Bristol-Myers Squibb Company

BRIEFING DOCUMENT FOR ABATACEPT (BMS-188667)

BIOLOGICAL LICENSE APPLICATION 125118

FOOD AND DRUG ADMINISTRATION

ARTHRITIS ADVISORY COMMITTEE

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EXECUTIVE SUMMARY

The purpose of this document is to provide background information on the development program for abatacept (BMS-188667) in the treatment of rheumatoid arthritis (RA) and to review the efficacy and safety data supporting the approval of the product.

Abatacept is a fully human recombinant fusion protein. It selectively modulates T-cell activation, and secondarily affects key mechanisms of inflammation and progressive joint destruction in RA. Abatacept has been developed for treatment of patients with moderately to severely active RA who have had an inadequate response to one or more DMARDS, such as methotrexate or TNF-blocking agents.

The clinical development program evaluated the effects of abatacept on signs and symptoms of RA, physical function, progression of structural damage, and health-related quality of life. In the safety evaluation, special attention was paid to the assessment of potential concerns for a therapeutic protein with immunodulatory activity, including infectious complications, malignancies, autoimmunity, infusion reactions, and immunogenicity.

Key efficacy results are shown in Table A.

Table A: Proportion of Patients with ACR 20 Response and Clinically Meaningful Change from Baseline in HAQ/mHAQ (Reduction of ≥ 0.3) at 6 Months during the Double-Blind Period

	IM101102		IM101100		IM101029	
	Abatacept (N = 424)	**Placebo (N = 214)**	**Abatacept (N = 115)**	**Placebo (N = 119)**	**Abatacept (N = 256)**	**Placebo (N = 133)**
ACR 20	67.9%[a]	39.7%	60.9%[a,b]	35.3%	50.4%[a]	19.5%
HAQ/mHAQ	61.1%[c]	45.3%	47.0%[d]	27.7%	47.3%[c]	23.3%

[a] Differences between abatacept and placebo were statistically significant ($p < 0.05$).

[b] 10 mg/kg abata-cept treatment group.

[c] Differences between abatacept and placebo were statistically significant ($p < 0.001$).

[d] Differences between abatacept and placebo were statistically significant ($p < 0.004$).

Population: All randomized and treated patients. Patients in IM101102 and 101100 were methotrexate inadequate responders. Patients in IM101029 were TNF-blocking agent inadequate responders.

Abatacept demonstrated consistent efficacy in reducing signs and symptoms of RA, inducing a major clinical response, inhibiting the progression of structural damage, and improving physical function and health-related quality of life. The efficacy findings were statistically robust and clinically meaningful. Efficacy was similar in patients who had had an inadequate response to non-biologic DMARDS, and in patients who had had an inadequate response to biologic RA therapies (the TNF-blocking agents).

Abatacept was generally safe and well-tolerated. This safety profile was sustained with long-term treatment. Relative to placebo, infections with abatacept were more common for serious infections the relative frequency was 3.0% (abatacept) vs 1.9% (placebo) but similar in type, severity, duration, treatment rendered, and outcome. Disseminated viral or bacterial infections, invasive fungal infections, and mycobacterial infections were rare and comparable in frequency to placebo.

Malignancy occurred with similar frequency in abatacept- and placebo-treated patients (1.3 vs 1.1%). The incidence of solid tumors was similar to that expected, based on reference rates in the US general population. The incidence of lymphoma was similar to that expected for a population with rheumatoid arthritis. Medically important autoimmune disorders and infusion reactions were infrequent, as was the development of anti-abatacept antibodies.

While the safety profile is favorable, there are inherent limitations to any clinical data set with respect to the assessment of infrequent events such as malignancy. Bristol-Myers Squibb (BMS) therefore proposes to conduct 2 large pharmacoepidemiology studies following product approval. These studies are intended to provide more definitive estimates of the incidence rates of serious infections and malignancies in patients treated with abatacept compared with those treated with non-biologic DMARDs or biologic RA therapies.

Abatacept, therefore, offers a clearly favorable benefit-risk profile, and a new therapeutic option for patients with moderately to severely active RA and an inadequate response to non-biologic DMARDS or TNF-blocking agents.

1 PURPOSE OF DOCUMENT

The purpose of this document is to provide background information on the development program for abatacept (BMS-188667) in the treatment of rheumatoid arthritis RA and to review the efficacy and safety data supporting the approval of the product.

2 REGULATORY HISTORY

BMS has had ongoing interactions with the FDA during the development of abatacept. Two (2) key milestones were the completion of a Special Protocol Assessment for study IM101029 (Abatacept in Patients with RA and an Inadequate Response to TNF-blocking agents) and the granting of Fast Track Status. The Special Protocol Assessment process for clinical protocols allows FDA and a sponsor to agree, within a specified timeframe, that a study is designed appropriately to provide the data the Agency needs to evaluate the safety and efficacy of a product in the patient population studied. Granting of Fast Track Status reflects recognition by the FDA that a product has the potential to address an unmet medical need in the treatment of an important aspect of a serious medical condition.

Bristol-Myers Squibb has filed a complete Biologics License Application under FDA's Continuous Marketing Application, Pilot 1, for the use of abatacept in the treatment of RA. The application was completed in March of 2005.

3 BACKGROUND/DEVELOPMENT RATIONALE

3.1 Current Treatment and Unmet Medical Need

Rheumatoid arthritis (RA) is a chronic, inflammatory, destructive, autoimmune disease of the synovial joints that affects approximately 1% of the world's population and commonly leads to severe, chronic functional disability and consequent reduction in quality of life.[1,2]

Therapy for RA has evolved significantly as our understanding of the disease has progressed. The finding that much joint damage occurs early in the disease course has led to treatment paradigms that emphasize early treatment with cellular proliferation

inhibitors, such as methotrexate. Moreover, advances in the molecular understanding of immunology and inflammation have led to the development of protein therapeutics (TNF-blocking agents and IL-1 receptor antagonists), which provide new avenues for the treatment of RA.

Despite these advances in RA disease management, however, many patients do not achieve an adequate response to therapy. Using ACR 50 as a marker of adequate response, less than 50% of patients treated with methotrexate respond.[3] Of patients who do not achieve an adequate response to methotrexate, less than 50% achieve an adequate response to TNF-blocking agents.[4] Thus, a substantial number of RA patients lack adequate clinical improvement with current therapies.

