a 7-year old boy. Based on anaemia prior to treatment and the particular genetic mutations involved in the ALL, the case was judged as unlikely to be related to the abatacept treatment.

Deaths and other serious adverse events (SAEs): There were no deaths reported during the study. SAEs were reported for a small number of subjects during each of the 3 treatment periods. There were no SAEs which did not also occur in the adult population.

Neoplasms: total of 6 in abatacept-treated subjects – one malignant (ALL above) and 5 benign (skin papillomata)

Auto-immune disorders: abatacept did not appear to initiate or exacerbate pre-existing autoimmune disorders (2 cases reported – erythema nodosum and increased vitiligo)

Growth: normal increases in height and body weight; effect on Tanner stages to be evaluated at the end of Period C.

Laboratory abnormalities: no consistent trends or safety concerns identified for ALT, AST, creatinine and/or neutrophils.

The evaluator was of the opinion that the efficacy and safety of abatacept had been satisfactorily demonstrated in children and adolescents with JRA/JIA. The clinical evaluator recommended a refinement to the indication to restrict the use of the drug to those subjects who have had an inadequate response to one or more disease modifying anti-rheumatic drugs (DMARDs). The latter was one of the important inclusion criteria of Study IM101033. The Canadian Product Monograph includes a similar restriction.

Risk-Benefit Analysis

Efficacy

The Delegate agreed with the clinical evaluator that Study IM101033 demonstrated that children and adolescents who received abatacept were more likely to have a longer time to disease flare compared with those randomised to placebo. Also the abatacept group had a significantly lower proportion of subjects who had a flare of their JIA/JRA compared with the placebo group. The issue of whether abatacept is efficacious with or without MTX needs further clarification. The protocol did not require concomitant MTX use. Subjects not taking MTX at enrolment were not started on MTX for study entry. Subjects receiving MTX were to have been maintained on a stable dose and route for at least 4 weeks prior to the first dose of study medication. MTX doses were to be decreased only for toxicity. The majority of subjects during all study phases received concomitant MTX: 74.2% in Period A, 81.7% and 75.8% (abatacept and placebo, respectively) during Period B and 79.1% during Period C. Thus, between 18.3% and 25.8% of subjects in the different populations were not taking MTX during the various study periods. Continued treatment with abatacept 10 mg/kg during the open-label extension phase Period C resulted in the maintenance of improvements in core disease symptoms seen during abatacept treatment in the double-blind phase Period B. Efficacy responses for the Period B-placebo cohort improved after abatacept treatment was re-introduced in Period C. Clinical improvement was also seen in Period C in the cohort of subjects who had failed to respond initially to abatacept (Period A non-responders).

Safety

Abatacept at 10 mg/kg IV, administered every 4 weeks for an average of approximately 35 months (including treatment in the lead-in Period A and the double-blind phase Period B) was generally safe and well tolerated in paediatric subjects with polyarticular JIA. The overall safety profile for abatacept during the open-label extension phase Period C up to data lock point 07 May 2008 was not different from that observed during the double-blind phase Period B.

Immunogenicity

The presence of antibodies to abatacept or CTLA4 did not correlate with any long-term clinical safety problems nor with any diminution in clinical efficacy. Nor did seropositivity have an effect on serum concentrations of abatacept. In the JRA/JIA population studied, seropositivity was generally transient and antibody titres generally low.

Summary

Overall, the Delegate was of the opinion that there was sufficient evidence of efficacy and safety for the registration of Orencia (abatacept [rch]) for the indication as revised by the clinical evaluator:

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 Delegate proposed to approve the submission for this indication but indicated that the sponsor should address the following issues in their pre-ADEC response:

