SCIENTIFIC DISCUSSION

1   Introduction

The biological antirheumatic agents, TNF-α blockers infliximab, etanercept and adalimumab as well as the IL-1-blocker anakinra belong to the first generation biological antirheumatics that have significantly improved the therapy of rheumatoid arthritis. In contrast to most previous Disease-Modifying Antirheumatic Drugs (DMARDs), the biologicals have been shown to rapidly relieve the symptoms and signs of rheumatoid arthritis (RA) as well to retard the progression of joint damage. Unfortunately, the biological antirheumatic medicinal products may have serious although rare adverse effects, such as infections, autoimmunity and hypersensitivity. Furthermore, a significant proportion of RA patients are refractory to the current biological antirheumatics.

Abatacept (ORENCIA) is an anti-rheumatic medicinal product. Its mode of action is to prevent T lymphocyte activation.

The initially proposed therapeutic indication is as follows: "*ORENCIA is indicated for reducing signs and symptoms, improving physical function and reducing the rate of progression of structural damage in adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to disease-modifying anti-rheumatic drugs (DMARDs), such as methotrexate or tumour necrosis factor (TNF) blocking agents.*
ORENCIA may be used in combination with DMARD therapy. In patients who tolerate methotrexate, but who are having an inadequate response to therapy, ORENCIA is usually given in combination with methotrexate. Abatacept is not recommended for use in combination with TNF blocking agents"

Abatacept is to be administered as a 30-minute intravenous infusion at a dose specified by body weight ($\geq$ 60 kg to $\leq$ 100 kg = 750 mg) and to be readministered 2 and 4 weeks after the first infusion, then every 4 weeks thereafter.

After review of the dossier, the indication has been revised and approved by the CHMP as follows: "*ORENCIA in combination with methotrexate is indicated for the treatment of moderate to severe active rheumatoid arthritis in adult patients who have had an insufficient response or intolerance to other disease-modifying anti-rheumatic drugs including at least one tumour necrosis factor (TNF) inhibitor. A reduction in the progression of joint damage and improvement of physical function have been demonstrated during combination treatment with abatacept and methotrexate*".

Treatment should be initiated and supervised by specialist physicians experienced in the diagnosis and treatment of rheumatoid arthritis.

2   Quality aspects

Introduction

ORENCIA is a biological product developed for immunosuppression by blocking T cell activation through inhibition of co-stimulatory signals and is indicated for treatment of rheumatoid arthritis. It is assumed that T cells are driving the autoimmune response that leads to synovitis and to other inflammatory features of rheumatoid arthritis. T cells require at least 2 signals for full activation, an antigen-specific signal (signal 1) and a co-stimulatory signal (signal 2). The drug substance, abatacept, was designed to bind to CD80 and CD86 receptors (B7 molecules) on antigen-presenting cells, thereby inhibiting the CD28-mediated co-stimulation of T cells (see the figure below).

Figure 1.   Mode of action
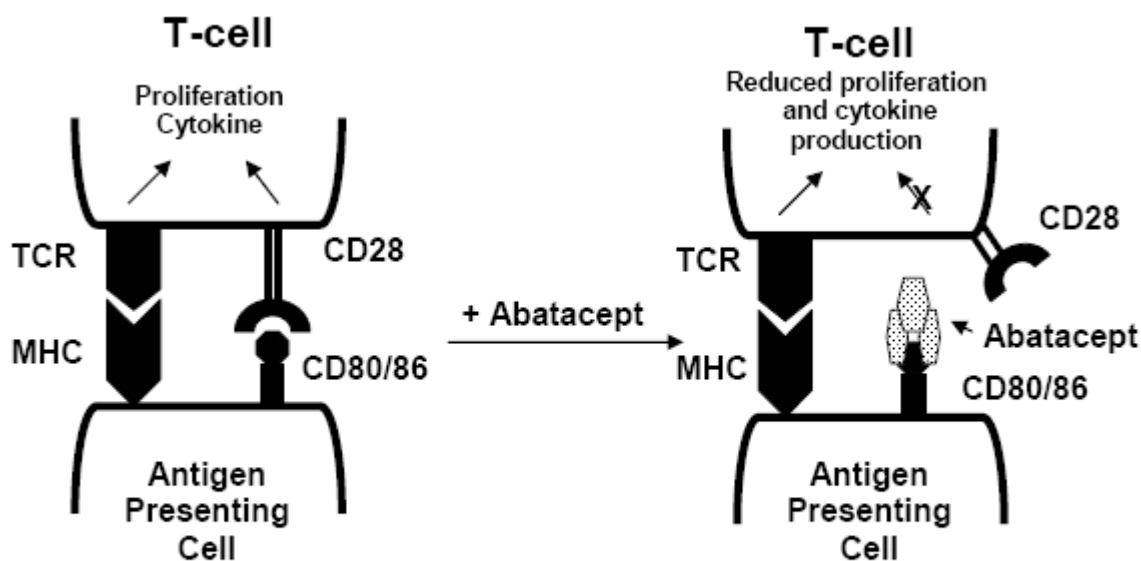
TCR = T-cell receptor; MHC = major histocompatibility complex

ORENCIA is a powder for concentrate for solution for infusion provided in Type 1 glass vials with a stopper (halobutyl rubber) and flip off seal (aluminium) with a silicone free syringe (polyethylene). Each vial contains 250 mg abatacept as well as the following excipients: maltose, sodium dihydrogen phosphate monohydrate, sodium chloride.

Drug Substance

Abatacept is the drug substance in ORENCIA. Abatacept is a soluble homodimeric fusion protein of two identical subunits covalently linked by one disulphide bond. Each subunit consists of the modified amino-acid sequences of:
- the extracellular domain of human cytotoxic lymphocyte associated antigen 4 (CTLA-4). CTLA-4 is a trans-membrane regulatory protein that is not expressed on the surface of resting T cells but is expressed following activation and down regulates activation of T-cells. Both CD28 and CTLA4 can bind to CD 80 (B7-1) and CD 86 (B7-2) molecules on the APC surface. CTLA4 binds to CD 80/86 with higher avidity than does CD28.
- human immunoglobulin IgG1 hinge, CH2 and CH3 regions (Fc).

Modifications to the original sequences were introduced to avoid unintended disulphide bridge formation and to reduce the ability of complement activation.

Manufacture

The drug substance is manufactured in accordance with Good Manufacturing Practice (GMP) at Bristol-Myers Squibb facilities in East Syracuse New York, USA ("process E") and by Lonza Biologics, New Hampshire, USA ("process F").

Abatacept is produced by fermentation in a transfected genetically engineered Chinese hamster ovary (CHO) cell line. For secretion into the medium, abatacept is expressed with an upstream signal sequence that is cleaved as the protein is secreted. The fusion protein gene contains the coding sequence for the CTLA-4 prepared from the H38 cell line and the Fc-region gene derived from a murine myeloma cell line producing mouse-human chimeric L6 antibody. The gene sequences were modified to substitute some amino acids as described above.

The expression plasmid was stably transfected by electroporation into a CHO-cell line, and an optimal cell clone was developed under methotrexate selection pressure.

The cell line was adapted to grow in a chemically defined medium, and animal-or human-derived raw materials are not used in the commercial manufacturing process, except for one material derived from bovine milk, which is considered safe. Serum is not used in the composition of the cell culture medium, including Working Cell Bank (WCB) cultivation and cell culture process media. A two-tier banking system was established to ensure continuous and consistent production. The establishment, characterisation and control of the Master Cell Bank (MCB) and Working Cell Banks were described and are adequate. The genetic stability was appropriately demonstrated by analysis of end of production cells and genetic stability studies.

Following fermentation and removal of production cells, the secreted substance is purified by a series of chromatographic and filtration steps to reduce the level of impurities (mostly high molecular weight proteins), to control the sialic acid to protein ratio, and to reduce the level of potential viruses. The downstream process consists of 4 chromatographic steps including a protein A affinity chromatography, one specific viral inactivation step and a viral nano-filtration step to clear potential viruses. Finally, abatacept is concentrated (at 50 mg/ml) and diafiltrated into the final buffer (25 mM phosphate, 50 sodium chloride, pH 7.5).

Materials used in the manufacture process are adequately controlled. The manufacturing process and in-process controls have been sufficiently described. Establishment of controls for critical steps and intermediates are described in detail and are adequate. Validation studies were presented, demonstrating clearance of process related impurities and consistency of the drug substance manufacturing process.

Abatacept has been characterised extensively using a battery of modern analytical state-of-the-art techniques. Abatacept is a homodimeric fusion protein of two identical subunits covalently linked by one disulphide bond. Each subunit consists of amino acids similar to the extracellular domain of human cytotoxic lymphocyte associated antigen 4 (CTLA-4) and human immunoglobulin IgG1 hinge, CH2 and CH3 regions (Fc). Modifications to the original sequences to avoid unintended disulphide bridge formation and to reduce the ability of complement activation were introduced. Three cysteine residues in the hinge region were substituted with serines by mutation of the human IgG1 gene sequence. There is one interchain disulphide bridge between the subunits in the CTLA-4 derived regions and four intrachain bridges within each chain of Abatacept. In addition, one proline was unintentionally substituted by serine in the CH2 region.

There are 357 amino acids in each subunit, the molecular weight is 92 300 Da (determined by mass spectrometry) of which 15 % is composed of carbohydrates. There are N-linked oligosaccharides and O-linked oligosaccharides in each chain. Terminal sialic acids of the carbohydrate moieties are said to be important for pharmacokinetics of the protein. In addition to heterogeneity derived from different glycoforms, there is N-terminal and C-terminal heterogeneity. Consequently, the drug substance is a mixture of different iso- and glycoforms of the protein. Biological properties of the drug substance have been characterised by using a binding assay and a human cell IL-2 inhibition assay.

Although it is difficult to fully characterise such a large, complex and heterogeneous fusion protein by the current available analytical methods, abatacept has been sufficiently characterised. The forced degradation studies have given information on the potential degradation routes such as aggregation, oxidation and deamidation of this light and temperature sensitive protein.

Abatacept manufactured by different processes were used during non-clinical and clinical development.

During the development of ORENCIA, several versions of abatacept were produced in different manufacturing processes. Differences in the fermentation scale and purification strategies were introduced during transition from one process to another to e.g. improve removal of impurities, to increase consistency and to optimise sialic acid content.

The first 4 manufacturing processes used a cell line grown in cell culture medium containing animal derived components. However, prior to the initiation of Phase III clinical trials, a fifth process was developed in which the original cell line was adapted to a chemically defined animal-component-free medium. Abatacept manufactured at Bristol-Myers Squibb was used in all Phase III clinical trials. Abatacept manufactured at Lonza Biologics was used in the extensions of the pivotal clinical trials. Comparability studies were conducted at various stages of drug development *in vitro* and *in vivo*. Due to the complexity and size of the protein, it was not possible to guarantee comparability only with the current analytical methodology. Differences in sialic acid content, in glycosylation profiles and in C-terminus observed between abatacept from the phase II and phase III processes were not considered to be an issue of major concern since comparability was studied *in vivo* in monkeys and in a pharmacokinetic study in humans.

The relevance of the differences between the manufacturing processes at Bristol-Myers Squibb and Lonza Biologics, which are both used for commercial production, were evaluated. In light of the information and data provided it was considered that although processes E and F are not identical, technical adaptations to the operational parameters were introduced for process F to allow manufacture at higher scale and therefore processes E and F are not considered to be alternative processes.

Specifications

The analytical procedures and their validation in general are appropriate for the assessment of the drug substance and stability indicating methods were identified. The set of specification and limits were adequately justified on the basis of data obtained from up to 94 batches. Specifications include among others: bacterial endotoxins LAL by gel clot, bioburden by membrane filtering, identity by capillary electrophoresis, identity by horizontal isoelectric focusing, identity and primary structure by tryptic digestion/peptide mapping, purity by size exclusion HPLC, identity and purity by Coomassie stain and silver stain SDS-PAGE, determination of free sulfhydryl groups by the Ellman's reagent assay, DNA by quantitative PCR, MCP-1 by ELISA, CHO Host Cell Protein by ELISA, Residual protein A by ELISA, sialic acid by hydrolysis and HPLC, N-linked carbohydrate profile by HPAEC-ED, amino monosaccharide composition by CE, neutral monosaccharide composition by CE, B7 binding by surface plasmon resonance, potency and protein concentration by UV adsorbance at 280 nm. The biological potency is measured in vitro using a human cell IL-2 inhibition assay.
Batch analysis results confirm consistency and uniformity of manufacture of abatacept.

Stability

Containers and storage conditions for the sterile filtered drug substance have been adequately documented and the proposed shelf-life is justified on the basis appropriate real-time, real-condition stability studies on 3 batches for process E and 3 batches for process F. The stability data generated from drug substance manufactured by process E and F were comparable.

Drug Product

Pharmaceutical Development

The drug product, ORENCIA, is a sterile lyophilisate of 250 mg abatacept per vial. The drug product contains phosphate buffer and sodium chloride derived from the drug substance solution and additional maltose monohydrate as a bulking and stabilising agent for lyophilisation. The formulation has been described and justified. As a pharmacopoeia monograph does not exist for maltose monohydrate, the quality of this corn-derived excipient is tested according to in-house specifications. The choice of the standard primary container-closure system is well justified (15 ml type I glass, stopper with a seal). The secondary packaging contains a silicone oil-free syringe for reconstitution.