This finding emphasizes the difficulty in RA management and the need for new therapeutic approaches with new mechanisms of action. The need is particularly acute in patients who fail to achieve an adequate response to TNF-blocking agents; these patients have no other approved treatment options. Development of new treatment options with new mechanisms of action will continue the advances in the management of patients with rheumatoid arthritis.

3.2 Role of T Cells

Antigen-specific T cells are thought to underlie the pathogenic immune response in RA. In RA, the synovial tissue becomes markedly hypertrophic. As the disease progresses, there is gradual proliferation and recruitment of synoviocytes, as well as recruitment of inflammatory cells into the synovium. Up to 50% of the infiltrating leukocytes in the synovium are T lymphocytes, primarily CD4+ T cells with an activated/memory phenotype.[5,6,7]

T-cells can proliferate, produce pro-inflammatory cytokines, and activate other cells of the immune system, as well as connective-tissue cells in the joint, which produce metalloproteinases, inflammatory mediators with subsequent bone and cartilage degradation.[8] Hence, the inhibition of T-cell activation would be predicted to diminish macrophage activation and pro-inflammatory cytokine production, autoantibody production, and the expression of metalloproteinases.

3.3 Pharmacologic Class of New Drug and Mechanism of Action

Abatacept (BMS-188667) is a recombinant fusion protein consisting of the extracellular domain of human CTLA4 and a fragment (hinge–CH2–CH3 domains) of the Fc domain of human IgG1.

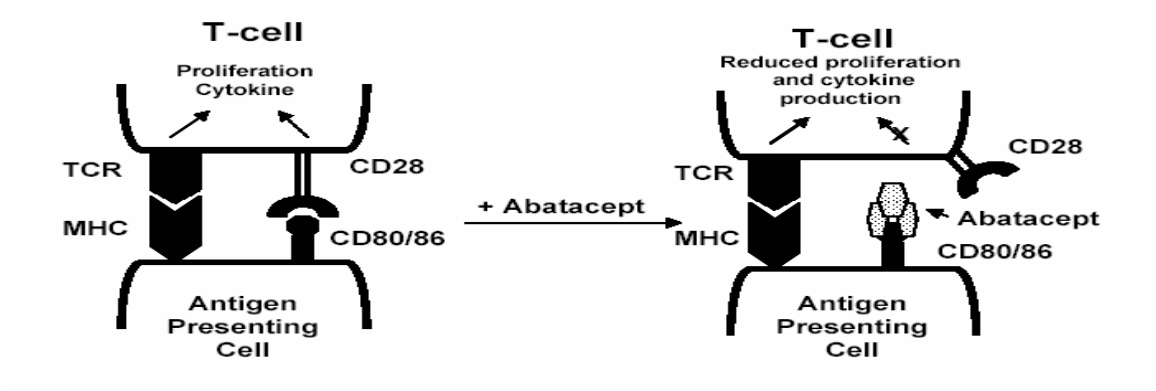
Abatacept is the first drug in a new class of agents, selective costimulation modulators, designed to block a key costimulatory signal required for T-cell activation.

Antigen-induced activation of T cells requires delivery of at least 2 signals to the T cell by antigen-presenting cells (APCs). The APC presents peptide antigen via major histocompatability (MHC) proteins. The antigen-MHC complex is recognized by the T-cell receptor (TCR) and is known as Signal 1. However, T cells also require a second signal known as costimulation to become fully activated and proliferate. A key costimulatory receptor on T cells is CD28. CD28 is constitutively expressed on resting T cells and binds to both CD80 (B7-1) and CD86 (B7-2) molecules on the APC surface (hereafter referred to as CD80/86.)

CTLA-4 is a trans-membrane protein expressed on the surface of T cells, and is an important down-regulator of T-cell activation. It binds CD80/86 with higher avidity than does CD28.

Abatacept reversibly binds to CD80/86 via its CTLA-4 portion. It thereby prevents CD80/86 from interacting with CD28 and providing a second signal for full T-cell activation (Figure 3.3). In vitro, abatacept partially inhibits human T-cell activation and production of cytokines without T-cell depletion. Abatacept has shown immunomodulatory activity in animal models of collagen-induced arthritis and in a variety of animal models of autoimmune disease and transplantation.

Figure 3.3: Effect of Abatacept on T-Cell Costimulation



3.4 Development Rationale

Abatacept selectively modulates T-cell activation. Because of the central role of the T cell in rheumatoid arthritis, modulation of T-cell activation would be expected to favorably affect multiple key mechanisms of inflammation and progressive joint destruction, including secretion of pro-inflammatory cytokines, proliferation of inflammatory cells, and production of autoantibodies. Abatacept, therefore, has the potential to provide significant benefit to patients with rheumatoid arthritis, including those patients with an inadequate response to non-biologic DMARDs or biologic RA therapies.

3.5 Proposed Indication

The proposed indication is:

> Abatacept is indicated for reducing signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function in adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more DMARDs, such as methotrexate or TNF-blocking agents. Abatacept may be used in combination with methotrexate or other non-biologic DMARD therapy.

3.6 Non-Clinical Pharmacology

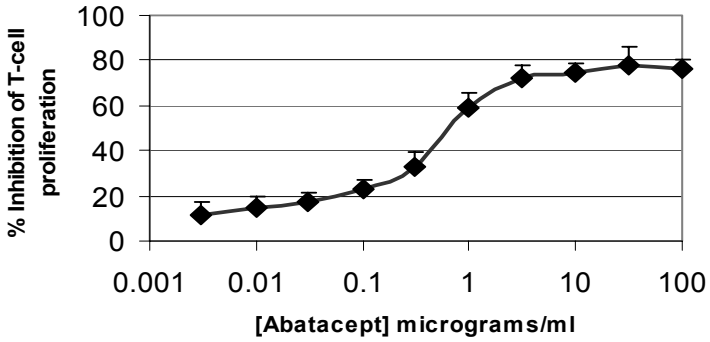
3.6.1 Human In-Vitro Studies

Abatacept partially inhibits antigen-induced human T-cell proliferation and cytokine production.

3.6.1.1 Mixed-lymphocyte Reaction and Cytokine Production

In human mixed-lymphocyte response (MLR) assays, abatacept inhibited T-cell proliferation by 50% to 80% at concentrations of 0.3 to 30 µg/mL (Figure 3.6.1.1A).

Figure 3.6.1.1A: Effect of Abatacept on T-cell Proliferation in an In Vitro Human Mixed Lymphocyte Response Assay



(mean ±S.D.)