1. An update to the registration status (with dates) for abatacept for the new indication in JIA/JRA in the USA, Europe/UK, Canada, New Zealand and Switzerland including any withdrawals, rejections or deferrals. This has been included in this AusPAR.
2. A summary of its post-marketing commitments to the US FDA with a summary of the anticipated timelines of completion (only a brief statement is required). The sponsor responded that the post-marketing commitments to the US FDA included the 3 animal studies referred to in 3, which have been submitted to and evaluated by the TGA, and the submission of the protocol, interim reports, and final study report for a JIA patient safety registry comprised of at least 500 patients. This protocol included a plan for more intensive scrutiny for the first 3 years, with annual follow ups (which could be telephonic) assessing for occurrence of malignancies, other autoimmune diseases, and serious infections, for a total of 10 years. Patients turning 18 years of age or older will continue to be followed until they completed the 10 year follow-up period. Information on these patients may be obtained via annual questionnaire/telephonic follow-up with attention to key adverse events rather than full clinic visit with examination. The protocol was submitted on 31 December 2008 with interim reports scheduled for 30 June 2014, 2019 and 2024 with the final report scheduled for 30 June 2029.
3. Confirmation that the 3 animal studies requested by the US FDA have been completed and that their complete study reports were indeed those evaluated by the TGA's pre-clinical evaluator (only a brief statement is required). The sponsor confirmed that the three animal studies requested by the US FDA have been

completed, and indeed were those reports submitted to, and evaluated by, the TGA as part of this application.

4. Confirmation that there are no further animal studies planned or further animal studies completed but not evaluated by the TGA (only a brief statement is required). The sponsor confirmed that no further animal studies are planned or have been completed but not evaluated by the TGA.
5. The sponsor is to indicate whether it is intended that Australian patients will have the opportunity to enter the planned JIA patient safety registry (only a brief statement is required). The sponsor replied that the Paediatric Rheumatology International trials Organisation (PRINTO), which is being used by BMS for the abatacept paediatric safety registry, has sites in Australia. BMS plans to request that PRINTO sites in Australia be included in the registry once abatacept is approved for JIA in Australia. However, the individual PRINTO sites in Australia will have to agree to participate and the sponsor cannot provide a guarantee for Australian patients at this time.
6. The Delegate's intention to make the provision, as a Category 1 application, of the completed study report for Study IM101033, (that is, when Period C has been fully reported), a condition of registration of abatacept (only a brief statement is required). The sponsor replied that as the Company will automatically submit the final report to the TGA when it becomes available, submission of the report as a Category 1 application should not be made a condition of approval for the indication.
7. The Delegate's intention to make the provision of the reports for the proposed study in children aged 2-5 years and for the proposed JIA patient safety register, a condition of registration of abatacept (only a brief statement is required). The sponsor indicated that it will provide to the TGA the paediatric assessment completed for JIA patients 2-5 years of age as required by the US FDA. It also asked the TGA to note that while a comprehensive medical assessment of the risk/benefit profile of abatacept will be completed for this specific JIA patient sub-population, it has not been established at this time if a clinical study investigating abatacept in this specific sub-group of JIA patients would indeed be conducted.
8. A brief summary in tabular form of the chief PK parameters of abatacept, comparing the results in paediatric JIA subjects with those in adult subjects with RA. This was provided.
9. A breakdown of the age distribution of patients in Study IM101033 by year of age (that is, 6 years, 7 years, 8 years, etc.). This was provided.
10. The actual numbers of children and adolescents, including a breakdown by age (< 12 years and 12 years and above), exposed to abatacept for a total of 6, 9, 12, 18, 24, 36 and 48 months so far. This was also provided.
11. An analysis of the efficacy of the combination of abatacept + MTX vs. that of abatacept alone. This was provided.
12. A brief summary of the case of the 7-year old boy with ALL with commentary on the attributability of the latter and a brief up-date of the commentary on the case of the 12-year old boy with MS/TLE. This was done.

The Delegate also requested the advice of ADEC on the following issues:

- whether there is sufficient clarity in the PI concerning the concomitant use of MTX with abatacept, in particular should Orencia be approved as monotherapy and/or in combination with MTX
- whether the proposal for further studies in patients aged 2-5 years and the JIA patient safety register should also be made conditions of registration here in Australia
- comment about the clinical evaluator's opinion that in Period B of Study IM101033 there was a possibility of an equal number of patients in the two groups who would have achieved a response to the placebo effect.