Manufacture

The drug product is manufactured at Bristol-Myers Squibb Holdings Pharma Ltd in Manati, Puerto Rico, in accordance with GMP.

The manufacturing process consists of formulation in the final buffer, 0.45 µm pre-filtration, two 0.22 µm filtration, filling in vials, lyophilisation, capping, external washing, labelling and secondary packaging. The process, the critical steps and in-process controls are well described. The process has been appropriately validated. Data from media fills demonstrate suitability of the aseptic process.

Product specification

The specifications for the drug product have been appropriately justified and are acceptable and batch results demonstrate consistency. Most of the analytical methods, which were appropriately validated, are identical to those used for testing of the drug substance. There are no additional impurities from the manufacturing of the drug product as compared to manufacturing to the drug substance. The proposed specification for high molecular weight species is higher for the drug product than for the drug substance, which is acceptable.

Stability

Real-time, real-condition stability data for the drug product were provided and justify the proposed shelf-life of two years at 2-8°C. The shelf-life specifications for the drug product do not differ from the release specifications. Storage in the original package for protection from light is supported by photostability studies.

Adventitious agents

TSE aspects of starting materials, reagents, excipients, adjuvants, drug substance. Information on the viral safety of the product (e.g. for biolgical medicinal products and others if relevant), including use of starting materials in respect of viral safety, the adequacy/suitability of the virus removal steps and of the precautions taken to ensure viral safety, viral validation studies.
In general, viral and TSE safety of ORENCIA are considered assured. Freedom of starting materials from adventitious agents is assured by appropriate sourcing and testing. The only material of bovine origin used in the manufacturing process is derived from bovine milk sourced from the USA. Compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products (EMEA/410/01 Rev. 2) has been demonstrated. Chinese hamster ovarian cells (CHO) are widely used for production of drug substances. The master and working cell banks for abatacept are tested for viruses. End of production cell banks from both drug substances processes E and F were prepared and tested as well. In-process pre-harvests are appropriately tested on each batch. The load of endogenous retrovirus-like particles has been addressed.
Four orthogonal steps for the manufacturing process at Bristol-Myers Squibb and at Lonza Biologics are validated for removal of viruses. Downscale viral clearance studies were conducted using appropriate model viruses (two enveloped viruses – A-MuLV and HSV-1 – and two non-enveloped viruses – PPV and Reo-3) and demonstrated effective virus removal (minimum of >12 $\log_{10}$). With respect to virus safety, and although process F contains one additional ultra-filtration and diafiltration step, study result demonstrated that processes E and F are comparable.
In summary, the virus safety of the product has been adequately demonstrated.

Discussion on chemical, pharmaceutical and biological aspects

Overall, information on development, manufacture and control of the drug substance and drug product has been presented in a satisfactory manner. The results of tests carried out indicate satisfactory consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in the clinic. At the time of the CHMP opinion, there were a number of minor unresolved quality issues having no impact on the Risk-benefit balance of the product. The applicant gave a Letter of Undertaking and committed to resolve these after the opinion, within an agreed timeframe.

3   Non-clinical aspects

Introduction

The pivotal toxicology studies supporting the safety of abatacept were conducted in compliance with Good Laboratory Practice (GLP) regulations.

Pharmacology

- Primary pharmacodynamics

Abatacept is a fusion protein containing extracellular domains of CTLA-4, a co-stimulatory molecule found on activated T cells. As the natural ligand of the CD80 and CD86 molecules, the CTLA-4 domains bind them with high avidity, displacing the other natural ligand, CD28, expressed on T cells. This blocking action deprives T cells from an important costimulatory signal, resulting in inefficient T-cell activation.

Abatacept binds to the CD64 Fc-receptor in monocytes but did not induce TNF-α production in monocytes. Abatacept is unlikely to induce cytokine release from monocyte/macrophages in its native form. However, abatacept-anti-abatacept immune complexes or aggregates of abatacept may behave differently.

Abatacept did not cause lysis in a complement dependent cytotoxicity assay, indicating that it lost its complement activating capacity most likely due to mutations in the hinge-CH2 region.

The capability of abatacept to interfere with T-cell activation is adequately proven in assays of lymphocyte activation, such as mixed lymphocyte reactions and antigen presentation assays. Proliferation and production of cytokines were both inhibited by the intended therapeutic concentrations of the drug. *In vivo* assessment of the general effects of abatacept also supports the expected mode of action, that is, prevention of the activation of naïve T cells. The effect of abatacept on secondary immune responses was also demonstrated but it was less pronounced than for the primary response. T cell priming without IL-2 production and cell proliferation can take place during abatacept exposure. Abatacept did not affect the non-antigen-specific innate immunity. Abatacept is not cytotoxic in the classical sense but antigen-stimulated T lymphocytes may undergo apoptosis.

Abatacept prevented collagen-induced arthritis in mice and in rats when given at the same time with the antigen. Its effects on pre-existing arthritis were less pronounced.

Unfortunately, there are no non-clinical data on the combination of abatacept and methotrexate. Abatacept has not been compared to any of the earlier-known anti-lymphocyte compounds (e.g. cyclosporin or leflunomide) in any of the *in vitro* or *in vivo* experiments.

Abatacept was immunogenic in the tested animal species. It is unclear whether the immunisation takes place during the exposure or only after discontinuation of the treatment since the anti-abatacept assays are suffering from the antigen-interference. Rechallenge of mice induced anaphylactoid reactions. This was the only significant finding related to safety pharmacology.

- Secondary pharmacodynamics

Not applicable

- Safety pharmacology programme

No formal safety pharmacological studies were performed.
Evaluations of the potential effects of intravenous (IV) administration of abatacept and BMS 224818 (a second generation molecule differing from abatacept by two amino acid residues within the CD80/86 binding domains, which confers a significant increase in binding avidity to CD86 relative to

that of abatacept in humans) on the cardiovascular, central/peripheral nervous, and respiratory systems were conducted as part of the pivotal repeat-dose toxicity studies in monkeys.

The results of these evaluations did not reveal any drug-related changes in cardiovascular, neurological, or respiratory functions following treatment for up to 1 year with abatacept (human exposure multiples up to 9.2) or 6 months with BMS-224818 (human exposure multiples up to 7.2). No drug-related changes were observed in histamine, complement (C3a), TNF-α, or IL-6 levels in the plasma or serum immediately following dosing.

In conclusion, there were no significant observations related to hemodynamics, ECG, or hypersensitivity / anaphylactoid reactions.

- Pharmacodynamic drug interactions

Pharmacodynamic drug interactions with abatacept were not investigated in nonclinical studies.

Pharmacokinetics

The pharmacokinetics of abatacept has been studied both after intravenous and subcutaneous administration in different animal species: mice, rats, rabbits, and monkeys. Doses of abatacept used in these non-clinical studies range from those recommended for humans on mg/kg basis to toxicology doses that provide a possibility to estimate the safety margin.

Some of the early toxicokinetic studies of abatacept carried out in conjunction with exploratory dose ranging and efficacy studies were not carried out in compliance with GLP. However, toxicokinetic and/or pharmacokinetic evaluations of abatacept to support pivotal toxicology studies were conducted according to GLP.

- Methods of analysis

The concentration of abatacept in serum was measured using double antibody sandwich enzyme-linked immunoassay (ELISA). Several assays were developed and validated during the development of abatacept for the determination of concentrations of abatacept in serum of mice, rat, rabbits, and monkeys and also in rat milk. The lower level of quantitation (LLQ) for abatacept in the mouse, rat, rabbit, and monkey serum were 1.4, 2.0, 1.0, and 1.5 ng/mL, respectively. The LLQ for abatacept in rat milk was 3.0 ng/mL. The calibration range was in the range of 1 - 40 ng/ml. If a predicted concentration of a study sample was greater than the highest standard the samples were diluted and reanalyzed. Separate ELISA method was developed to quantify antibodies formed against abatacept in monkeys as well.

- Main pharmacokinetic parameters

Pharmacokinetic evaluation of abatacept has demonstrated a profile typical of monoclonal antibodies, with dose-dependent but not dose-proportional increases in Cmax and AUC values and increases in elimination half-lives with increasing doses that were accompanied by decreasing clearance rates. This profile is probably the result of saturation of the major antibody clearance pathway (Fc-mediated phagocytosis).

Results of pharmacokinetic studies showed that the systemic exposure to abatacept increased as a function of dose. Subcutaneous bioavailability was approximately 85% in mice, and between 41% and 63% in rats. Accumulation was demonstrated following repeated intravenous or subcutaneous administration. Approximately 1- to 30-fold greater exposures than those in humans given 10 mg/kg monthly were obtained.

The elimination half-life of abatacept in mice and rats was approximately 3 to 6 days. In rabbits and monkeys, $t_{1/2}$ ranged from 5.2 to 7.5 days in monkeys and was 2.4 days in rabbits.

The total body clearance (CL) of abatacept in mice, rats, rabbits, and monkeys ranged from 0.5 to 2.0 mL/h/kg. The steady state volume of distribution (Vss) was comparable among the animal species tested and ranged from 0.07 to 0.24 L/kg.

In pregnant rats, a dose-related increase of abatacept concentration in foetal sera indicated that abatacept is able to cross the placental barrier. Overall, abatacept concentrations were 1.7 to 2.4-times higher in maternal sera as compared to foetal sera. In lactating rats, the milk to serum ratios for abatacept were 0.08 to 0.09. Abatacept was also detected in pup sera but the origin of this activity is unclear (from maternal milk or from maternal circulation).

Gender differences in pharmacokinetic parameters were seen in repeated dose studies in monkeys with higher exposure in males.

No studies were conducted to evaluate the metabolism and the metabolic pathways of abatacept in animals or to determine the potential for any drug-drug interactions of abatacept. No other studies except excretion to milk were conducted to evaluate the distribution of abatacept.

Toxicology

Abatacept was tested in an extensive battery of safety evaluation studies. The animals (species) used in the various studies have been selected on due scientific grounds and correspond to the international guidelines. Apart from those in the single-dose toxicity studies, the administered doses can be considered correctly selected. The quality and stability of the test material (as administered during the various studies) were properly controlled and validated. All pivotal studies have been conducted in compliance with GLP regulations.

- Single dose toxicity

Single-dose studies were confined to a single species and to the administration of tolerable doses that however do not provide relevant information with regard to potential clinical effects following accidental overdose to humans. In single-dose monkey studies, abatacept was well tolerated at doses up to 100 mg/kg and did not induce other toxicity than effects related to its pharmacodynamic effects.

- Repeat dose toxicity (with toxicokinetics)

In repeated toxicity studies of intravenous administration of abatacept, the exposure/dose seemed to be linear, with accumulation for at least one year. There were no significant findings in physical examinations. The macroscopic and microscopic analysis of organs in mice did not reveal major pathological findings, except the decrease in the weight of thymus and the increase in the weight of spleen. In the histological analysis, there was a depletion of germinal centers in the spleen and lymph nodes in monkeys. These changes have been shown to be fully reversible. In the recovering lymph nodes, there was an increased cell proliferation, reflective of a rebound from the depression of activity. In addition, there was mild to moderate karyomegaly in the renal tubular epithelial cells in mice. The significance of this finding to man is unknown since the aetiology is unknown and no changes in renal function was observed. Serum IgG was depressed in the intermediate and high dose groups but returned towards normal by the end of post-dose follow up.

- Genotoxicity

Abatacept was not genotoxic or mutagenic and did not induce chromosomal aberrations.

- Carcinogenicity

Lymphomas and mammary tumours were increased. In this mouse strain, Mouse Lymphoma Virus (MLV) is often involved with lymphomas and mouse mammary tumour virus (MMTV) in mammary tumours. A reduced immune response to these viruses during abatacept exposure is a plausible explanation for the increase of both lymphomas and mammary tumours.

Therefore, the current data demonstrate that abatacept-induced immunosuppression is associated with virus-related lymphoproliferation and lymphomas, as well as virally induced mammary tumours in animal models. For the time being, safety data from the clinical studies is insufficient for the exclusion of a moderate increase of certain rare malignancies.

- Reproduction Toxicity

Embryo-foetal toxicity studies were conducted in mice, rats and rabbits. In mice, the incidence of cervical bifurcation was increased in the medium dose groups. It appears that this finding may not be significant since the effect was not dose-dependent and the incidence of skeletal malformations falls within the historical ranges. Abatacept was shown to cross the placenta in rats and significant dose-dependent concentrations were demonstrated in foetuses of rats and rabbits. The studies conducted in mice, rats and rabbits did not suggest acute toxicity to foetuses or adverse impact of their development. Studies of prenatal and postnatal development, including maternal function, did not suggest adverse effects. However, there were subtle alterations to the immune functions characterised by inflammation of the thyroid and increased T-cell-dependent antibody response in pups. The long-term significance of these findings has not been investigated. Thus, the use of abatacept during pregnancy is not recommended.

- Local tolerance

Local tolerance studies did not indicated adverse effects of intravenous administration.

- Other toxicity studies

Mouse models of infections caused by murine cytomegalovirus and *Pneumocystis carinii* infections did not show clear evidence for an increased susceptibility. The model for latent tuberculosis in mice demonstrated reactivation of tuberculosis in TNF-α-blocker-treated but not in abatacept-treated mice.