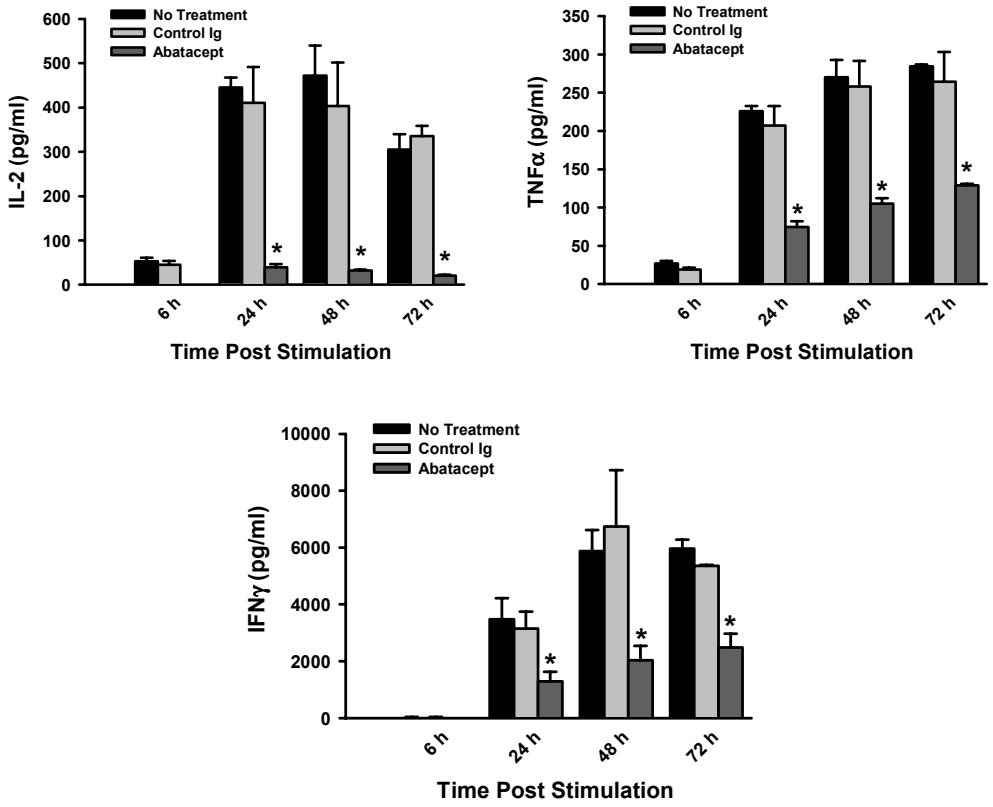
The maximum inhibitory effect of abatacept occurred at concentrations of the drug less than or equal to trough concentrations of abatacept in RA patients treated with drug (~20-30 µg/mL).[9]

In addition to inhibiting primary naive T-cell responses, abatacept partially inhibited human memory responses to tetanus toxin by 50 to 70% as measured by T-cell proliferation.

Abatacept also inhibited the antigen-specific production of the T-cell cytokines IL-2, IFN-γ and TNF-α in human allogeneic mixed-lymphocyte cultures (Figure 3.6.1.1B) and

induced T-cell hyporesponsiveness to antigenic re-stimulation.[10] TNF-α and IFN-γ are important mediators of the pathogenic immune response in RA. This inhibition was observed at a concentration of abatacept (30 μg/ml) within the range of trough concentrations achieved with the proposed dose.

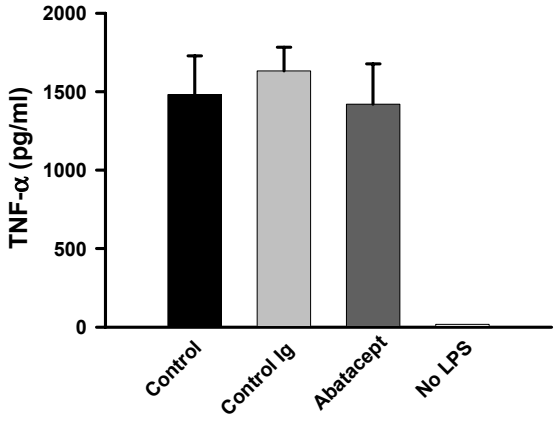
Figure 3.6.1.1B: Effect of Abatacept (30 μg/mL) on IL-2, TNF-α and IFN-γ Production in an In Vitro Human Mixed-Lymphocyte Response Assay



(mean ±S.D., *p<.001)

In addition to measuring the effect of abatacept on T cells and T cell-dependent immune responses, the effect of abatacept on T cell-independent immune responses was assessed in a model of innate immunity (macrophage-derived TNF-α production). Abatacept treatment did not impair the production of TNF-α from macrophages in vitro after a 6-hour exposure to the bacterial endotoxin lipopolysaccharide (LPS) (Figure 3.6.1.1C). Together with the finding that abatacept inhibits antigen-presenting cell-driven TNF-α production, these data demonstrate a selective effect of abatacept on cytokine production induced by a T-cell dependent, adaptive immune response (antigen-presenting cell/T-cell interaction) versus an innate immune response (LPS-activation of macrophages).

Figure 3.6.1.1C: Effect of Abatacept (30 μg/mL) on LPS-Induced TNF-α Production in Human Monocytes



3.6.1.2 Non-Clinical In Vivo Studies

Abatacept was studied in the collagen-induced arthritis (CIA) model of RA and in models of T cell-dependent antibody production. Studies with CTLA4-Ig were also performed in models of several other autoimmune diseases, including systemic lupus erythematosus. These studies demonstrated that abatacept inhibited autoimmune disease progression and T cell-dependent antibody responses.[11,12,,13,14,15,16,17,18]

3.6.1.3 Summary

Collectively, these data suggest that abatacept, by modulating T-cell activation, will target multiple inflammatory pathways in patients with RA. Proposed pharmacodynamic effects include inhibition of the production of key pro-inflammatory cytokines and T-cell dependent autoantibodies, such as rheumatoid factor, without T-cell depletion. This mechanism of action is supported by the biomarker data from the clinical program. Human in-vitro data suggest that direct microbial stimulation of protective innate immune responses will not be significantly affected by abatacept.

3.7 Non-Clinical Toxicology

Non-clinical safety studies were conducted in mice, rats, rabbits, and cynomolgus monkeys. Abatacept may be administered chronically without induction of anti-abatacept antibodies based on its mechanism of action (inhibition of T cell-dependent antibodies). This property allowed long-term, non-clinical rodent studies to be conducted in which substantial exposure was achieved. Studies of this type are infrequently performed with a human therapeutic protein because these agents usually induce an antibody response in rodents that prevents sufficient exposure from being achieved over the duration of the study.