The Australian Drug Evaluation Committee (ADEC), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, agreed with the Delegate's proposal.

ADEC recommended approval of the submission to include the indication:

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

The ADEC agreed with the Delegate and the clinical evaluator that the efficacy and safety of abatacept has been satisfactorily demonstrated in children and adolescents with juvenile rheumatoid arthritis (JRA)/ juvenile idiopathic arthritis (JIA). The Committee further noted that there is sufficient clarity concerning the concomitant use of MTX with abatacept in the PI. The data available suggests that abatacept is no less efficacious when used as monotherapy, additionally it will provide an alternative option in consideration of the difficulties in administering MTX in paediatric population at times. The Committee noted that currently paediatric rheumatologists are adding subjects with JIA using biologics to the Australian Rheumatology Association Database (ARAD), but the establishment of a JIA patient safety database is also encouraged.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Orencia powder for IV infusion vials containing abatacept (rch) 250 mg for the new indication:

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

Attachment 1. Product Information

PRODUCT INFORMATION

ORENCIA®
(abatacept)

(LYOPHILIZED POWDER FOR IV INFUSION))

NAME OF THE MEDICINE

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

DESCRIPTION

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

PHARMACOLOGY

General

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

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

Pharmacodynamics

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

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

Pharmacokinetics

Healthy adults and adult RA

Absorption

Abatacept is administered intravenously.

Distribution

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

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

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

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

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

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

Metabolism and elimination

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

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

Special populations

Paediatric and Adolescent Patients. Population pharmacokinetic analysis of abatacept serum concentration data from patients with juvenile idiopathic arthritis (JIA) aged 6 to 17 years following administration of abatacept 10 mg/kg revealed that the estimated clearance of abatacept, when normalized for baseline body weight, was higher in JIA patients (0.44 ml/h/kg) versus adult RA 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

Clinical trials

The efficacy and safety of ORENCIA® were assessed in five 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). Studies I, II, III, and IV 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.

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, and V patients were randomized to receive a fixed dose approximating 10 mg/kg of ORENCIA® or placebo for 12 months (Studies III and V) 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 and IV 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. The ACR 50 response with ORENCIA® was significantly greater than placebo at months 2 and 3, respectively, for Studies III and IV, with continued improvement in the ACR50 response rate through the double-blind period (month 12 in Study III and month 6 in Study IV). In the placebo-controlled periods of Studies II and III, ACR response rates were maintained to 12 months in ORENCIA®-treated patients. In the open-label extension of Studies II, III, and IV, durable and sustained ACR 20, 50, and 70 responses have been observed through 48, 24, and 18 months, respectively, of ORENCIA® treatment.

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 the open-label extension of Studies II, III, and IV, improvements in the individual ACR components were maintained through 48, 24, and 18 months, respectively, of ORENCIA® treatment.

Table 2: ACR Responses in Placebo-Controlled Trials

	Percent of Patients			
	Inadequate Response to MTX		**Inadequate Response to TNF Blocking Agent**	
	Study III		**Study IV**	
Response Rate	ORENCIA® [a] +MTX n=424	Placebo +MTX n=214	ORENCIA® [a] +DMARDs[c] n=256	Placebo +DMARDs[b] n=133
ACR 20				
Month 3	62%***	37%	46%***	18%
Month 6	68%***	40%	50%***	20%
Month 12	73%***	40%	NA	NA
ACR 50				
Month 3	32%***	8%	18%**	6%
Month 6	40%***	17%	20%***	4%
Month 12	48%***	18%	NA	NA
ACR 70				
Month 3	13%***	3%	6%*	1%
Month 6	20%***	7%	10%**	2%
Month 12	29%***	6%	NA	NA
Major Clinical Response[c]	14%***	2%	NA	NA

* p<0.05, ORENCIA® vs placebo.

** p<0.01, ORENCIA® vs placebo.

*** p<0.001, ORENCIA® vs placebo.

[a] Fixed dose approximating 10 mg/kg (see section 3.1).