Abatacept is immunogenic in animal models. The evaluation of immunogenicity studies is hampered by the lack of optimal anti-abatacept assays. The current assays suffer from poor sensitivity and from obvious antigen interference. Thus, the reliability of the antigenicity results is compromised. Nevertheless, anti-abatacept antibodies are detected after discontinuation of abatacept exposure as well as during low abatacept exposure. It is probable that both the immunosuppressive effect and the circulating antigen (abatacept) are responsible for the small number of positive results. Re-administration of abatacept to mice was associated with anaphylactoid reactions. Thus, it is possible that a significant immune reaction may develop after discontinuation of the treatment. Such an immune reaction may cause a risk of autoimmunity and, upon re-administration, of hypersensitivity reactions and loss of efficacy.

Ecotoxicity/environmental risk assessment

Abatacept is exempt from Environmental Risk Assessment due to the nature of the product, in accordance with the draft guideline on this matter. The excipients of ORENCIA are common ingredients which are well characterized and do not pose significant risk the environment. It is concluded that abatacept solution for intravenous infusion is of no immediate risk to the environment and no proposals for labelling provisions are necessary to reduce any potential environmental risks.

Discussion on the non-clinical aspects

The abatacept used in pivotal non-clinical studies is not comparable with abatacept used in pivotal clinical studies, with the exception of the 1-year monkey study which used Process E material (as pivotal clinical studies). However, the safety margins can be calculated with sufficient confidence on the basis of toxicokinetic data.

The main toxicological findings that are relevant to the clinical use are related to:
- Reversible immunosuppression

- Carcinogenicity (virus-induced malignancies)
- Anaphylactoid reactions associated with re-administration
- Transfer of abatacept across the placenta

It should be noted that the toxicological studies were performed without any concomitant medication whereas in clinical trials, abatacept was used with other antirheumatic medicinal products, notably methotrexate.

4 Clinical aspects

Introduction

GCP

The applicant has stated that all clinical trials were performed in accordance with GCP.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Pharmacokinetics

The assays that were used for measurement of abatacept concentrations were validated and found to have appropriate sensitivity.

The pharmacokinetic properties of abatacept have been studied in psoriasis and multiple sclerosis (phase 1) and in rheumatoid arthritis (phase II and III). There were several versions of the product and the early versions used in the phase I was <u>not comparable</u> to the versions used in phase II and III. Therefore, this summary deals mainly with studies in RA patients. One single dose, parallel group study (IM101017) was conducted in healthy volunteers in order to compare the Phase II (Process D) and III (Process E) materials. Healthy subjects (15 per treatment) were administered a 30-minute IV infusion of 10 mg/kg abatacept manufactured by either Process D or Process E. Results are shown in the Table below.

Table 3. Pharmacokinetic data (Study IM101017)

Pharmacokinetic Parameter	Abatacept	
	Process D (N = 15)	Process E (N = 13)
Cmax (µg/mL) Geometric Mean (CV%)	271.5 (14%)	284.7 (23%)
AUC(INF) (µg.h/mL) Geometric Mean (CV%)	43758.2 (17%)	44403.0 (18%)
Tmax (h) Median (min, max)	1.00 (0.50, 6.00)	0.50 (0.50, 2.00)
T-HALF (Days) Mean (SD)	16.82 (4.50)	16.68 (3.24)
CLT (mL/h/kg) Mean (SD)	0.23 (0.06)	0.23 (0.04)
Vss (L/kg) Mean (SD)	0.10 (0.02)	0.09 (0.02)

The results show that the two versions of abatacept were comparable.

Data obtained showed a volume of distribution (Vss) of 0.09 to 0.10 L/kg, which indicated that, in accordance to animal studies, abatacept was confined primarily to the extracellular fluid volume.

The single dose PK study IM101065 investigated the comparability of the two versions of abatacept (processes E and F) that are intended for market. The results showed that the versions are strictly <u>not</u> equivalent.

Table 4: Statistical Analysis Results for Abatacept Cmax, AUC(0-T), and AUC(INF) Between BMS Abatacept Group (Process E) and Lonza Abatacept Group (Process F)[a] (Study IM101065)

Pharmacokinetic Variables	Adjusted Geometric Mean		Ratio of Geometric Means		
	Process	Geometric Mean	Ratio	Point Estimate	90% Confidence Limits
Cmax (µg/mL)	Process E	242.9	F vs E	0.974	(0.878, 1.082)
	Process F	236.7			
AUC(0-T)[b] (µg•h/mL)	Process E	31526.4	F vs E	1.145	(1.034, 1.267)
	Process F	36086.3			
AUC(INF) (µg•h/mL)	Process E	32821.5	F vs E	1.141	(1.023, 1.273)
	Process F	37446.7			

Simulations were carried out to predict trough serum levels following multiple dosing of Process E and Process F abatacept using the Phase III dose regimen. Based on the simulations, steady-state trough levels of approximately 19 µg/mL and 21 µg/mL were obtained, with overlapping standard deviations, for Process E abatacept and Process abatacept, respectively.

During regulatory assessment, the applicant presented a new analysis of the safety experience of subjects treated with abatacept drug substance manufactured at Syracuse, Lonza, or both sites in 6 abatacept clinical studies, including the long-term open-label extensions of the 5 core rheumatoid arthritis studies and an open-label study to evaluate the safety of abatacept when co-administered with background non-biologic disease modifying anti-rheumatic drugs in a clinical practice setting (IM101064). In this analysis, no adverse events unique AEs to either Lonza or Syracuse drug substance were identified. According to the applicant, these data do not support any suspicion of a quantitative or qualitative difference in the safety profile of the product based on its sourcing. For the EU, the applicant proposed to market a product based on abatacept from only one site.

- PK studies in rheumatoid arthritis

Three multiple dose abatacept trials were carried out in the target rheumatoid arthritis (RA) population. In one study, PK profiles of abatacept were obtained after the first and last dose following intravenous (IV) administration of abatacept at doses of 0.5, 2, and 10 mg/kg. In the 2 remaining studies PK profiles were obtained over the dosing interval between Days 60 and 90 from subjects dosed at 2 and 10 mg/kg.

The results showed that over the range of doses studied, both Cmax and AUC values for abatacept increased in a proportion that was comparable to the dose increment on Day 1, but increased slightly more than dose proportionally on Day 57. For doses of abatacept increasing in the ratio of 1: 4: 20, the mean values for Cmax increased in the ratio of 1: 3.5: 19.7 (Day 1) and 1: 7.6: 35.1 (Day 57). For AUC, the ratios were 1: 3.8: 19.4 (Day 1) and 1: 4.3: 29.7 (Day 57). The elimination half-life $t_{1/2}$ values obtained in this study ranged from 5.0 to 10.6 days, which was slightly shorter than $t_{1/2}$ values obtained in other studies. The data also suggested that accumulation was minimal range from 0.9-1.7.

In these RA subjects, the mean $t_{1/2}$, total body clearance (CL), and distribution volume (Vss) values were around 13 days, ~ 0.2 mL/h/kg, and ~ 0.07 L/kg, respectively. Based on the current dosing schema (dosing at 2 and 4 weeks after the first infusion, then once a month thereafter) steady-state conditions for abatacept were reached by the third monthly dose. Serum concentrations were above steady-state trough concentrations during the first 2 months of treatment. Comparison of the trough (Cmin) values at Days 60, 90, and 180 indicated that, at the clinically used dose levels, abatacept does not accumulate following monthly dosing. The mean Cmin steady-state values for all subjects receiving monthly IV doses of 2 and 10 mg/kg abatacept ranged between 4.4 to 6.7 µg/mL and 22.0 to 28.7 µg/mL, respectively. These concentrations are within the range of concentrations that are effective in blocking T cell responses *in vitro*.

A Population Pharmacokinetic study (POPPK) was conducted in conjunction with the Phase III programme. The POPPK parameters were estimated by using a validated POPPK model to fit the pooled Phase II and Phase III data. The pooled dataset comprises the model building, internal validation, and the external validation datasets, and has a total of 388 subjects.

The results from the POPPK analyses revealed that there was a trend towards higher clearance of abatacept with increasing weight. However, these effects on clearance are not expected to be clinically important after dose adjustment for body weight. No trends were noted for age or renal function. After correction for body weight, gender was not found to influence the PK of abatacept. Several commonly co-administered medications (MTX, corticosteroids, NSAIDs, and TNF-blocking agents) were also investigated, and were not found to influence abatacept clearance. Therefore, these co-medication therapies would not be expected to have clinically relevant effects on abatacept PK. Overall, none of the covariates analyzed appeared to be clinically significant or necessitate any dose modification to the target dose of abatacept. Comparison of the simulated dose-adjusted steady-state AUC values also supports the Phase III fixed dose regimen in providing comparable exposure across the dose groups. The estimated % inter-individual variability on clearance form model-building dataset was 27.9.

There were no formal drug-drug-interaction studies. Such interactions are not expected considering the nature of the products. Clinical data from studies with concomitant treatment with various anti-rheumatic agents do not suggest any interactions.

Fixed vs. weight-based dosing

A simplified dosing regimen with three fixed doses was used in phase III studies. The dose was selected on the basis of trough serum abatacept concentrations that were needed in vitro to suppress T cell function. On the basis of predicted and observed trough concentrations, all three dose levels, in the respective weight categories, provided a mean abatacept concentration above 10 µg/mL that is needed for the inhibition of T cell proliferation in vitro. In addition, the efficacy as measured by the ACR20 was similar in all dose groups. The frequencies of both AEs and SAEs were also similar at the three dose levels.

The presented data suggest that abatacept has a relatively flat exposure-response for both safety and clinical efficacy. The proposed dosing provides an adequate exposure to abatacept for all adult patients.

- Special populations

PK studies in special populations have not been conducted

- Pharmacokinetic interaction studies

There were no formal drug-drug-interaction studies. Clinical data from studies with concomitant treatment with various anti-rheumatic agents do not suggest any interactions.

Pharmacodynamics

- Mechanism of action

Abatacept is a fusion protein that consists of the extracellular domain of human cytotoxic T-lymphocyte antigen 4 (CTLA4) linked to the modified Fc portion of human immunoglobulin G1 (IgG1). It is the first drug in a new class of agents, costimulation modulators, which prevents the interaction of the T-cell's CD28 with the antigen presenting cell's CD80/CD86 by binding avidly to the latter. As a consequence, T-cells are prevented from receiving the required second costimulatory signal needed for full activation resulting in inhibition of multiple aspects of T-cell-driven autoimmunity and inflammation.

- Primary pharmacology

Initial *in vitro* studies using human peripheral blood mononuclear cells evaluated the ability of abatacept to inhibit T-cell proliferation and cytokine production. Based on the *in vitro* findings, it was anticipated that serum trough abatacept concentrations of 10 to 30 μg/ml would be required to observe maximal clinical efficacy. Increasing abatacept concentrations (up to 100 μg/ml) did not result in greater suppression of T-cell proliferation.

Consistent with the *in vitro* results, T cell-dependent immune responses were inhibited in animal models at doses of abatacept where serum trough concentrations were approximately 10 μg/ml or greater. The *in vitro* studies and *in vivo* animal model data suggested that trough serum concentrations of abatacept between 10 and 50 μg/ml will provide maximal biologic efficacy.

The effect of abatacept on the induction of antibodies against T cell-dependent antigens, Keyhole Limpet haemocyanin and bacteriophage ϕX174, were investigated in psoriasis patients. The data indicated that abatacept 8 mg/kg and above appeared to consistently block antibody responses by more than 95% in over 80% of the subjects.

Study IM101049 was a Phase I exploratory study in 80 healthy subjects to evaluate the effect of a single dose of 750 mg abatacept on the antibody response following vaccinations with tetanus toxoid and a 23-valent pneumococcal vaccine. In this study, abatacept was administered either 2 or 8 weeks prior to vaccinations or 2 weeks after vaccination. The data from this study indicated that a single dose of 750 mg abatacept did not inhibit the ability of healthy subjects to develop a 2-fold or greater antibody response above baseline to either vaccine. However, there was a trend towards a diminished response by healthy subjects when the vaccines were administered 2 weeks and to a much lesser extent, 8 weeks after abatacept.

Clinical efficacy

The abatacept clinical development programme in RA included 6 studies: 3 Phase II and 3 Phase III studies in subjects ≥18 years of age with moderate to severe RA. These include 3 studies that provide the principal data in support of the efficacy of abatacept (IM101100, IM101102, and IM101029), as well as 3 studies that provide additional efficacy information (IM101031, IM101101, and IM103002). Efficacy data were collected on 3066 randomised and treated subjects who received abatacept (n=2045) or placebo (n=1021) during the controlled, double blind study periods (Table 5)

The overview of the abatacept clinical development programme is given in Figure 2 below.

Figure 2. Overview of the Abatacept Clinical Development
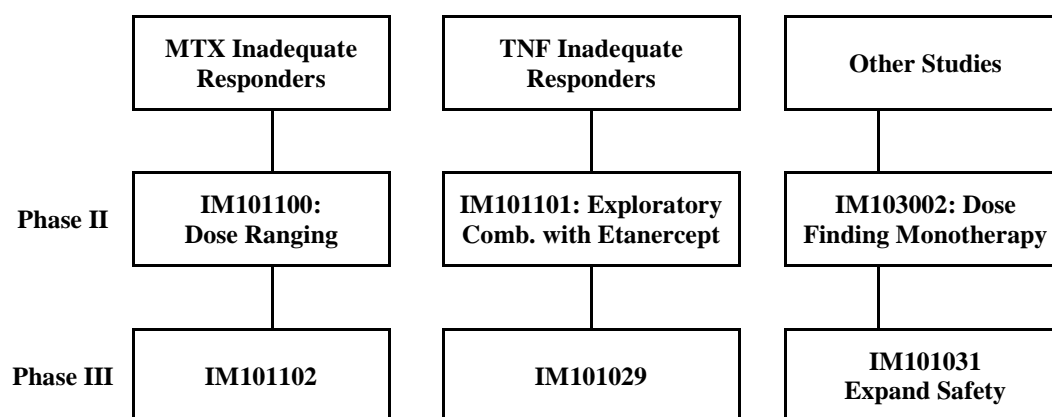
In addition, five of the above mentioned RA studies were extended into open label abatacept-treatment periods. Another 9 RA studies have been initiated, including a Phase III study to evaluate the safety and efficacy of abatacept in juvenile RA.