3.7.1 General Toxicology

In non-human primate studies, intravenous (IV) administration of abatacept as a single dose of up to 100 mg/kg or as repeat doses of up to 50 mg/kg every other day for 30 days or every week for 1 year was not associated with any significant drug-related toxicity. Reversible pharmacologic effects in the repeat-dose studies consisted of minimal decreases in serum immunoglobulin (Ig) G and mild to moderate decreases in the number and diameter of lymphoid germinal centers in the spleen and/or lymph nodes (1-year study), reflective of decreased germinal center activity. No hyperplastic, preneoplastic or neoplastic changes were observed in the peripheral blood cells or lymphoid tissues of any monkey. In the 1-year study, functional activity of the immune system was demonstrated at all doses by a robust antibody response to the T cell-dependent antigen keyhole limpet hemocyanin (KLH) following immunization after an 8-week, dose-free period. Abatacept treatment for 1 year did not result in any clinical manifestations associated with a viral infection, even though viral screening indicated previous exposure in all monkeys to one or more of the following viruses: lymphocryptovirus, Herpes B, rhesus cytomegalovirus, or simian papovavirus. The no-observable-adverse-effect level (NOAEL) in the 1-year study was 50 mg/kg/weekly, which resulted in a systemic exposure, based on area under the concentration (AUCs) versus time curves, that was 9-fold greater than human exposure at the clinical dose.

In mice, subcutaneous (SC) administration of abatacept once weekly for 26 weeks at doses up to 200 mg/kg was well tolerated. At doses of 65 and 200 mg/kg, reversible, pharmacologic effects consisted of transient decreases in mean serum IgG levels and, in

male mice, inhibition of ex vivo B- and T-cell activation, and decreases in the percentages of splenic B cells. Increases in the frequency and severity of karyomegaly in renal tubular epithelial cells, which were accompanied by mild, multifocal, chronic inflammation, lymphocytic infiltration, and tubular cell degeneration, were observed microscopically at 65 and 200 mg/kg. However, no effects on renal function were evident based on clinical pathologic parameters. These renal changes were interpreted as an exacerbation of spontaneous, age-related changes that have no known relevance to humans. The no-observable-effect level (NOEL) and the NOAEL in this study were 20 and 200 mg/kg/weekly, respectively, providing estimated human exposure multiples of 0.9 and 4.7, respectively.

3.7.2 Genotoxicity

No mutagenicity or clastogenicity was observed with abatacept in a battery of in vitro studies.

3.7.3 Carcinogenicity

In a mouse carcinogenicity study, abatacept was given SC once each week at doses of 20, 65, or 200 mg/kg for up to 88 weeks. These doses provided human exposure multiples of 0.8, 1.9, or 3.0 based on AUC. Sustained immunosuppressive activity occurred at all dose levels as demonstrated by suppression of a drug-specific antibody response.

Increased frequency of lymphoma (all doses) and mammary gland tumors (intermediate- and high-dose females) were observed. Across all 3 doses, the frequency of lymphoma ranged from 28% to 58% in a non-dose related fashion. The incidence of mammary gland adenocarcinoma in the 65 and 200 mg/kg/week female dose groups ranged from 10% to 14%, respectively.

In mice, retroviruses (MLV and MMTV) have been reported to cause lymphoma and mammary tumors, respectively.[19,20,21,22] Endogenous ecotropic-specific MLV DNA was detected in the genome of CD-1 mice used in this study, and Charles River Laboratories personnel have stated that CD-1 mice are not retrovirus free (verbal communication). Ecotropic-specific DNA comes from a retrovirus. Results from transmission electron microscopic evaluation of mammary tumors from this study identified large numbers of

virions in the cytoplasm, budding from the plasma membrane, and in the extracellular space. Ultrastructural characteristics of the viral particles were consistent with those of murine mammary tumor viruses and immunohistochemistry with an anti-MMTV antibody confirmed the presence of this oncovirus in mammary tumors from both control- and abatacept-treated mice. These findings strongly support the conclusion that the increased malignancies in this study are secondary to long-term, abatacept-induced immunosuppression and the control of these specific oncoviruses.

Additional non-clinical information on malignancy was provided by the 1-year, IV toxicity and toxicokinetic study in cynomolgus monkeys. Pre-study screening indicated prior exposure in 38 of 40 monkeys in this study to lymphocryptovirus. This virus is known to induce chronic, asymptomatic infection in cynomolgus macaques. Sustained immunosuppression in the presence of lymphocryptovirus can result in viral reactivation, lymphoproliferative disease and development of B-cell lymphoma. Despite exposure to abatacept at up to 9-fold the human exposure, there were no neoplasms or preneoplastic changes noted in this study.

Additional information about non-clinical carcinogenicity is available in Supplemental Report 3.7.3.

3.7.4 Reproductive Toxicology

Abatacept was evaluated in a complete battery of reproductive and development toxicity studies. As part of this, abatacept was shown to cross the placenta and was present in the mother's milk. In rats, abatacept had no adverse effects on male or female fertility at doses up to 200 mg/kg, 11-fold the human exposure. Embryo-fetal development studies conducted with abatacept in mice, rats and rabbits at doses up to 20 to 30 times the human dose at 10 mg/kg have revealed no evidence of harm to the offspring. In rats and rabbits, drug exposure was up to 30- and 29-times higher, respectively, than the exposures in humans given 10 mg/kg abatacept once monthly.

In a pre- and postnatal development study with abatacept in rats, no effects were observed in pups of dams given abatacept at doses up to 45 mg/kg, representing 3-fold the human exposure, whereas limited changes in immune function were observed in the female pups of dams administered abatacept at a dose of 200 mg/kg, representing 11-fold

the human exposure. These findings were limited to a 9-fold increase in the mean T cell-dependent antibody response in female pups and inflammation of the thyroid in 1 female pup out of 10 female pups evaluated at this dose. These findings are considered to represent the lower threshold limit for effects of abatacept on immune parameters in the F1-generation rats, as these changes were either limited to only 1 sex or 1 animal, and no other immune parameters were affected (splenic-lymphocyte and natural-killer cell phenotypes, serum Ig levels, presence of anti-nuclear antibodies, or clinical or histopathologic examinations).