[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.

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.

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.

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 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 4. During the open-label periods of Studies II, III, and IV, the improvement in physical function has been maintained through 48, 24, and 18 months, respectively.

Table 4: 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 and the Mental Component Summary.

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 open-label therapy with ORENCIA®, improvements in health-related outcomes and quality of life have been maintained for up to 4 years.

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 a ≥30% worsening in at least 3 of the 6 JIA core set variables with ≥30% improvement in not more than 1 of the 6 JIA core set variables; ≥2 cm of worsening of the Physician or Parent Global Assessment was necessary if either was used as 1 of the 3 JIA core set variables used to define flare, and worsening in ≥2 joints was necessary if the number of active joints or joints with limitation of motion was used as 1 of the 3 JIA core set variables used to define flare.

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

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

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

INDICATIONS

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

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

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

CONTRAINDICATIONS

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

PRECAUTIONS

Combination with TNF blocking agents

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

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

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

Hypersensitivity

Hypersensitivity reactions can be observed during treatment with any injectable protein. Such reactions have been reported with ORENCIA® administration in clinical trials, where patients were not required to be pretreated to prevent hypersensitivity reactions. In patients treated with ORENCIA® in controlled and open-label clinical trials, the events of hypersensitivity, anaphylaxis, and drug hypersensitivity were rarely reported. 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.

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.

Interactions with other medicines

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

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

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

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

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

Other Interactions

Blood Glucose Testing.

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

Genotoxicity

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

Carcinogenicity

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

Effects in non-human primates

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

Effects on fertility

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

Use in pregnancy (Category C)

Abatacept may affect the immune system in the fetus. Embryofetal development was unaffected by doses of up to 300 mg/kg/day in mice, 200 mg/kg/day in rats, and 200 mg/kg every 3 days in rabbits (approximately 29-fold the human drug exposure based on AUC). Abatacept was shown substantially to cross the placenta in rats, and minimally in rabbits. Offspring were unaffected by abatacept doses of up to 45 mg/kg given every 3 days to rats from early gestation through to the end of lactation (3-fold the human drug exposure based on AUC). With a dose of 200 mg/kg every 3 days (approximately 11-fold the human drug exposure based on AUC) female pups showed enhanced T cell dependent antibody responses and a single case (out of 20 pups) of thyroid chronic inflammation. Whether these findings indicate a potential for the development of autoimmune diseases in humans exposed *in utero* is uncertain. There are no adequate and well-controlled studies in pregnant women. The use of ORENCIA during pregnancy is not recommended.

Use in lactation

Abatacept has been shown to be present in rat milk and in the serum of suckling pups. It is not known whether abatacept is excreted in human milk or absorbed systemically after ingestion.

Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in breast-fed infants from abatacept, women on abatacept should not breast feed. The long half-life of abatacept should also be considered when discontinuing therapy.

PaediatricUse

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

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

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

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

Non-clinical studies relevant for use in the paediatric population

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

Use in the elderly

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

Patients on controlled sodium diet

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

Use in Patients with Chronic Obstructive Pulmonary Disease (COPD)

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

Information for Patients

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

ADVERSE EFFECTS

Adult

General

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

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

Overall adverse events reported irrespective of consideration to causality to treatment in the placebo-controlled clinical trials in RA patients are listed in Table 5.

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 6).

Table 5: 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 6: 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%

Table 6: Intensity of Adverse Events in Double-Blind, Controlled Study Periods: Study IV vs Study III

	Percent of Patients			
Study III, Inadequate Response to MTX				
ORENCIA®	75.1%	60.3%	15.2%	1.2%
Placebo	73.5%	55.3%	12.8%	0.9%

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

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

Infections and infestations

Common:	Lower respiratory tract infection (including, bronchitis), urinary tract infection, herpes simplex, upper respiratory tract infection (including tracheitis, nasopharyngitis), rhinitis
Uncommon:	Tooth infection, infected skin ulcer, onchomycosis

Neoplasms benign and malignant (including cysts and polyps)