In general, the design, conduct, analysis and reporting complied with the relevant guidelines.

Table 5: Overview of Completed RA Double-Blind, Controlled Study Periods

Study No. Phase	Study Design	Background Anti-Rheumatic Therapy	Subjects in Comparator Group	No. of Subjects Randomized and Treated with Abatacept		Total
				10 mg/kg or Fixed-Dose	Other Doses (mg/kg)	
Studies in Subjects with an Inadequate Response to Methotrexate						
IM101100 Phase IIB	Randomized, dose-ranging, placebo-controlled, double-blind in subjects with active RA while on MTX	Day 1-180: MTX (10–30 mg/wk) Day 181-360: Adjustment allowed (+ 1 other non-bio^{logic} RA therapy)	119	115	105 (2.0 mg/kg)	339
IM101102 Phase III	Randomized, placebo-controlled, double-blind in subjects with active RA while on MTX	Day 1-169: MTX (10–30 mg/wk) Day 170-365: Adjustment allowed (+ 1 other non-biologic RA therapy)	219	433	0	652
Study in Subjects With an Inadequate Efficacy Response to TNF-Blocking Agents						
IM101029 Phase III	Randomized, placebo-controlled, double-blind in subjects with active RA on background DMARDs who have failed therapy with TNF-blocking agents	Day 1-169: Any non-biologic RA therapy or anakinra	133	258	0	391

Table 5: Overview of Completed RA Double-Blind, Controlled Study Periods

Study No. Phase	Study Design	Background Anti-Rheumatic Therapy	Subjects in Comparator Group	No. of Subjects Randomized and Treated with Abatacept		Total
				10 mg/kg or Fixed-Dose	Other Doses (mg/kg)	
IM101031 Phase III	Randomized, placebo-controlled, double-blind safety study in subjects with active RA, with or without pre-existing comorbidities, on background DMARDs and/or biologics	Day 1-85: Stable doses: ± Non-biologic RA therapy ± Biologic RA therapy Day 86-365: Adjustment allowed: ± Non-biologic RA therapy ± Biologic RA therapy	482	959	0	1441
Other Studies						
IM101101 Phase IIB	Randomized, placebo-controlled, double blind in subjects with active RA while on ETAN	Day 1-180: Stable dose: ETAN (25 mg 2x/wk) Day 181-360: Adjustment allowed (– ETAN, + 1 non-biologic RA therapy)	36	0	85 (2.0)	121
IM103002 Phase IIA	Randomized, dose-ranging, placebo-controlled, double-blind in subjects with active RA who have failed at least 1 DMARD or ETAN	None	32	32	26 (0.5) 32 (2.0)	122
Totals			**1021**	**1797**	**248**	**3066**

In the D120 responses, the company provided an additional clinical study report: Study IM101043: A Phase III, Multi-Centre, Randomised, Double-Blind, Placebo-Controlled Comparative Study of Abatacept or Infliximab in Combination with Methotrexate in Controlling Disease Activity in Subjects with Rheumatoid Arthritis Having an Inadequate Clinical Response to Methotrexate.

The following **endpoints** were used in the clinical studies:

For **ACR** core data set and response definitions data were collected in 7 components (tender joint count/standardised 68 joint count, swollen joint count/ standardised 66 joint count, subject global assessment of pain, subject global assessment of disease activity, physician global assessment of disease activity, subject assessment of physical function using HAQ, CRP). The ACR 20, 50 and 70 definitions of response correspond to a 20 %, 50 % or 70 % improvement over baseline in tender or swollen joints and a 20 %, 50 % or 70 % improvement in 3 of the 5 remaining core data set measures. A Major Clinical Response (MCR) is defined as maintenance of an ACR 70 over a continuous 6-month period.

VAS 100 mm scale was used for subject global pain and subject global assessment of disease activity and physician global assessment of disease activity. Physical function was evaluated using the disability index of a validated functional status and degree of disability instrument modified **HAQ**.

The questionnaire includes questions assessing physical function in 8 domains: dressing, arising, eating, walking, hygiene, reach, grip and common activities. The questions were evaluated on a 4-point scale, the higher scores indicating grater dysfunction.

The **radiographic evaluation** of structural damage progression was performed by using the Genant-modified Sharp grading scheme. The erosion score was determined from 14 sites in each wrist and hand and 6 joints in each foot scored using a 8-point scale from 0 to 3.5, A joint narrowing score was determined from 13 sites in each wrist and hand and 6 sites in each foot scores using a 9 point-scale from 0 to 4.

The **SF-36** questionnaire, validated for use of RA patients, was used to assess the impact of abatacept on health-related quality of life. The questionnaire covers four physical (physical function, role-physical, bodily pain, and general health) and four mental (vitality, social function, role-emotional, and mental health) subscales of health dimensions. The higher score indicates better quality of life. SF-36 score were collected during Screening, Days 1, 90, 180 and 360.

Disease activity score **(DAS)28:** DAS28 is a continuous disease measure that is a composite of 4 variables: the 28 tender joint count, the 28 swollen joint count, ESR or CRP, and subject assessment of disease activity measure on a visual analogue scale.1 DAS28 has numeric thresholds that define high disease activity (> 5.1), low disease activity (< 3.2) and remission (< 2.6). A clinically significant response is a decrease in DAS28 score of > 1.2 from baseline. By utilizing the European League Against Rheumatism (EULAR) response criteria, the DAS28 also incorporates a categorical response measure that defines a good, moderate, or no response.

Absolute DAS28 Score	DAS28 Improvement from Baseline		
	> 1.2	0.6 - 1.2	< 0.6
< 3.2	Good	Moderate	No
3.2 - 5.1	Moderate	Moderate	No
> 5.1	Moderate	No	No

Source: IM101043 Protocol (Appendix 5.1A).

- Dose finding study (pilot)

Study IM103002: A pilot, multi-centre, randomised, double blind, placebo controlled study to evaluate the safety, preliminary clinical activity and immunogenicity of multiple doses of BMS-188667 and BMS-224818 administered intravenously to subjects with rheumatoid arthritis.

The *major objective* of this pilot study was to assess the relative safety and preliminary efficacy (clinical activity) and immunogenicity of BMS-188667 and BMS-224818 in subjects with rheumatoid arthritis (RA) and to assess the suitability for continued clinical development. This trial included males or females (not nursing and not pregnant), 18 - 65 years of age.

The active RA was evidenced by ≥ 10 swollen joints and ≥ 12 tender joints and Erythrocyte Sedimentation Rate (ESR) $\geq$28 mm/hr or morning stiffness $\geq$45 minutes.

The study medication dose levels planned for intravenous infusion were: BMS-188667 (CTLA4Ig) 0.5, 2.0, and 10.0 mg/kg, BMS-224818 (LEA29Y) 0.5, 2.0, and 10.0 mg/kg, placebo for BMS-188667 and placebo for BMS-224818. The subjects were randomized in parallel fashion to 1 of 8 dosing arms (target sample size): BMS-188667 at 0.5 mg/kg (N = 30), 2 mg/kg (N = 30) or 10 mg/kg (N = 30); BMS-224818 at 0.5 mg/kg (N = 30), 2 mg/kg (N = 30) or 10 mg/kg (N = 30); placebo for BMS-188667 (N = 15) or placebo for BMS-224818 (N = 15). The placebo groups were pooled for analysis purposes. The study medication was administered by intravenous infusion over one hour on Days 1, 15, 29, and 57. Due to the long serum half-life of these agents, it was anticipated that effective drug exposure would be present for a minimum of 85 days. BMS-188667 was derived from manufacturing Process D and was formulated as a 200 mg/vial sterile, non-pyrogenic lyophile.

The primary endpoint was the number of subjects who achieved a 20% ACR response (ACR 20) on Study Day 85.

The ACR 20 response on Study Day 85 is shown in Table below. Clear trends for increasing response with dose occurred for both active treatments. At the 10-mg/kg dose levels of BMS-188667 and BMS-224818, the percentage of subjects achieving ACR 20 response was 53.1% and 61.3%, respectively. This pilot study was not powered to detect statistically significant between-group differences. However, the 95% confidence interval of the difference in ACR 20 response for the BMS-224818, 10 mg/kg group, compared with placebo, excluded "0".

	Placebo (N = 32)	BMS-188667 0.5 mg/kg (N = 26)	BMS-188667 2 mg/kg (N = 32)	BMS-188667 10 mg/kg (N = 32)	BMS-224818 0.5 mg/kg (N = 32)	BMS-224818 2 mg/kg (N = 29)	BMS-224818 10 mg/kg (N = 31)
ACR 20 responders, N (%)	10 (31.3)	6 (23.1)	14 (43.8)	17 (53.1)	11 (34.4)	13 (44.8)	19 (61.3)
Difference from placebo, %	NA	-8.2	12.5	21.9	3.1	13.6	30.0
(95% CI)		(-31.0, 14.6)	(-11.0, 36.0)	(-1.7, 45.5)	(-19.9, 26.1)	(-10.0, 37.8)	(6.5, 53.5)

- Main / supportive studies

Study IM101100: A Phase IIB, multi-centre, randomised, placebo-controlled study to evaluate the safety and clinical efficacy of two different doses of BMS-188667 administered intravenously to subjects with active rheumatoid arthritis while receiving methotrexate

The *primary objective* of this trial was to compare the clinical efficacy of two different doses of abatacept (BMS-188667; 10 and 2 mg/kg) combined with methotrexate (MTX), with MTX plus placebo in subjects with active rheumatoid arthritis (RA) as assessed by ACR 20 at 6 months.

This trial included adult patients, aged 18 years or older of either sex. The patients were to meet the criteria of the American Rheumatism Association (1987) for the diagnosis of RA and the criteria of the ACR (1991) RA functional classes I, II or III. The time from the initial diagnosis of RA was to be more than 1 year. The patients must have been on MTX treatment for at least 6 months with a weekly dose of 10-30 mg, and at a stable dose for 28 days prior to treatment.

For MTX monotherapy (patients were only receiving MTX, oral corticosteroids, and NSAIDs, and did not require washout/stabilization of other DMARDs), the patients had to have the following disease activity at screening: ≥ 10 swollen joints (66 joint count) and ≥ 12 tender joints (68 joint count) and CRP ≥ 1.0 mg/dL.

Subjects were randomised 1:1:1 to one of the following treatment groups: abatacept 10 mg/kg by intravenous infusion, abatacept 2 mg/kg by intravenous infusion or abatacept placebo by intravenous infusion. Infusion doses were based upon the subject's body weight

Altogether 524 patients were screened. Of these, 339 patients were randomised. Among subjects randomised 115 were randomised to abatacept 10 mg/kg, 105 to abatacept 2 mg/kg and 119 to placebo. Mean doses of MTX (15-16 mg/wk) and oral corticosteroids (6-7 mg/day) on Day 1 were comparable among all three treatment groups

A greater proportion of subjects in the abatacept group completed the 360 days of treatment compared with the placebo group: 78% of those randomized to the 10 mg/kg group, 71% randomized to the 2 mg/kg group and 60% randomized to the placebo group. During the first 180 days, more subjects in the placebo group discontinued the study than in the abatacept groups (35% in the placebo group, 24% in the 2 mg/kg group, 15% in the 10 mg/kg group). From Day 181 to Day 360, a similar proportion of subjects in each group discontinued the study.

The primary efficacy variable was ACR 20 response at Day 180 (6 months). There was a statistically significant (61% vs 35%, p < 0.001) difference in ACR 20 response at Day 180 for the 10 mg/kg (plus MTX) group compared with the placebo (MTX alone) group, and no significant difference in ACR 20 responses at Day 180 between the 2 mg/kg (plus MTX) group and the placebo group (Table below).

Parameter	Abatacept 10 mg/kg + MTX (N=115)	Abatacept 2 mg/kg + MTX (N=105)	Placebo + MTX (N=119)
n (%)	70 (60.9)	44 (41.9)	42 (35.3)
Estimate of the difference with respect to placebo (95% CI)	25.6 (12.8, 38.4)	6.6 (-6.2, 19.4)	N/A
p-value[a]	< 0.001	0.31	N/A

ITT Population.
N= total number of subjects in each treatment group; n= subset of N.
Subjects who discontinued the study due to lack of efficacy (ie, worsening RA) were considered ACR non-responders at all subsequent time points. For all subjects who discontinued for other reasons, their last ACR response was carried forward.