3.7.5 Safety Pharmacology

No drug-related findings were observed in a battery of in vivo safety pharmacology evaluations that included respiratory and neurologic function, electrocardiograms, heart rate and sounds, and blood pressure conducted as part of repeat-dose toxicity studies in monkeys for up to 1 year. In addition, no drug-related changes were observed following dosing with respect to anaphylactoid clinical signs or increases in serum or plasma histamine, complement C3a, TNF-α, or IL-6, mediators associated with hemodynamic changes and/or anaphylactoid responses.

3.7.6 Local Tolerance

Abatacept was not significantly irritating when administered by IV, paravenous, intra-arterial or SC injection.

3.7.7 Immunogenicity

Abatacept, a fully human protein, was immunogenic in mice, rats, dogs, and monkeys. However, as expected, abatacept-specific antibodies were generally detected only after abatacept serum levels dropped below levels of immunosuppressive activity. Thus, in each species tested, abatacept suppressed the antibody response against itself. Once abatacept-specific antibodies were present, clearance of drug from the blood vascular compartment was often accelerated. The appearance of abatacept-specific antibodies was not associated with any acute or target-organ toxicity in any species when drug exposure was continuous. However, in mice and dogs, the presence of circulating abatacept-specific antibodies was associated with clinical signs of toxicity (hypersensitivity

reactions) following an IV challenge dose of abatacept. Clinical data indicating a low risk of immunogenicity and hypersensitivity reactions are discussed in Section 6.2.6.5 (Immunogenicity).

3.7.8 Conclusions

In conclusion, the results of an extensive drug safety evaluation with abatacept support its safety in humans at the proposed dose. The murine carcinogenicity study suggests a potential risk for prolonged immunomodulation to result in the development of virally mediated malignancies. These findings are not unexpected and were not viewed to preclude development in humans. The human experience with malignancy is described in Section 6.2.6.2 (Malignancy).

4 CLINICAL DEVELOPMENT PROGRAM

4.1 Overview of Clinical Development Program

Abatacept has been studied in healthy subjects and patients with RA, psoriasis and multiple sclerosis. The clinical development program in RA is the focus of this document and is described in detail in Section 4.1.1. Studies in other populations are summarized briefly in Section 4.1.2.

4.1.1 RA Clinical Studies

The abatacept clinical development program in RA included a total of 3 Phase II and 3 Phase III studies in patients ≥ 18 years of age with moderately to severely active rheumatoid arthritis. These trials were all randomized, double-blind and placebo-controlled. Each trial was followed by an open-label, uncontrolled period, except for IM103002.

Three (3) of these studies are considered to provide the principal proof of efficacy because they evaluated the effect of abatacept:

- at or approximating 10 mg/kg, the proposed dose;
- on key efficacy measures such as ACR 20, 50, and 70 responses, inhibition of the progression of structural damage, physical function and quality of life;

- using appropriate design and structural methods to provide confirmatory data; and
- were at least 6 months in duration.

These 3 studies were:

- IM101102, a 12-month Phase III trial in patients with an inadequate response to methotrexate;
- IM101100, a 12-month Phase IIb trial in patients with an inadequate response to methotrexate; and
- IM101029, a 6-month Phase III trial in patients with an inadequate response to TNF-blocking agents.

Efficacy results from the double-blind, controlled portion of these 3 trials are described in Section 5 (Clinical Efficacy) of this document. Long-term efficacy data are presented from the open-label period of the Phase IIb trial, IM101100. Efficacy data from the open-label periods of the Phase III trials are not included in this document because the cumulative experience in the open-label portions of these trials at the time of filing was limited.

Three (3) other RA trials were performed:

- IM101031, a large, 12-month Phase III safety study in patients with or without comorbidities and concurrently treated with various non-biologic DMARDs and/or biologic RA therapies;
- IM103002, a 3-month Phase IIa dose-finding trial of abatacept monotherapy;
- IM101101, a 12-month exploratory Phase II study in combination with etanercept, in patients with an inadequate response to etanercept.

These trials are not grouped with the 3 studies that provide the principal proof of efficacy because they were intended primarily to evaluate safety (IM101031), were less than 6 months in duration (IM103002), or utilized a dose of abatacept that was less than the intended dose of approximately 10 mg/kg (IM101101). Nevertheless, these studies provide additional information on efficacy and are briefly summarized in Section 5 as well.

Data from 5 of these 6 trials (the 'core' RA studies) with a double-blind treatment period of at least 6 months have been integrated for safety analyses. The integrated safety database includes safety data from both the double-blind, controlled period of these trials and the open-label, uncontrolled period that followed the double-blind portion of each trial. Data from IM103002, which represents less than 3% of RA experience, have not been included in these analyses because of its short treatment duration (3 months), and are presented separately.

The integrated safety database includes:

- 1955 patients exposed to abatacept during the double-blind, placebo-controlled portions of the studies, and
- 2688 patients exposed to abatacept overall.

The number of patients treated with abatacept overall (2688) is larger than the number treated in the double-blind period (1955) because patients treated with placebo during the double-blind period were treated with abatacept in the open-label period.

Figure 4.1.1 presents an overview of the abatacept clinical development program. Table 4.1.1 lists the double-blind RA studies, ongoing open-label periods of the RA studies, and other ongoing studies in RA.