Uncommon:	Basal cell carcinoma

Blood and the lymphatic system disorders

Uncommon:	Thrombocytopenia, leukopenia

Psychiatric disorders

Uncommon:	Depression, anxiety

Nervous system disorders

Very Common:	Headache
Common:	Dizziness
Uncommon:	Paraesthesia

Eye disorders

Uncommon:	Conjunctivitis, visual acuity reduced

Ear and labyrinth disorders

Uncommon:	Vertigo

Cardiac disorders

Uncommon:	Tachycardia, bradycardia, palpitations

Vascular disorders

Common:	Hypertension, flushing
Uncommon:	Hypotension, hot flush

Respiratory, thoracic and mediastinal disorders

Common:	Cough

Gastrointestinal disorders

Common:	Abdominal pain, diarrhoea, nausea, dyspepsia
Uncommon:	Gastritis, mouth ulceration, aphthous stomatitis

Skin and subcutaneous tissue disorders

Common:	Rash (including dermatitis)
Uncommon:	Increased tendency to bruise, alopecia, dry skin

Musculoskeletal, connective tissue and bone disorders

Uncommon:	Arthralgia, pain in extremity

Reproductive system and breast disorders

Uncommon	Amenorrhea

General disorders and administration site conditions

Common:	Fatigue, asthenia
Uncommon:	Influenza like illness

Investigations

Common:	Blood pressure increased, liver function test abnormal (including transaminases increased)
Uncommon:	Blood pressure decreased, weight increased

Infections

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

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

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 10,365 patient-years, the incidence rate of malignancy was 1.41 per 100 patient-years. The incidence rates per 100 patient-years were 0.74 for non-melanomatous skin cancer, 0.59 for solid malignancies and 0.12 for hematologic malignancies. The most frequently reported solid organ cancer was lung cancer (0.16 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 7.

Table 7: 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

In the clinical studies with ORENCIA®, pre-medication to prevent hypersensitivity was not required. Acute infusion-related events (reported within 1 hour of the start of the infusion) in Studies III, IV, and V were more common in the ORENCIA®-treated patients than the placebo patients (9.8% for ORENCIA®, 6.7% for placebo). The most frequently reported events (>1.0%) were dizziness (2.1% for ORENCIA®, 1.3% for placebo), headache (1.8% for ORENCIA®, 1.2% for placebo), and hypertension (1.2% for ORENCIA®, 0.4% for placebo).

Acute infusion-related events that were reported in >0.1% and≤1% of patients treated with ORENCIA® included cardiopulmonary symptoms such as hypotension, increased blood pressure, decreased blood pressure, and dyspnea; other symptoms included nausea, flushing, urticaria, cough, hypersensitivity, pruritus, rash, and wheezing. Most of these reactions were mild to moderate. A small proportion of patients in both the ORENCIA® and placebo groups discontinued due to an acute infusion-related event (0.4% for ORENCIA®, 0.2% for placebo).
Of 2688 patients treated with ORENCIA® during 4764 patient years in controlled and open-label clinical trials, there was one report of an anaphylactic reaction. In patients treated with ORENCIA® in controlled and open-label clinical trials, the events of hypersensitivity, anaphylaxis, and drug hypersensitivity were rarely reported. Other events potentially associated with drug hypersensitivity, such as hypotension, urticaria, and dyspnea, each occurred uncommonly and generally occurred within 24 hours of ORENCIA® infusion.

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

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

vs. 0%), including COPD exacerbation (1 of 37 patients [2.7%]) and bronchitis (1 of 37 patients [2.7%]).

Autoantibodies

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

Immunogenicity

Antibodies directed against the ORENCIA® molecule were assessed by ELISA assays in rheumatoid arthritis patients treated for up to 3 years with ORENCIA®. Sixty-two of 2237 (2.8%) patients developed binding antibodies. In patients assessed for antibodies at least 56 days after discontinuation of ORENCIA®, 15 of 203 (7.4%) developed antibodies.