Parameter	Abatacept 10 mg/kg + MTX (N=115)	Abatacept 2 mg/kg + MTX (N=105)	Placebo + MTX (N=119)
ACR 50			
n (%)	42 (36.5)	24 (22.9)	14 (11.8)
Estimate of the difference with respect to placebo (95% CI)	24.8 (13.8, 35.7)	11.1 (1.2, 20.9)	N/A
p-value[a]	< 0.001	0.027	N/A
ACR 70			
n (%)	19 (16.5)	11 (10.5)	2 (1.7)
Estimate of the difference with respect to placebo (95% CI)	14.8 (7.5, 22.2)	8.8 (2.7, 14.9)	N/A
p-value[a]	< 0.001	0.005	N/A

ITT Population
N= total number of subjects in each treatment group; n= subset of N.
Subjects who discontinued the study due to lack of efficacy (ie, worsening RA) were considered ACR non-responders at all subsequent time points. For all subjects who discontinued for other reasons, their last ACR response was carried forward.

The percentages of subjects who achieved a MCR at Day 360 were significantly higher in both the 10 and 2 mg/kg groups (7.8% and 5.7%, respectively) when compared with the placebo group (0.8%; p = 0.008 and 0.036, respectively). At each study visit, the ACR-N was consistently higher in the 10 mg/kg group than in the 2 mg/kg and placebo groups.

Subjects treated with 10 mg/kg had improvements in physical function (mHAQ) at both Day 180 and Day 360 that were significantly higher relative to improvements for the placebo group.

Conclusion

The results of the primary efficacy variables analysis show that there was a statistically significant difference in the outcome between the abatacept group and the placebo group in the ITT population. The 10mg/kg group was constantly superior to placebo. However, 2mg/kg also showed activity. Thus, it remains unclear whether a middle dose, e.g. 5mg/kg, would also be effective in the maintenance therapy setting. The advantage of a lower maintenance dose would be the avoidance of unnecessary immunosuppression. The potential risk, besides a relapse, is the emergence of anti-abatacept antibodies when the immunosuppressive abatacept blood level is not reached over the whole period between the doses. The applicant offers a follow up measure in the context of a new randomised clinical study in early rheumatoid arthritis.

Study IM101102: A Phase III, multi-center, randomised, placebo-controlled study to evaluate the efficacy and safety of BMS-188667 in combination with methotrexate vs methotrexate alone in subjects with active rheumatoid arthritis and inadequate response to methotrexate.

The *primary objectives* were to compare the clinical efficacy of abatacept combined with MTX versus placebo plus MTX in subjects with active RA currently receiving MTX on symptomatic relief as measured by ACR 20 response following 6 months of treatment (Day 169), physical function as measured by the disability index of the HAQ at 12 months (Day 365), and structural damage as assessed by erosion score using a Genant-modified Sharp scoring method at 12 months treatment (Day 365).

The *secondary objectives* were to determine the effect of abatacept in combination of MTX on structural damage as assessed by total score and joint space narrowing score using a Genant-modified Sharp scoring method at 12 months treatment (Day 365), to assess the ACR 20, ACR 50 and ACR 70 over time, determine the proportion of subjects receiving abatacept in combination with MTX who achieve major clinical response (continuous ACR 70 for 6 months) counts Day 169, assess the immunogenicity of abatacept in combination with MTX, assess the changes in surrogate markers (RF, CRP, ESR, sIL-2R) at 6 months, assess the change in functional status by HAQ and health related quality of life (SF-36), and to assess the PK of abatacept.

This trial <u>included</u> adult patients, aged 18 years or older of either sex, who were willing to participate in the study and had signed the informed consent. The patients were to meet the criteria of the American Rheumatism Association (1987) for the diagnosis of RA and the criteria of the ACR (1991) RA functional classes I, II or III. The time form the initial diagnosis of RA was to be more than 1 year. The patients must have been on MTX treatment for at least 3 months with at least a weekly dose of 15 mg, and at a stable dose for 28 days prior to treatment. MTX weekly doses of 10 mg were permitted for subjects who could not tolerate higher doses.

For MTX monotherapy, the patients had to have the following disease activity at randomization: ≥ 10 swollen joints (66 joint count) and ≥ 12 tender joints (68 joint count) and CRP ≥ 1.0 mg/dL.

For combination DMARD therapy, the patients had to have the following disease activity at screening: ≥ 6 swollen joints (66 joint count) and ≥ 8 tender joints (68 joint count) and no restriction on CRP.

The main <u>exclusion criteria</u> were pregnancy or breast-feeding, active vasculitis of a major organ system, severe, progressive, or an uncontrolled renal, hepatic, haematological, gastrointestinal, pulmonary, cardiac, neurological or cerebral disease, patients with malignancy-suspicious mammogram, history of cancer within last 5 years (other than non-melanoma skin cell cancers cured by local resection), history of drug or alcohol abuse, serous bacterial infections in 3 months, active infections, anaemia and thrombocytopenia.

Subjects were <u>randomised 2</u>:1 to either of the following treatment groups: abatacept fixed dose by intravenous infusion (500mg for subjects < 60 kg, 750 mg for subjects from 60 to 100 kg and 1 gram for subjects > 100 k) plus MTX or placebo plus MTX. During the first 6 months, the patients were maintained on a stable dose of MTX (minimum 15 mg/week, decreased only for toxicity), corticosteroids and concomitant medications for the treatment of RA.
The baseline characteristics and baseline radiographic scores were similar for both treatment groups.

The antirheumatic medications at randomization were comparable in the treatment groups: 312 (72.1%) of abatacept groups subjects and 149 (68 %) of placebo group patients were having corticosteroids. At Day 169, the mean dose of MTX was 16 mg/wk in the abatacept groups and 15 mg/wk in the placebo group. At Day 365, the mean dose of MTX was 15 mg/wk in both treatment groups. At Day 169, the mean corticosteroid maintenance dose was 5 mg/day in the abatacept group compared with 4 mg/day in the placebo group. At day 365, the mean corticosteroid maintenance dose was 4 mg/day in the abatacept group compared with 5 mg/day in the placebo group.

The most common reason for study discontinuation was lack of efficacy in the placebo group (18 %) compared to abatacept group (3 %), and the AEs in the abatacept group (4 %) compared with the placebo group (2 %).

RESULTS

Abatacept +MTX was shown to be superior to MTX alone in all three co-primary efficacy endpoints.

A significant improvement in ACR 20 was seen on Day 15 in the abatacept group (p<0.05). The improvement in ACR 20 remained significant at Day 29 and continued through Day 365. Significant improvement (p<0.001) in ACR 50 was seen on Day 57 in the abatacept group and continued through Day 365. Significant improvement (p<0.001) in ACR 70 was demonstrated on Day 85 in the abatacept group and continued through Day 365. A sustained ACR 20 response was seen by Day 57 in approximately 50 % of subjects in the abatacept group compared with 29 % of subjects in the placebo group. The ACR 70 response was maintained over a continuous 6-month period. By Day 365 significantly more subjects treated with abatacept achieved a MCR (14 %) compared to subjects on placebo (2 %), p<0.001. In 6 % of the subjects in the abatacept group achieved MCR over a continuous 9-month period compared to placebo group (0.1 %), p=0.002. The disease activity at Day 169 and 365 was significantly lower in the abatacept group subjects compared with placebo group subjects.

In conclusion, Abatacept +MTX has a modest but definite anti-inflammatory effect in patients with advanced RA. This effect is reflected in improved function and reduced pain. Abatacept has also shown to reduce the rate of radiologically measured joint damage. The effect appears rather small as compared to published results with TNF-α blockers.

Study IM10029: A Phase III, multi-centre, randomised, placebo-controlled study to evaluate the efficacy and safety of BMS-188667 in subjects with active rheumatoid arthritis on background DMARDS who have failed anti-TNF therapy

The *primary objectives* were to compare the clinical efficacy of abatacept in active RA on background DMARDs versus placebo on background DMARDs on the following: clinical efficacy as measured by ACR 20 response rate at 6 months and improved physical function as measured by the disability index of the HAQ at 6 months.

The *secondary objectives* included comparison of ACR 50 and ACR 70 at Day 169 (Month 6), assessment of the ACR 20, ACR 50 and ACR 70 over time, assessment of the change in functional status by HAQ and health related quality of life (SF-36), and to assess the PK of abatacept.

For patients with prior (to the screening) anti-TNF therapy, the patients had to have the following disease activity at randomization: ≥ 10 swollen joints (66 joint count) and ≥ 12 tender joints (68 joint count) and CRP ≥ 1.3 mg/dL.

For patients with current (at screening) etanercept or infliximab therapy, the patients had to have the following disease activity at screening: ≥ 6 swollen joints (66 joint count) and ≥ 8 tender joints (68 joint count) and no restriction on CRP at screening. All subjects who were on etanercept at screening visit were required to undergo a 28-day washout period of their etanercept. The wash out for infliximab was 60 days. The patients had to have the following disease activity at randomization: ≥ 10 swollen joints (66 joint count) and ≥ 12 tender joints (68 joint count) and CRP ≥ 1.3 mg/dL.

If patients had failed etanercept of infliximab in the past, they had to be on a stable anti rheumatic therapy but still fulfill the activity criteria for entry: a minimum of 10 swollen and 12 tender joints.

After initiation of the study, adalimumab treatment became available in the USA. Subjects enrolled in the study could have received adalimumab prior to the study, but they were not eligible unless they failed prior treatment with either etanercept or infliximab for inadequate efficacy.

The anti-TNF-therapy failure was defined as inadequate efficacy response to etanercept and/or infliximab after being treated for at least 3 months. Acceptable failure documents included one or more of the following: Medical records, letter provided by a referring physician, or other "reason for referral" documents (e.g., insurance authorization form), provided they contain the relevant information to support anti-TNF therapy failure for inadequate efficacy. For subjects currently receiving anti-TNF therapy, the relevant documents were required to state that the subject was failing anti-TNF therapy for inadequate efficacy as determined by a physician's clinical assessment, and that the subject had a minimum of 10 swollen and 12 tender joints. In subjects previously treated with anti-TNF therapy, the relevant documents were required to indicate that the subject failed anti-TNF therapy for inadequate efficacy as determined by a physician's clinical assessment, and that they were currently in active disease (a minimum of 10 swollen and 12 tender joints) at the time of enrollment.

Overall, of the 391 subjects randomised and treated, 39% were current anti-TNF users compared with 61% who were prior anti-TNF users.

Oral corticosteroid treatment had to be reduced to the equivalent of ≤ 10 mg prednisone daily for 28 days and stabilized for 25 out of 28 days prior to treatment.

The study was performed in 101 sites worldwide; 69 sites in the USA, 24 sites in Europe, 8 in Canada. The study period was from December 2002 to June 2004. Altogether 738 patients were enrolled. Of these, 393 patients were randomised. Of these, 391 were treated. Among subjects randomised and treated 258 were randomised to abatacept and 133 to placebo. Subjects completing the double-blind period could continue in the open-label period.

A greater proportion of subjects in the abatacept group (86 %) completed the 169 days of treatment compared with the placebo group (74 %). The most common reason for study discontinuation was lack of efficacy in the placebo group (20 %) compared to abatacept group (5 %). AEs were the reason for discontinuation in 4 % of subjects in both groups. One subject in the abatacept group who discontinued the study for an SAE subsequently died on Day 104. One of the subjects who received placebo and discontinued experienced an SAE the day before the first infusion.

The baseline demographics and disease features were similar in the groups. The mean age of patients was 53-55 years and the mean duration of RA was 11-12 years. There was a high disease activity at baseline, e.g. in terms of the number of swollen joints (22).

Data are presented on the disease activity before discontinuation of the anti-TNF at screening and at baseline after discontinuation. These data demonstrate that the disease activity was decreased below the pre-treatment level during abatacept treatment

Table below shows responders as defined by ACR20 at Day 169:

	Abatacept (N=256)	Placebo (N=133)
Number of responders (%)	129 (50.4)	26 (19.5)
Estimate of the difference with respect to placebo (95% CI)	30.8 (20.6, 41.1)	N/A
p-value	<0.001	N/A

Population: All randomized and treated subjects.

The improvement in ACR 20 was seen on Day 15 in the abatacept group (p<0.01). At Day 169, an ACR 50 response was achieved by significantly more subjects in the abatacept group compared with the placebo group (20% vs. 4%, p < 0.001). Similarly, an ACR 70 response was achieved by significantly more subjects in the abatacept group compared with the placebo group (10% vs. 2%, p = 0.003).

Significantly more subjects in the abatacept group compared with the placebo group achieved a HAQ response that was clinically meaningful (defined as an improvement of at least 0.3 units in the HAQ disability index), 47 % vs. 23 %, p< 0.001.

Study IM101101: A multicentre, randomised, double blind, placebo controlled study to evaluate the safety and clinical efficacy of intravenous infusions of BMS-188667 (Abatacept, 2 mg/kg) given monthly in combination with subcutaneous injections of Etanercept (25 mg) given twice weekly to subjects with active rheumatoid arthritis

The *objective of the study* was to compare the clinical efficacy of abatacept (2 mg/kg) to placebo given on a background of etanercept after 6 months of treatment in subjects with active RA with an inadequate response to etanercept, as assessed by ACR 20 (using a modified definition of the ACR criteria based on tender joints, swollen joints, and 2 of the 4 remaining core components, excluding CRP).

This was a 12-month randomised, double-blind, placebo-controlled, parallel-design study. Adult subjects with active RA despite etanercept therapy who met the inclusion/exclusion criteria for this study were randomized 2:1 to treatment with either abatacept (2 mg/kg, IV monthly) plus etanercept (25 mg SC twice weekly) or placebo (IV monthly) plus etanercept (25 mg SC twice weekly).
DMARDs other than etanercept were not permitted. Low-dose stable corticosteroids (at 10 mg daily or less) and/or stable non-steroidal anti-inflammatory drugs (NSAIDs), including acetylsalicylic acid (ASA), use was allowed.