Figure 4.1.1: Overview of the Abatacept Clinical Development Program

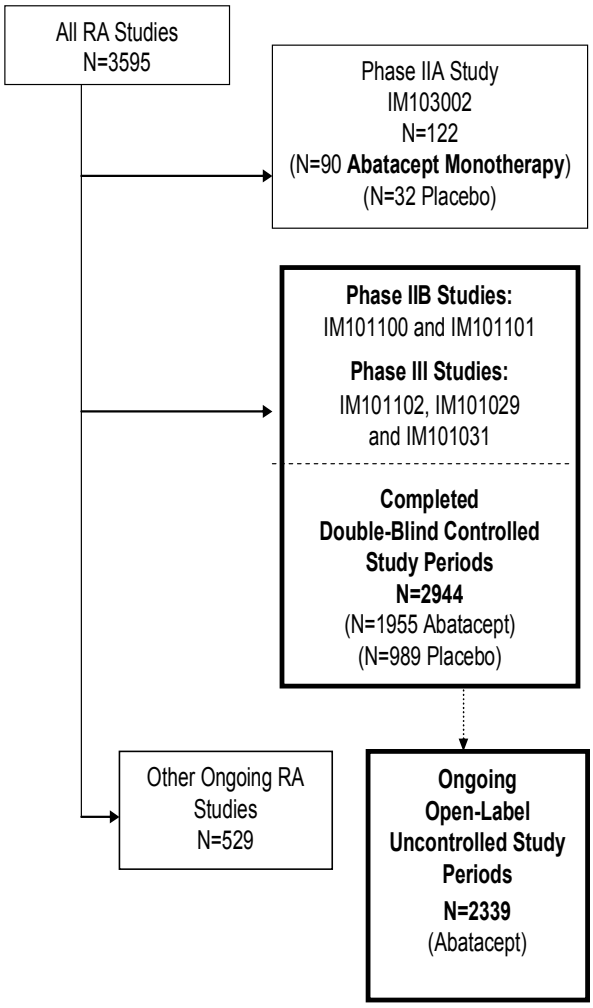


Table 4.1.1: Abatacept Clinical Program in RA Patients

Study No. Status	Design	Treatment	Number of Treated Patients
Rheumatoid Arthritis			
Completed, Double-Blind, Controlled			
Phase II Dose-Ranging Study			
IM103002 Completed	Phase IIA, randomized, double-blind, placebo-controlled, 3 month study in patients who had failed at least one DMARD or etanercept	Abatacept 0.5, 2 or 10 mg/kg IV or Placebo IV on Days 1, 15, 29, 57	**Abatacept** 0.5 mg/kg=26, 2 mg/kg=32, 10 mg/kg=32 Placebo=32
Phase II Studies, Other			
IM101100 Double-Blind Period Completed	Phase IIB, randomized, double-blind placebo-controlled, 12-month study period in patients with an inadequate response to MTX	Abatacept 2 or 10 mg/kg IV plus MTX (10-30 mg/wk PO) or Placebo IV plus MTX (10-30 mg/wk PO) Abatacept and Placebo: IV infusions on Days 1, 15, 30 and monthly thereafter	**Abatacept** 2 mg/kg=105, 10 mg/kg=115 Placebo=119
IM101101 Double-Blind Period Completed	Phase IIB, randomized, double-blind placebo-controlled, 12-month study period in patients with an inadequate response to etanercept	Abatacept 2 mg/kg IV plus etanercept 25 mg SC BIW or Placebo IV plus etanercept 25 mg SC BIW[a] Abatacept and Placebo: IV infusions on Days 1, 15, 30 and monthly thereafter	**Abatacept** 2 mg/kg=85 Placebo=36

Table 4.1.1: Abatacept Clinical Program in RA Patients

Study No. Status	Design	Treatment	Number of Treated Patients
Phase III Studies			
IM101102 Double-Blind Period Completed	Phase III, randomized, double-blind, placebo-controlled, 12-month study period in patients with an inadequate response to MTX	Abatacept fixed dose that approximated 10 mg/kg IV plus MTX at least 15mg/wk PO or Placebo IV plus MTX at least 15 mg/wk PO Abatacept and Placebo: IV infusions on Days 1, 15, 29 and then every 28 days up to and including Day 337	**Abatacept** N=433 Placebo, N=219
IM101031 Double-Blind Period Completed	Phase III, randomized, double-blind, placebo-controlled, 12-month study period in patients receiving DMARDs and/or biologic RA therapy	Abatacept fixed dose that approximated 10 mg/kg IV plus background therapy or Placebo IV plus background therapy Abatacept and Placebo: IV infusions on Days 1, 15, 29 and then every 28 days up to and including Day 337	**Abatacept** N=959 Placebo, N=482
IM101029 Double-Blind Period Completed	Phase III, randomized, double-blind, placebo-controlled, 6-month study period in patients who have failed TNF-blocking agents	Abatacept fixed dose that approximated 10 mg/kg IV plus DMARDs or Placebo IV plus DMARDs Abatacept and Placebo: IV infusions on Days 1, 15, 29 and then every 28 days for a total of 7 doses	**Abatacept** N=258 Placebo, N=133

Table 4.1.1: Abatacept Clinical Program in RA Patients

Study No. Status	Design	Treatment	Number of Treated Patients
Ongoing, Open-Label, Uncontrolled Periods			
Phase II Studies			
IM101100 Open-label Period Ongoing	Phase IIB, open-label, uncontrolled study period	Abatacept fixed dose that approximated 10 mg/kg IV given monthly plus MTX 10-30 mg/wk PO	**Abatacept** N=219
IM101101 Open-Label Period Ongoing	Phase IIB, open-label, uncontrolled study period	Abatacept fixed dose that approximated 10 mg/kg IV given monthly with or without etanercept 25 mg SC BIW Amended to require discontinuation of concurrent etanercept	**Abatacept** N=80
Phase III Studies			
IM101102 Open-Label Period Ongoing	Phase III, open-label, uncontrolled study period	Abatacept fixed dose that approximated 10 mg/kg IV monthly plus DMARDs	**Abatacept** N=539
IM101031 Open-Label Period Ongoing	Phase III, open-label, uncontrolled study period	Abatacept fixed dose that approximated 10 mg/kg IV monthly plus DMARDs or biologic therapy Amended to require discontinuation of concurrent etanercept, infliximab, adalimumab or anakinra.	**Abatacept** N=1184
IM101029 Open-Label Period Ongoing	Phase III, open-label, uncontrolled study period	Abatacept fixed dose that approximated 10 mg/kg IV monthly plus DMARDs	**Abatacept** N=317

Table 4.1.1: Abatacept Clinical Program in RA Patients

Study No. Status	Design	Treatment	Number of Treated Patients
New, Ongoing Studies			
Phase I			
IM101015 Ongoing	Phase I, open-label, uncontrolled study in patients with have failed TNF-blocking agents to evaluate changes in synovial immune responses	Abatacept fixed dose that approximated 10 mg/kg IV on Days 1, 15, 29, 57, 85, 113 plus DMARDs	**Abatacept** N=16
IM101034 Ongoing	Phase I, open-label, dose-escalation study in Japanese patients	Abatacept: 2, 8 and 16 mg/kg IV administered as single doses or multiple doses on Days 1, 15, 29 and 57 plus DMARDs	**Abatacept** N=22