Samples with confirmed binding activity to CTLA-4 were assessed for the presence of neutralizing antibodies. Eight of 13 evaluable patients were shown to possess neutralizing antibodies.

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. The potential clinical relevance of neutralizing antibody formation is not known.

Postmarketing experience

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

Laboratory findings

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

Paediatric and Adolescent

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

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

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

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

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

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

Adverse events regardless of causality occurring in ≥5% of pediatric patients receiving ORENCIA® in period B (double-blind phase) of the three part study conducted in paediatric and adolescent patients with polyarticular JIA are listed in Table 8 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 8: 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 pediatric clinical trial, 10.6% of ORENCIA treated patients that had negative antinuclear antibody titers at baseline had positive titers at Day 113. In Period B, 5.9% of ORENCIA treated patients and 4.0% of placebo patients that had negative antinuclear antibody titers at baseline had positive titers at Day 169.

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

Immunogenicity

Antibodies directed against the entire abatacept molecule or to the CTLA-4 portion of abatacept were assessed by ELISA assays in patients with polyarticular JIA following repeated treatment with ORENCIA®. The rate of seropositivity while patients were receiving abatacept therapy was 0.5% (1/189) during Period A; 13.0% (7/54) during Period B; and 11.4% (17/149) during Period C. For patients in Period B who were randomized to placebo

(therefore withdrawn from therapy for up to 6 months) the rate of seropositivity was 40.7% (22/54). Anti-abatacept antibodies were generally transient and of low titer. The absence of concomitant methotrexate (MTX) did not appear to be associated with a higher rate of seropositivity in Period B placebo recipients. The presence of antibodies was not associated with adverse events or infusional reactions, or with changes in efficacy or serum abatacept concentrations. Of the 54 patients withdrawn from ORENCIA® during the double-blind period for up to 6 months, none had an infusion reaction upon re-initiation of ORENCIA®.

Malignancies

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

DOSAGE AND ADMINISTRATION

For adult patients with RA, ORENCIA® should be administered as a 30-minute intravenous infusion utilizing the weight range-based dosing specified in Table 9. Following the initial administration, ORENCIA® should be given at 2 and 4 weeks after the first infusion, then every 4 weeks thereafter. Methotrexate, other non-biologic DMARDs, corticosteroids, salicylates, nonsteroidal anti-inflammatory drugs (NSAIDs), or analgesics may be used during treatment with ORENCIA®.

Table 9: Dose of ORENCIA® [a] in Adult RA

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

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

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

Renal impairment, hepatic impairment

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

Paediatric and adolescent

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

Use in the elderly

No dose adjustment is required (see PRECAUTIONS).

Concomitant therapy

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

PREPARATION AND ADMINISTRATION INSTRUCTIONS

Use aseptic technique.

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

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

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

OVERDOSE

ORENCIA® is administered as an intravenous infusion under medically controlled conditions. Doses up to 50 mg/kg have been administered without apparent toxic effect. In case of overdosage, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions and appropriate symptomatic treatment instituted.

In the event of an overdose or poisoning contact the Poisons Information Centre on 131126.

PRESENTATION

ORENCIA® is a lyophilized powder for intravenous infusion; it is supplied as an individually packaged, single-use vial with a silicone-free disposable syringe. All components of the syringe are latex-free. The product is available in the strength of 250 mg of abatacept in a 15-mL vial.

Storage and Stability conditions:

ORENCIA® lyophilized powder must be refrigerated at 2°C to 8°C.

Do not use beyond the expiration date.

Protect the vials from light by storing in the original package until time of use.

Poisons Schedule: S4

DISTRIBUTED BY:

Bristol-Myers Squibb Australia Pty Ltd
556 Princes Highway
NOBLE PARK VIC 3174

AUSTRALIAN REGISTRATION NUMBERS:

ORENCIA® is a lyophilized powder for intravenous infusion:	AUST R 130100
SYRINGE:	AUST R 12743

DATE OF TGA APPROVAL: 4th March 2010

{Orencia – Post-ADEC Product information 11th Feb 2010}

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