At 6 months, subjects who achieved at least a 50% reduction in their swollen and tender joint counts were to discontinue etanercept and continue on their original treatment assignment of abatacept or placebo for an additional 6 months. In the case of flare, these subjects were permitted to restart etanercept therapy after 15 days. Addition of an oral DMARD (hydroxychloroquine, sulfasalazine, leflunomide or MTX) was permitted during this second 6 months period.

The baseline demographics and disease characteristics were similar in the groups. Surprisingly, a minority of patients had been exposed to other DMARDs than etanercept prior to the study.

The adherence to the treatment was worse than in other abatacept studies. The most common reasons for discontinuation were lack of efficacy and adverse events (see Table below).

Table 8.1.1:   Reasons for Discontinuation: Days 1 to 180 (Study IM101101)

	Number (%) of Subjects	
	Abatacept 2 mg/kg + Etanercept (N = 85)	Placebo + Etanercept (N = 36)
No. Discontinued	20 (23.5)	14 (38.9)
Adverse Event	6 (7.1)	1 (2.8)
Lack of Efficacy	9 (10.6)	12 (33.3)
Lost to Follow-Up	1 (1.2)	0
Withdrawal of Consent	3 (3.5)	1 (2.8)
Non-Compliance	1 (1.2)	0
Completed 180 Days of Therapy	65 (76.5)	22 (61.1)

All treated subjects.

The Table below summarizes the results on ACR20 responses. The treatment effect is modest at best.

Modified ACR Response Rates: Percentage of Subjects Meeting Criteria

	Abatacept 2 mg/kg + Etanercept (N=85)	Placebo + Etanercept (N=36)
Day 180		
ACR 20	48.2	30.6
ACR 50	25.9	19.4
ACR 70	10.6a	0
Day 360		
ACR 20	48.2	30.6
ACR 50	28.2	16.7
ACR 70	9.4	5.6

ITT Population

a Statistically significant compared with the placebo group (p = 0.04).

Subjects in the abatacept group had an improvement in physical function (mHAQ) at Day 180 that was statistically significant (p < 0.01) relative to the improvement for the placebo group; however this significant difference was not sustained at Day 360.

When compared with the placebo group, subjects in the abatacept group demonstrated clinically and statistically significant improvements in 6 of the 8 domains of the SF-36 (Quality of Life) at Day 180 and 5 of the 8 domains at Day 360, compared with baseline.

Safety

Subjects in the abatacept group had higher rates of related AEs, SAEs, including two malignancies, related SAEs and discontinuations due to AEs compared with the placebo group. Infections (mainly respiratory infections) were more common in the abatacept group than in the placebo group (64% vs 31%). Five subjects discontinued the study due to an infection - 4 in the abatacept group. In asthmatic subjects, the rate of peri-infusional AEs was numerically higher in the abatacept group. Five patients, all in the abatacept group, discontinued the abatacept treatment due to SAEs: angioneurotic edema, complex partial seizures, leukocytoclastic vasculitis, chest pain, and serious infection.

Conclusion

The tolerability of the etanercept-abatacept combination was poor as compared to etanercept alone. There are potential safety signals, notably the infections but also hypersensitivity reactions. Considering these potential problems and the moderate effect, the applicant does not recommend combination treatment with anti-TNF. This information is provided in the proposed SPC:

Study IM101031: A Phase III, Multi-Centre, Randomised, Double-Blind, Placebo-Controlled Clinical Use Study to Evaluate the Safety and Tolerability of BMS-188667 Administered Intravenously to Subjects with Active Rheumatoid Arthritis (RA) With or Without Medical Co-Morbidities Receiving Disease Modifying Anti-Rheumatic Drugs (DMARDs) and/or Biologics Approved for RA

The *primary objective* of this study was the assessment of safety. Subjects with active RA, with or without co-morbidities and receiving background non-biologic RA therapy and/or biologic RA therapy were randomized in a 2:1 ratio to receive abatacept or placebo. Background therapy was held stable for 3 months, after which it could have been altered according to response. The duration of the double-blind phase was 12 months. Approximately 2 years of data have been collected in the double blind and open-label periods combined.

A total of 161 study centres treated subjects in this study: 91 sites in the United States; 24 sites in Europe; 8 sites in Canada; 4 sites in Australia; 3 sites in Argentina; 10 sites in Brazil; 7 sites in Mexico; 3 sites in Peru; 2 sites in Thailand; 4 sites in Taiwan; and 5 sites in Turkey.

Eligible subjects were randomized to 1 of 2 treatment groups: abatacept fixed dose approximating 10 mg/kg or placebo intravenous (IV) infusion. All subjects continued their background therapy for rheumatoid arthritis (non-biologic or biologic disease-modifying drugs or combination) throughout the double-blind treatment period. Double-blind study medication (abatacept or placebo) was administered on Days 1, 15, 29, and every 28 days thereafter, for a total of 14 doses. Dose modification of double blind study medication was not permitted. Abatacept dose was (500 mg for subjects < 60 kg, 750 mg for subjects 60 to 100 kg and 1 g for subjects > 100 kg).

A total of 1441 subjects were randomized and treated: 959 in the abatacept group and 482 in the placebo group. The duration of RA was approximately 10 years. Non-biological DMARDs were used by more than two thirds of patients, with methotrexate being the most common (75%–78%). Biologic RA therapy was used by 9% to 10% of subjects, and between 62% to 63% of subjects used oral and/or injectable corticosteroids. In both treatment groups, the percentage of subjects with selected co-morbidities was 6 to 7% for type 1 or 2 diabetes, 6% for asthma, 4% for chronic pulmonary obstructive pulmonary disease, and 1 to 2% for congestive heart failure.

Median percentage improvements from baseline in subject- and physician-reported disease outcomes (subject pain assessment, subject global assessment, physician global assessment) at Day 365 were higher for abatacept-treated subjects (47.5%, 47.1%, and 63.3%, respectively) compared with placebo-treated subjects (26.0%, 30.4%, and 43.0%, respectively). Median percentage improvements from baseline in physical function (HAQ disability index) (28.6% vs. 14.3%) were greater for subjects treated with abatacept compared to placebo at Day 365.

Safety

Overview of Safety During Double-blind Period (IM101031)

	Number (%) Subjects	
	Abatacept N = 959	Placebo N = 482
Deaths	5 (0.5)	4 (0.8)
SAEs	123 (12.8)	59 (12.2)
Related SAE	23 (2.4)	13 (2.7)
Discontinuation due to SAE	23 (2.4)	7 (1.5)
AEs	866 (90.3)	417 (86.5)
Related AEs	534 (55.7)	239 (49.6)
Discontinuation due to AE	52 (5.4)	20 (4.1)

There were no remarkable differences between the abatacept or placebo arms for infections, autoimmune disease or malignancies.

Mammograms were to be performed for female subjects at screening and after completing 1 year of treatment at Day 365. Three women had abnormalities on their follow-up mammograms that were indicative of malignancy, including 1 in the abatacept group and 2 in the placebo group. Increased blood pressure was reported more commonly in the abatacept group.

Conclusion

The results are assuring for the risk of infections and malignancies. However, the size of the database is not sufficient to uncover rare adverse events and this study does not provide sufficient data to support use of abatacept with other DMARDs other than MTX. Nevertheless, abatacept may be added on to methotrexate-based combinations that are commonly used in the medical practice.

- Progression of joint damage

The impact of abatacept on the progression of joint destruction was investigated by using joint radiographs. Radiographic techniques were standardised both with regard to the radiographic procedures and their assessment. A validated and generally accepted method was used to score the radiographs for erosions and joint space narrowing (Genant HK *et al*, 1998).

Study IM101102 is pivotal for the radiographic evaluation of joint damage. The change in erosion score was a co-primary endpoint. Changes in JSN and total scores were evaluated as secondary endpoints. The primary analysis was ITT with available paired assessments and included all radiographic data regardless of whether the subject discontinued study drug. The distribution of changes was significantly different between treatment groups in favour of abatacept for erosion (p = 0.029), JSN (p = 0.009) and total score (p = 0.012). The mean and median changes from baseline in radiographic measurements at 1 year indicated a reduction of approximately 50% in radiographic progression compared with placebo. Similar effects were noted for JSN and total score. A total of 467/536 (87%) subjects treated in the open-label period were included in the Day 729 primary analysis. These subjects had radiographic assessments at baseline, Day 365, Day 729 or at early termination.

Subjects originally randomised to abatacept who continued to receive abatacept in the open-label period (2 years) demonstrated less progression of structural damage over the 2 year period with minimal progression during the second year compared with subjects originally randomised to placebo who received abatacept in open-label period (1 year). This study provided robust evidence for the reduction of the rate of joint destruction during abatacept treatment.

Two other studies (IM 10100 & IM 101101) had radiographic evaluation as a tertiary outcome measure, but were not powered to detect differences.

- Special populations

Children and adolescents were excluded from the past clinical trials. There is an ongoing clinical study in juvenile polyarthritis (IM101033 trial)

A total of 323 patients *65 years of age and older*, including 53 patients 75 years and older, received abatacept in placebo-controlled clinical trials. Similar efficacy was observed in these patients and in younger patients.

- Additional study

During evaluation of the Marketing Application, BMS submitted results of a further pivotal trial (Study IM101043).

Study IM101043: A Phase III, Multi-Centre, Randomised, Double-Blind, Placebo-Controlled Comparative Study of Abatacept or Infliximab in Combination with Methotrexate in Controlling Disease Activity in Subjects with Rheumatoid Arthritis Having an Inadequate Clinical Response to Methotrexate

This was a randomised, double-blind, double-dummy, placebo-controlled, 3 group, active control (infliximab), multi-centre, multinational, 12-month study divided into 2 periods: Period 1 (Days 1 - 197) and Period 2 (Days 198 - 365). Adult subjects with active RA who were inadequate responders to

MTX, and who met the inclusion and exclusion criteria for the study, were randomised 3:3:2 to the following groups for 6 months: ABA, INF or placebo (PLA). Treatment with placebo was limited to 6 months to validate the clinical response rates of the 2 active treatment groups. In Period 2, subjects in the PLA group were reallocated to receive abatacept (after Day 197 termed the PLA-ABA group). Subjects in the ABA or INF groups during Period 1 continued their treatment during Period 2. All subjects had the opportunity to receive open-label abatacept after completing the first 12 months of the study, if they continued to meet eligibility requirements.

The *primary efficacy outcome measure* was reduction in DAS28 at 6 months (Day 197) in the ABA group compared with the PLA group. Other secondary efficacy endpoints are presented in the methods section (see the Table below)

All subjects who received at least 1 dose of study medication during the double-blind period were evaluated for safety. Adverse events (AEs), serious adverse events (SAEs) including deaths, discontinuations due to AEs, clinical laboratory test abnormalities, changes in vital signs, and physical examinations, were examined. The immunogenic potential of abatacept and infliximab was assessed based on levels of anti-abatacept antibodies and human anti-chimeric antibody (HACA), respectively, using validated sensitive, enzyme-linked immunosorbent assay (ELISA) methods.

Statistical analysis

The primary analysis was the comparison of the ABA and PLA groups with respect to changes from baseline to Day 197 in DAS28 using an analysis of covariance (ANCOVA) model with treatment group as the effect and baseline value as the covariate. Point estimates, 95% confidence intervals (CI) and p-values were computed for the treatment difference within the framework of the ANCOVA model.
A summary of DAS28 scores at Day 197 were prepared for the following subgroups: age, gender, race, geographic region, duration of RA, swollen joint counts, tender joint counts, CRP levels, and RF factor status. No statistical tests were performed for the subgroup analyses.

Trial - and concomitant treatment

Subjects in the INF group received infliximab (3 mg/kg IV). Subjects in the PLA-ABA group received normal saline (NS) IV on Days 1 to 196 and abatacept IV on Days 197 to 365. During the study, subjects were to have received a stable dose of MTX (minimum 15 mg weekly). Use of parenteral MTX was acceptable as clinically indicated. To minimize potential MTX toxicity, all subjects received folic acid, folinic acid, or leucovorin according to the MTX product label.

The concomitant therapy was allowed as follows:

Days 1 - 197
Increases in MTX were not permitted; decreases were permitted due to toxicity. Other DMARDs were not permitted. Low-dose stable glucocorticoids ($\leq$ 10 mg daily prednisone equivalent) and/or stable non-steroidal anti-inflammatory drugs (NSAIDs), including acetyl salicylic acid (ASA), were allowed. For subjects experiencing pain not adequately controlled by the baseline and study medications, analgesics not containing ASA or NSAIDs were permitted; however, additional NSAIDs or rescue analgesics were not permitted 12 hours before a joint evaluation.

Days 198 - 365
Adjustments in glucocorticoids (maximum of 10 mg prednisone equivalent daily) and
MTX (maximum of 25 mg weekly) were permitted. If clinically indicated, 1 of the following DMARDs could be added at the investigator's discretion: hydroxychloroquine, sulfasalazine, gold, or azathioprine. DMARDs were to be used according to the manufacturer's recommendations. Analgesics were permitted as described above for Days 1 - 197.

Patient disposition

Of the 748 subjects who were enrolled, 156 were randomized to the ABA group, 165 were randomized to the INF group, and 110 were randomized to the PLA group (this group received abatacept plus MTX for the second 6 months).