Table 4.1.1: Abatacept Clinical Program in RA Patients

Study No. Status	Design	Treatment	Number of Treated Patients
Phase III			
IM101033 Ongoing	Phase III, randomized withdrawal study in children and adolescents with active polyarticular juvenile RA 3 Periods: 1) Open-label; 2) Randomized, placebo-controlled, double blind; 3) Open-label, uncontrolled study periods.	Period A: Abatacept 10 mg/kg IV on Days 1, 15, 29, 57, 85 and 113 Period B: Abatacept 10 mg/kg IV or Placebo monthly for 6 months Period C: Abatacept 10 mg/kg IV monthly	**Abatacept** N=112
IM101043 Ongoing	Phase III, randomized, double-blind, placebo-controlled, study comparing abatacept with placebo and infliximab with placebo in patients with an inadequate response to MTX	Abatacept fixed dose that approximated 10 mg/kg IV plus MTX at least 15mg/wk PO or Infliximab IV 3 mg/kg plus MTX at least 15 mg/wk PO or Placebo IV plus MTX at least 15 mg/wk PO Abatacept and Placebo: IV infusions on Days 1, 15, 29 and then every 28 days up to and including Day 337 Infliximab Days 1, 15, 29, 43, 57 and 85 and then every 56 days up to and including Day 337	**Blinded Study Drug** N=379

[a] Patients who achieved at least a 50% reduction in their joint count (both swollen and tender joints) at 6 months were to discontinue etanercept and continue on their original treatment (abatacept or placebo).

BIW- twice a week, DMARD- disease modifying anti-rheumatic drug, IV- intravenous, MTX- methotrexate, PO- oral, RA- rheumatoid arthritis, SC subcutaneous, TNF tumor necrosis factor

4.1.2 Other Clinical Trials with Abatacept

Apart from the clinical trials conducted in patients with RA, 6 other clinical trials have been conducted with abatacept. These are:

- IM101017, a Phase I study in healthy subjects to evaluate PK comparability following a manufacturing process change;
- IM101001, IM101003 and IM101004, 3 Phase I studies and IM101005, a Phase II study in patients with psoriasis vulgaris. These early studies provided PK and preliminary safety data. Development in psoriasis was stopped in order to focus resources on development in RA.
- IM101200, a Phase II study in patients with MS. This study is discussed in Section 6.2.6.3 (Autoimmune Disorders).

4.2 Clinical Pharmacology

4.2.1 Classical Pharmacokinetic (PK) Studies

Dose-proportional and linear pharmacokinetics have been demonstrated for abatacept. At the target IV dose of 10 mg/kg, the mean half-life (T-HALF) of abatacept was approximately 13 days. With the current dosing regimen (doses at Weeks 0, 2, and 4, and monthly thereafter), abatacept serum concentrations are higher initially (69.4 µg/mL), then reach steady-state conditions (22-29 µg/mL) typically by the third monthly dose (fifth dose overall). Abatacept does not accumulate after monthly dosing.

Abatacept is a therapeutic protein that achieves highly specific receptor targeting. Glycoproteins such as abatacept do not have specific interactions with molecules that are metabolized by the liver. As such, no formal drug-drug interaction studies were conducted, consistent with ICH Topic S6 (Guidance on Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals, July 1997).

Preclinical in vivo assessments indicated that abatacept does not have any direct or indirect cardiovascular liabilities, and as such no formal studies were carried out to evaluate QTc prolongation or other cardiovascular effects in humans. Based on its molecular weight of ~ 100 kD, abatacept is not expected to have access to ion channels,

and therefore should not alter ion currents or channel selectivity as may occur with small molecule drugs.[23]

4.2.2 Population PK Analyses

Serum concentration and time data from Phase II and Phase III studies were used to perform population PK analyses to assess the effects of covariates on the PK of abatacept. The following covariates were evaluated: body weight, age, gender, concomitant medication, disease state/duration at baseline, serum creatinine, and the hepatic enzymes, ALT and AST.

Neither age nor gender were found to have an effect on the clearance or volume of distribution of the central compartment of abatacept after accounting for the effect of weight on clearance. Several commonly co-administered medications (MTX, corticosteroids, NSAIDs, and TNF-blocking agents) were also investigated, and were not found to influence the PK of abatacept. Baseline disease status (tender joint counts and swollen joint counts) and the duration of RA were not associated with significant changes in the PK of abatacept. Finally, serum creatinine and AST/ALT levels had no effect on the PK of abatacept. This is not surprising considering that abatacept is not metabolized by liver enzymes and is not excreted by the kidney because of its high molecular weight. The results from the analyses revealed that there was a trend towards higher clearance of abatacept with increasing weight. However, this effect has been mitigated because dosing in the Phase III studies and the proposed dose for the market have been based on weight ranges.

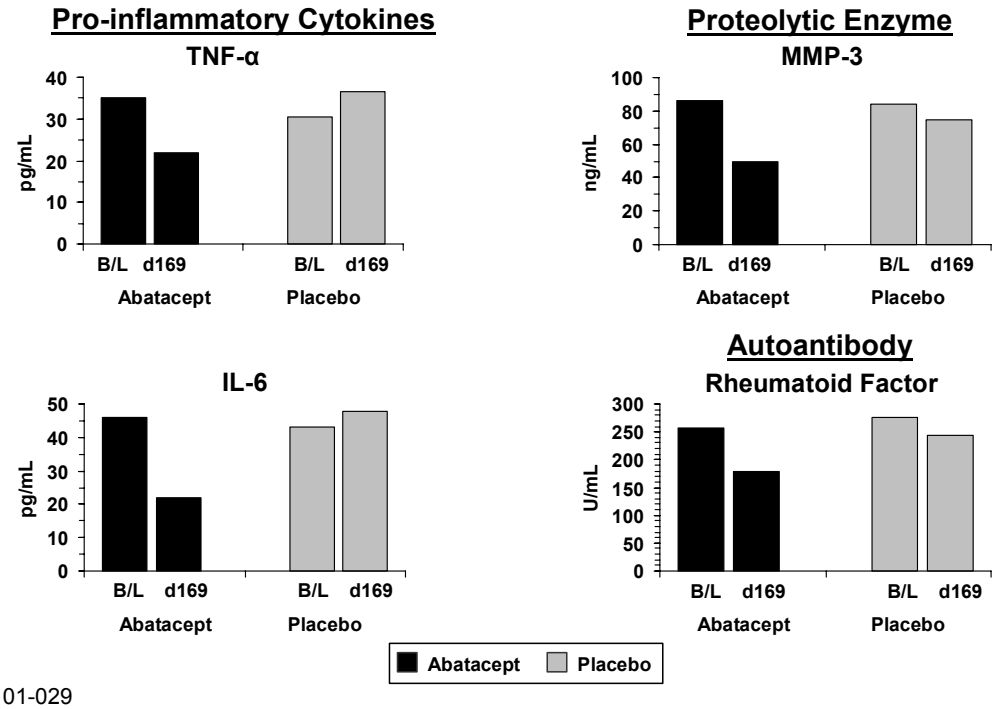
4.2.3 Pharmacodynamic Markers Affected by Abatacept

Non-clinical and human in-vitro data suggested that abatacept would target several key immunopathogenic mechanisms in RA including the production of:

1) pro-inflammatory cytokines;
2) other effector molecules such as matrix metalloproteinases produced by activated synovial cells; and
3) T cell-dependent autoantibodies such as rheumatoid factor (RF).