During the first 197 days of the double-blind period, the rate of premature discontinuation was low among subjects treated with placebo (2.7%); the corresponding rates of discontinuation for the INF and ABA groups were 7.9% and 5.8%, respectively

The number of patients with DMARDs other than MTX was 4.8 % in the infliximab group, 0.6 % in the abatacept group and 3.6 % in the placebo-abatacept group (Days 198-365).

R̲E̲S̲U̲L̲T̲S̲

The primary objectives

The reduction in DAS28 scores at Day 197 for ABA was greater compared with PLA (-2.53 vs -1.48, p < 0.001). A greater proportion of subjects in the ABA group compared with the PLA group had clinically significant improvement in disease activity (defined as a decrease in DAS28 score ≥ 1.2, 82% vs 52%), low disease activity (defined as DAS28 score ≤ 3.2, 21% vs 11%) and were in remission (defined as DAS28 score < 2.6, 11% vs 3%).

The secondary objectives

At Day 197, a greater reduction in DAS28 scores was also observed for INF compared with PLA (-2.25 vs -1.48, p < 0.001). A greater proportion of subjects in the INF group compared with the PLA group had clinically significant improvement in disease activity (defined as a decrease in DAS28 score ≥ 1.2, 72% vs 52%), low disease activity (defined as DAS 28 score ≤ 3.2, 26% vs 11%) and were in remission (defined as DAS 28 score < 2.6, 13% vs 3%).

A pre-specified exploratory analysis was conducted to compare DAS28 responses for the ABA and INF groups at Day 197. A similar proportion of subjects in the ABA and INF groups had clinically significant improvement in disease activity (defined as a decrease in DAS28 score ≥ 1.2, difference between proportions of 9.6%, 95% CI -0.5 to 19.6). Similar proportions were also seen for low disease activity (defined as DAS28 score ≤ 3.2) 20.7% vs 25.6%, difference of -5.0%, 95% CI -15.1 to 5.1 and for remission (defined as DAS28 score < 2.6) 11.3% vs 12.8%, difference of -1.5, 95% CI -9.4 to 6.5). The mean DAS 28 scores over time (day 1-365) are presented in Figure below.
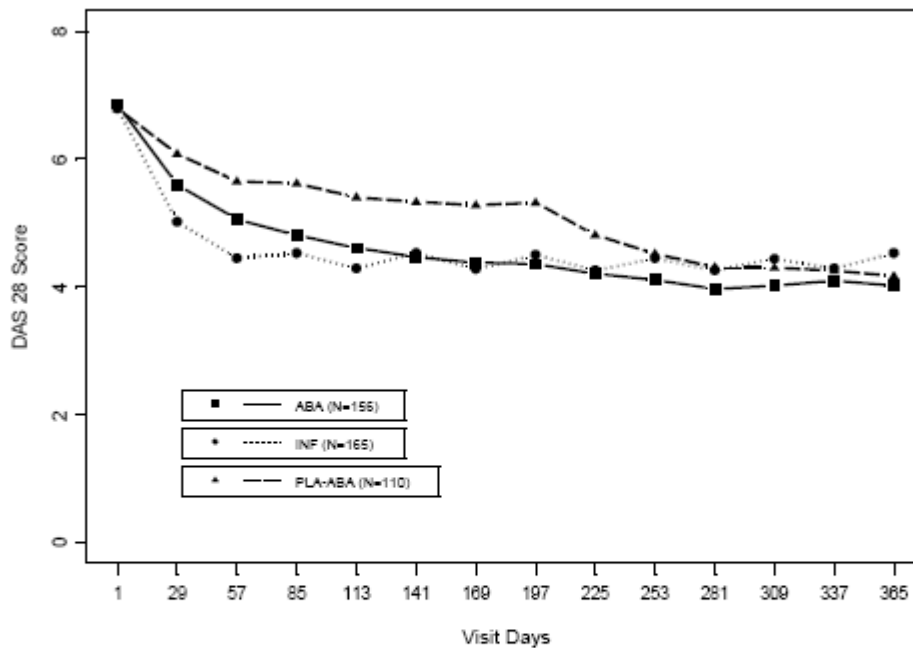
Population: All randomized and treated subjects
One additional DMARDs (ie, hydroxychloroquine, sulfasalazine, gold or azathioprine) could be added on
or after Day 197
ABA = Abatacept, INF = Infliximab, and PLA-ABA = Placebo to Abatacept
Subjects in the PLA-ABA group received placebo for the first 6 months and abatacept for the second
6 months.
Program Source: G:\IM_RA\Figures\102_pgm\im10.1.1.2

At Day 197, greater mean reductions in HAQ-DI from baseline were observed for the ABA group compared with the PLA group (p < 0.001). Mean reductions from baseline in the HAQ-DI subscales were consistent with those for HAQ-DI. Similarly, greater mean reductions from baseline were observed for the HAQ-DI (p < 0.001) and its subscales at Day 197 for the INF group compared with the PLA group.

Subjects in the ABA group had greater improvements from baseline in the physical (p < 0.001) and mental (p = 0.004) summary measures at Days 197 than subjects in the PLA group. Subjects in the INF group had greater improvements from baseline in the physical (p = 0.002) and mental (p = 0.027) summary measures at Days 197 than subjects in the PLA group

Subjects in the PLA-ABA group had their efficacy measures summarised but were not compared to the other groups between Days 198 and 365.

Safety

The mean exposure to study drug during the first 6 months of the double-blind period was similar to the planned duration of 197 days in all 3 treatment groups (191.7 to 194.4 days), consistent with low overall rate of early withdrawal during Days 1 – 197. The median number of infusions of study drug was 9 in all 3 treatment groups, and fewer than 2% of subjects in any group received 3 or fewer injections.

During Days 1 - 197, the AE profile was generally similar for the ABA + MTX and PLA + MTX groups, both in terms of the overall frequencies of AEs and related AEs as well as discontinuations due to AEs or SAEs. The overall frequencies of AEs, related AEs, and SAEs, were also similar for INF + MTX and PLA + MTX groups during Days 1 - 197.

The majority of acute infusional events reported during Days 1 - 197 in all 3 treatment groups were mild or moderate in intensity. During Days 1 - 197, the frequency of pre-specified infections (ie, mycobacterial, herpes virus family, invasive fungal and opportunistic infections) was similar for the ABA (7.7%) and PLA (7.3%) groups, but was higher among subjects in the INF group (10.9%).

Conclusion

The study was not designed to demonstrate non-inferiority or superiority of abatacept compared to infliximab, but rather to validate the efficacy responses (assay sensitivity), and to directly compare the safety profile of the active biologic treatment groups to placebo at 6 months. The results on the primary efficacy endpoint confirm that the abatacept-MTX combination is superior to placebo-MTX combination. The same is true for the infliximab-MTX combination over placebo-MTX combination. The efficacy based on disease activity (DAS28) seems to be maintained over time to day 365. The improvement over placebo was also shown in physical function and quality of life. The radiographic outcomes were not assessed. The patients were permitted to have additional DMARDs and adjustment of the MTX dose from the day 198 on. The number of patients with DMARDs other than MTX was 4.8 % in the infliximab group, 0.6 % in the abatacept group and 3.6 % in the placebo-abatacept group.

Overall, no new safety concerns with Abatacept use were identified from this study. During days 1 - 365, the proportion of subjects with severe AEs was similar for the abatacept (13.5%) and infliximab (13.9%) groups. The number of infections and infestations and infusional events was somewhat lower in the abatacept group than in the infliximab group, but the overall number of cases was low. The results should be interpreted with caution until further comparative data are available. The results of the open-label extension period should be submitted when available.

- Discussion on clinical efficacy

The clinical programme assessed provides robust data on the efficacy of Abatacept. The new product has a modest anti-inflammatory effect in advanced RA. As a result, there is relatively rapid symptom relief and improvement of function. In addition, abatacept has a small but definite effect on the radiological progression of joint damage.

It remains unclear whether a reduced dose, e.g. 5mg/kg, would also be effective in the maintenance therapy setting.

The tolerability of its use in combination with etanercept was poor however with potential safety signals detected. For time being, Abatacept is not recommended as combination treatment with anti-TNF.

Clinical safety

- Patient exposure

In the Phase II/III RA clinical program, 2778 subjects were exposed to abatacept in the double blind and open-label periods combined. This includes 2688 subjects from the 5 core RA studies IM101100, IM101101, IM101102, IM101029, IM101031) and 90 subjects from the Phase IIA study, IM103002.

Approximately 83% of subjects (2311 subjects) were exposed to abatacept (all doses) for at least 12 months and approximately 50% of subjects (1378) were exposed to abatacept (all doses) for at least 24 months in the double blind and open-label periods combined. The enrolled patients were mainly women with seropositive RA with approximately 10 years duration. The disease was active at the time recruitment.

All of the core RA studies excluded subjects with severe or uncontrolled co-morbid conditions. Subjects with less severe, controlled co-morbid conditions were enrolled.

The presence or absence of four co-morbid conditions of particular interest (diabetes mellitus, asthma, COPD, and chronic heart failure) at baseline was determined through specific questions on the case report form for the large safety study, IM101031. The number of subjects in this study with the noted co-morbid conditions at baseline was: diabetes mellitus (type 1 and type 2) (N=96), asthma (N=83), COPD (N=54), and CHF (N=18).

Overall, abatacept was well tolerated in the double blind, controlled study periods. Most subjects (88.8%) reported at least one AE during the double-blind study periods. A small increase in the proportion of subjects reporting SAEs (14.0% vs 12.5%) and discontinuation due to SAEs (2.8% vs 1.6%) was observed with abatacept relative to placebo

- Adverse events

Higher frequencies of AEs in the abatacept group compared with the placebo group were reported for the following system organ classes (SOCs): *infections and infestations* (54.1% vs 48.7%), *gastrointestinal disorders* (39.0% vs 35.8%) and *nervous system disorders* (32.2% vs 27.6%). Severe and very severe infections were reported by a small proportion of subjects (severe: 2.9% vs 2.6%; very severe: 0.2% vs 0.4% in the abatacept and placebo groups, respectively). Dyspepsia was the only gastrointestinal event reported by ≥2% of subjects in the abatacept group compared with the placebo group. Few events of dyspepsia were severe (0.2% in each group) or very severe (<0.1% vs 0%). Nervous system disorders were slightly more common in the abatacept group compared with the placebo group, mainly due to higher frequencies of headache (18.3% vs 12.7%) and dizziness (9.5% vs 7.0%). Approximately half of all reports of headache and dizziness were reported as peri-infusional (onset within 24 hours after the start of the infusion): headache 8.2% and 5.1% and dizziness 4.9% and 3.8% in the abatacept and placebo groups respectively.

The only other event reported by ≥2% of subjects in the abatacept group compared with the placebo group was hypertension (6.6% vs 4.6%). Mouth ulceration and aphthous stomatitis may be associated with herpes simplex, which was more common with abatacept than placebo (1.9% vs 1.0%).

- Serious adverse event/deaths/other significant events

Serious adverse events were reported by 14.0% of subjects in the abatacept group compared with 12.5% of subjects in the placebo group. No particular type of SAE was increased in abatacept-treated patients as compared to placebo, except infections that were more frequently reported in the abatacept group compared with the placebo group (3.0% vs 1.9%). A total of 16 subjects died during the double-blind periods: 9 subjects (0.5%) in the abatacept group and 7 subjects (0.7%) in the placebo group. One patient who received abatacept died of pulmonary aspergillosis. Risk of serious adverse events, including infections, is higher in the elderly.

Malignancies were not increased in abatacept treated patients. Lymphoma was reported in 1 abatacept-treated subject during the double-blind period and additional 3 cases during the open-label period.

Infections were rarely serious and there was not specific pattern, except an increase in Herpes simplex infections. Common bacterial infections may also be increased.
- Special populations

Children and adolescents were excluded from the past clinical trials.

In the *elderly* involved as a minor fraction in the placebo-controlled clinical trials, the frequency of SAEs was higher in abatacept-treated subjects ≥65 years of age compared with placebo-treated subjects (25,1% vs 16,9%). Approximately two-thirds of this difference was accounted for by differences in the rates of serious infection (5,6% vs 2,7%) and malignancies (6,2% vs 2,7%).

In the double blind and open-label periods of the 5 core studies, 8 *pregnancies* that involved women treated with abatacept were reported. Of these 8 women, 7 received MTX and one received leflunomide as a concomitant medication.

Three subjects experienced a spontaneous abortion during the first trimester (one had a history of 2 previous spontaneous abortions, one had a history of a previous unsuccessful pregnancy, and one had no prior history of pregnancy). Two subjects terminated the pregnancies by an induced abortion. Three pregnancies were ongoing. In addition, 1 spouse of a subject became pregnant and delivered a normal, healthy baby.

In a Phase II MS study (IM101200), 3 women became pregnant: 2 study subjects and 1 partner of a study subject. One subject delivered a healthy baby 10 months after discontinuation from the study; the other subject had an elective abortion at 4 weeks gestation and the partner had a spontaneous abortion (miscarriage) at approximately 2 months gestation.

- Immunogenicity

Abatacept was associated with a relatively low (2.8%) frequency of immunogenicity in RA subjects. The frequency of immunogenicity in subjects who missed doses was not increased. Subjects who discontinued therapy were more frequently immunopositive (immune responses on days 56 and/or 85 after the last dose) than subjects who did not discontinue (7.4% vs 2.6%).

Estimates of PK parameters (clearance, central compartment volume, steady-state AUC, and steady-state Cmin values) were comparable in immunopositive subjects and the larger population of subjects who did not develop immunogenicity. Neutralizing antibody activity was documented in 9 of 14 samples in 8 of 13 subjects.

Due to the small number of subjects across studies that developed an immune response, conclusions concerning the impact of immunogenicity on safety and efficacy cannot be made. However, the development of immunogenicity in subjects did not appear to be associated with adverse safety and efficacy outcomes. Further assessment of immunogenicity and possible clinical consequences remains important and is currently addressed in the context of the Risk Management Plan. The current ELISA assay is complex and not amenable to large-scale use. As a follow-up measure, the applicant will report the results from clinical samples with a new (MSD) anti-abatacept assay (compared to the old ELISA assay).

- Discussion on clinical safety

Abatacept is well tolerated by most patients. Severe infections are likely to be encountered during post-marketing use. An increase in *Herpes simplex* infections has already been encountered. Common bacterial infections also seem to be associated with abatacept-treatment. On the basis of the mechanism of action, it was anticipated that intracellular infections might increase. This will have to be followed up post-marketing. The risk of malignancies and autoimmune disorders is impossible to assess at this point.

For time being, there is no direct evidence for immune-mediated adverse effects or loss of efficacy. However, the assays for anti-abatacept antibodies are insensitive and there is an antigen interference that may cause false negative results in the anti-abatacept assay. The risk of hypersensitivity after treatment interruption and re-exposure is difficult to assess, especially for abatacept monotherapy. The applicant provided preliminary data from a clinical study in juvenile polyarthritis, in which patients were re-exposed to abatacept, either alone or in combination with methotrexate. Abatacept-antibodies were detected after discontinuation of the abatacept treatment. However, the presence of the abatacept-antibodies was not associated with any particular adverse events after reintroduction of abatacept. These data are reassuring but preliminary and hence no conclusions can be reached.

The increase in certain adverse events in the elderly may be explained on the basis of age-dependent increase of some concomitant diseases in general. However, immunosenescence is thought to be involved in the increase of infections and malignancies in the elderly. Thus, additional immunosuppression by abatacept may be more harmful for the elderly. Further data will be obtained for this age group from the ongoing clinical trials and from the ongoing and planned pharmacoepidemiological studies.

The issues of infections, immunogenicity, malignancies and autoimmune disorders will be included in the Risk Management Plan (RMP). The risk management plan will include two pregnancy registries. For time being, the use of abatacept during a pregnancy is not recommended. It is anticipated that abatacept will be used "off label" in children and adolescents. This has been taken into account in the pharmacovigilance plan. Further studies need to be carried out as a post-marketing commitment.

5 Pharmacovigilance

Detailed description of the Pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

Risk Management Plan

The MAA submitted a risk management plan, which included a risk minimisation plan.

There is already a large database for abatacept in the proposed use:

Period	No. of patients Patient time	Abatacept		Placebo
		Total	**Recommended dose**	
Double-blind period	No. of subjects	1955 (258/1697)	1765	989 (133/856)
	Person-years	1687	1526	794
Open label extension	No. of subjects	2339	2339	-
	Person-years	3077	3077	-
Total	No. of subjects	2688	2624	989
	Person-years	4764	4603	794

With a sample size of 1955 subjects exposed to abatacept during double-blind periods, it was estimated that there would be sufficient power to detect event rates of at least 0.2%. Obviously, the sample size and duration of exposure to date are insufficient to adequately characterize a rare event with long latency such as malignancy. Such events have to be addressed post-marketing. There is an ongoing open label follow up of the placebo-controlled clinical studies with 2339 patients.

The _identified and potential risks_ as well as the _important missing information_ are listed in the following Table:

Identified safety risks	- infection with special reference to tuberculosis (TB), - infusion-related reactions.
Potential safety risks	- malignancies, with special reference to lymphoma, non-melanoma skin cancer (NMSC), lung cancer and breast cancer, - autoimmune disorders, - immunogenicity, - pregnancy.
Important missing information	- children, - vaccination, - hepatic and renal impairment, - combination biologic therapy, - elderly.

The applicant proposed to undertake epidemiology studies in several countries as part of its ongoing assessment of abatacept safety. One study is using NDB the United Health Care medical and pharmacy claims database in the United States. The other 4 studies are nested in existing RA registries:

1. Prospective cohort using the Antirheumatic Therapy in Swedish database

2. Prospective cohort study using the British Society of Rheumatology Biologics Register (BSRBR)
3. Prospective cohort study using Rheumatoid Arthritis Observation of Biologic Therapy (RABBIT, DE).
4. Prospective cohort study using National Databank of Rheumatic Diseases (RALLY, United States)

In addition, reference is made to two pregnancy registries (US Pregnancy Registry OTIS / EU Pregnancy Registry ENTIS)

Table Summary of the risk management plan

Safety issue	Proposed pharmacovigilance activities	Proposed risk minimisation activities
Identified Risks		

Infections
    Tuberculosis
    COPD
	-Routine pharmacovigilance activities
	- Special CRFs for spontaneous ADRs of special interest
	- Open extensions of pivotal clinical trials up to 5 years
	- Epidemiology studies:
	US Claims Database (IM101-045A, UHC), US Registry (IM101-045B, RALLY) and three EU registries (IM101-125, ARTIS; IM101-126, BSRBR; IM101-127, RABBIT) will assess (hospitalized) infections and tuberculosis (annual reports and relative risk abatacept vs non-biologic DMARDs at pre-defined milestones)
		- Specific subsections on infections and/or ADRs in patients with COPD in sections 4.3, 4.4 and 4.8 of the SmPC
		- Alert Card will be used to inform patients of the need for an adequate history and screening for infections

Infusion-related reactions	-Routine pharmacovigilance activities - Open extensions of pivotal clinical trials up to 5 years - Relevant epidemiology Studies	- Specific subsection on allergic or infusion-related reactions in sections 4.4 and 4.8 of the SmPC.
Potential Risks		

Malignancies
    Lymphoma
    NMSC
    Lung cancer
    Breast cancer
	- Routine pharmacovigilance activities
	- Special CRFs for spontaneous ADRs of special interest
	- Open extensions of pivotal clinical trials up to 5 years
	- Epidemiology studies:
	US Registry (IM101-045B, RALLY) and three EU registries (IM101-125, ARTIS; IM101-126, BSRBR; IM101-127, RABBIT) will assess malignancies including lymphoma, NMSC, lung cancer, and breast cancer (annual reports and relative risk abatacept vs non-biologic DMARDs at pre-defined milestones)
		- Specific subsection on malignancies in sections 4.4 and 4.8 of the SmPC.

Induction/exacerbation of autoimmune disease	-Routine pharmacovigilance activities - Special CRFs for spontaneous ADRs of special interest - Open extensions of pivotal clinical trials up to 5 years - Relevant epidemiology studies	- Specific subsection on auto-immune disease or auto-antibodies in sections 4.4 and 4.8 of the SmPC.

Immunogenicity	- Open extensions of pivotal clinical trials up to 5 years - Follow-up Measure to validate new assay for anti-abatacept antibodies.	- Specific subsection on immunogenicity in section 4.8 of the SmPC
Effects during pregnancy	- Routine pharmacovigilance activities - Open extensions of pivotal clinical trials up to 5 years - Epidemiology studies: A US pregnancy registry (IM101-121) assessing safety in both the mother and offspring up to one year following delivery, conducted by the Organization of Teratology Information Specialists (OTIS) for 5 years with annual reports (exposure to abatacept vs. other anti-rheumatic therapy during pregnancy). A second similar pregnancy registry to be initiated in the EU utilizing the ENTIS network. Outcomes of pregnancies occurring in the other epidemiology studies to be included in the annual reports.	- Section on pregnancy in section 4.6 of the SmPC
Missing Information		
Paediatric population	- Routine pharmacovigilance activities - Study IM101033 - Relevant epidemiology Studies	- Section 4.2 of the SmPC indicates that there is no experience in children or adolescents and that abatacept is not recommended for children until further data is available.
Vaccination	-Routine pharmacovigilance activities - Sub-study IM101064	- Specific subsection on vaccination and ORENCIA treatment in section 4.4 of the SmPC
Hepatic and renal impairment	-Routine pharmacovigilance activities	- Section 4.2 of the SmPC indicates that abatacept has not been studied in this patient population and that no dose recommendations can be made
Combination therapy	-Routine pharmacovigilance activities - Relevant epidemiology Studies	- Subsection on combination therapy in section 4.4 and 4.5 of the SmPC
Elderly population	-Routine pharmacovigilance activities - Open extensions of pivotal clinical trials up to 5 years - Epidemiology studies	- Statements on the use of ORENCIA in the elderly in sections 4.4 and 4.8 of the SmPC.

Two identified risks have been considered for the Patient Alert Card: infections and infusion-related reactions. Of these, the risks related to infections appear the most relevant for on-treatment follow-up of subjects to minimize risks through direct information to the patients.

The CHMP, having considered the data submitted in the application is of the opinion that the following risk minimisation activities are necessary for the safe and effective use of the medicinal product:

6   Overall conclusions, risk/benefit assessment and recommendation

Quality
The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety. Minor unresolved quality issues having no impact on the Risk-benefit balance of the product will be addressed as part of post-authorisation commitments undertaken by the applicant within an agreed timeframe.

Non-clinical pharmacology and toxicology

An increased incidence of lymphomas and breast cancers were observed in mice. These tumours are attributed to suppression of the immune defence against tumorigenic viruses. Viruses associated with human cancers include human papilloma virus (HPV), hepatitis B and C, human herpes virus-8 (HHV-8), and Epstein Barr virus (EBV). Lymphomas have been detected in monkeys exposed to heavy immunosuppressive regimens with other medicinal products. Interestingly, with one of these medicinal products, B cell proliferation was observed in spleen and lymph nodes of some monkeys. This B cell proliferation may have been due to lymphocryptovirus that is related to human Epstein Barr Virus.

So far, tumours were an isolated finding in mice. This may not necessary be the case although mice may have exceptionally high risk of malignancy.

Efficacy

The new medicinal product has a modest anti-inflammatory effect in advanced RA. As a result, there is relatively rapid symptom relief and improvement of function. In addition, abatacept has a definite effect on the radiological progression of joint damage although the clinical significance of this finding cannot be fully established yet. Abatacept has not been compared to other biological antirheumatic products in adequate clinical trials. On the basis of the available data, the benefit/risk of abatacept has not yet been established to the same degree as anti-TNF-α-blockers. However, abatacept may have an important role in RA therapy as it seems to be effective in TNF-α-blocker-resistant RA.

Safety

The acute tolerability of abatacept is good as compared to traditional antirheumatic products and comparable to that of the current biological antirheumatics. However, the main concern is in the potential rare and unexpected severe adverse effects of abatacept. Abatacept belongs to a new class of immunosuppressive, non-cytotoxic medicinal products. It aims to blocks partially the T-cell activation that follows antigen-binding to the T-cell antigen receptor via MHC-1 molecules. Thus, it will inhibit both the primary and to a lesser extent secondary T cell-mediated immune responses but not already established immunological memory or effector functions. T-cell-dependent B-cell functions are also suppressed. Abatacept is unlikely to affect T cell-independent and the non-antigen-specific innate immunity. This relative selectivity is an advantage in suppressing excessive or autoreactive immune responses. Nevertheless, blocking the main pathway of antigen-specific immunity is likely to have undesired consequences. The immune system is a complex network aiming to maintain the delicate balance between stimulatory and inhibitory stimuli. Therefore, it is very difficult to predict the long-term effects of abatacept treatment. Abatacept is not cytotoxic in its classical sense but T lymphocytes that bind antigens but that are not entering to growth and proliferation cycles, may undergo apoptosis.

At the present, there are signals for an increased risk of infections and possibly of certain autoimmune disorders. The association of immunosuppression to an increased risk of cancer in well known. The incidence and type of malignancies are dependent on the degree and possible the type of immunosuppression. The increased risk of malignancies is due to an increase of certain types of cancer such as lymphomas, cervical, skin, and head and neck cancers. These carcinomas have also been associated with viruses.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

Having considered the safety concerns in the risk-management plan, the CHMP considered that the proposed activities adequately address these.

- User consultation

User testing has been performed on the Patient Information Leaflet and from the results it can be concluded that the relevant information is accessible and understandable for the patients.

Risk-benefit assessment

For time being, there is no clear signal in the clinical database. However, the safety database is insufficient for the exclusion of a moderate increase of certain rare malignancies such as lymphomas. Considering the rarity of the conditions of interest, special post marketing risk management measures are needed. Thus, the modest efficacy of abatacept must be weighed against its potential risks.

Treatment should be initiated and supervised by specialist physicians experienced in the diagnosis and treatment of rheumatoid arthritis.

A risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that:

- pharmacovigilance activities in addition to the use of routine pharmacovigilance were needed to investigate further some of the safety concerns

Plus
- the following additional risk minimisation activities were required:

  ➢ Patient Alert Card

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the risk-benefit balance of ORENCIA in combination with methotrexate is indicated for the treatment of moderate to severe active rheumatoid arthritis in adult patients who have had an insufficient response or intolerance to other disease-modifying anti-rheumatic drugs including at least one tumour necrosis factor (TNF) inhibitor was favourable and therefore recommended the granting of the marketing authorisation.