This proposed mechanism of action was explored in the clinical program by comparing serum levels of biomarkers before and after treatment. Consistent with the central role of T-cell activation in the pathogenesis of RA, abatacept reduced systemic levels of the pro-inflammatory cytokines TNF-α and IL-6, the proteolytic enzyme matrix metalloproteinase-3 (MMP-3), and autoantibody (RF). Representative data are shown from the Phase III study in inadequate responders to TNF-blocking agents (IM101029) in Figure 4.2.3:

Figure 4.2.3: Mean Values of Biomarkers at 6 Months in Patients with Inadequate Response to TNF-Blocking Agents



IM101-029

B/L = baseline; d 169 = Study Day 169

In addition, conversion from RF+ to RF- status occurred in 8.4% of abatacept-treated patients vs 0% of placebo-treated patents in this study. Reductions in these markers were also observed in the Phase II dose-ranging study IM101100 (dose-dependent effects of 2 and 10 mg/kg versus placebo) and with fixed-dose abatacept in the Phase III study IM101102 (see Section 4.3 [Dose Selection]). In addition, abatacept reduced systemic

levels of T-cell activation (measured by soluble levels of the IL-2 receptor) and endothelial-cell activation (measured by soluble levels of the adhesion molecules ICAM-1 and E-selectin) in all 3 studies. Collectively, these data support the conclusion that abatacept, by selectively targeting T-cell activation, inhibits the production of effector molecules such as TNF-α and matrix metalloproteinases from synovial cells that mediate joint inflammation and structural damage.

4.3 Dose Selection

Initial dose selection for clinical studies was guided by in vitro human and in vivo animal studies. In vitro, abatacept concentrations of approximately 10 μg/mL inhibited human T-cell proliferation and cytokine production by approximately 60 to 80%. Higher concentrations did not yield greater inhibition. Consistent with in vitro results, antibody responses to T cell-dependent antigens were inhibited in animal models when serum trough concentrations were maintained ≥ 10 μg/mL. In an exploratory study in mice, there was inconsistent suppression of a KLH-antibody response when mean trough concentrations of abatacept were ≤ 8 μg/mL, but strong suppression when mean trough concentrations were approximately 50 μg/mL.

Doses of 0.5, 2.0, and 10 mg/kg were selected for the initial Phase II RA study (IM103002). The 10 mg/kg dose was predicted to achieve a trough serum concentration of approximately 10 to 30 μg/mL. A low dose of 0.5 mg/kg was selected since this dose had demonstrated some biologic activity both in vitro and in earlier studies in psoriasis patients. Finally, a mid-dose of 2 mg/kg using the same schedule was selected because it was predicted to achieve trough serum concentrations of approximately 3 to 10 μg/mL, ie, near maximal inhibitory levels in vitro and in non-human primate in vivo experiments. In this study, ACR response rates were similar between the 0.5 mg/kg group and placebo. Both the 2 and 10 mg/kg doses resulted in similar efficacy; however, the study was not powered to detect differences between the active doses. Mean trough (Cmin) abatacept serum concentrations were within predicted ranges: approximately 0.4, 3, and 17 μg/mL for the 0.5, 2, and 10 mg/kg doses, respectively.

To further assess the efficacy of the 2 and 10 mg/kg doses, a larger Phase II study (IM101100) was conducted in which patients were treated with placebo, abatacept

2 mg/kg, or abatacept 10 mg/kg. In this study, 10 mg/kg was consistently more effective than 2 mg/kg and exhibited a safety profile similar to that of the 2 mg/kg dose. Median trough abatacept serum concentrations were approximately 3 to 4 µg/mL and 20 to 22 µg/mL for the 2 and 10 mg/kg doses, respectively. Therefore, abatacept 10 mg/kg yielded mean trough levels in the range predicted to be maximally efficacious based upon in vitro human and in vivo animal data, and this dose was demonstrated to be maximally effective in humans with RA.

A fixed abatacept dose approximating 10 mg/kg based on weight ranges was selected as the dose for the Phase III program to simplify therapy and minimize dosing errors (Table 4.3).

Table 4.3: Fixed Dosing Regimen Approximating 10 mg/kg for Phase III

Weight	Monthly Dose (Total mg)	Monthly Dose (mg/kg)
< 60	500	> 8
60–100	750	7.5–12.5
> 100	1000	≤ 10

5 CLINICAL EFFICACY

5.1 Introduction

Data from 6 randomized, double-blind, placebo-controlled studies are presented in this section. These include 3 studies that provide the principal data in support of the efficacy of abatacept (IM101102, IM101100, and IM101029) as outlined in Section 4.1 (Overview of Clinical Development Program), as well as 3 studies that provide additional information (IM101031, IM101101, and IM103002).

5.2 Efficacy Endpoints

The effects of abatacept with respect to relief of signs and symptoms of RA, improvement in physical function, inhibition of the progression of structural damage and

improvement of patient-reported quality of life were evaluated using validated outcome measures, as summarized in the FDA (February 1999) and EMEA (December 2003) guidances for industry on clinical development programs for products for the treatment of RA.

The efficacy of abatacept in improving signs and symptoms of RA was evaluated using the ACR 20 response rate[24] at 6 months as a co-primary efficacy objective in all 3 principal efficacy studies. ACR 50 and 70 response, and improvement in the individual components of the ACR core data set, were also assessed at 6 and 12 months. Major clinical response (achievement of ACR 70 response for a continuous 6-month period, MCR) was assessed in Studies IM101102 and IM101100. Onset of action and maintenance of effect (with up to 2 years of open-label therapy following 1 year of double-blind therapy) were assessed by the ACR response. The DAS28 composite[25] was also used to support the ACR efficacy results for signs and symptoms of RA.

The efficacy of abatacept in improving physical function was measured by the Health Assessment Questionnaire Disability Index (HAQ-DI)[26,27] or the modified HAQ-DI (mHAQ), a shortened version of the HAQ-DI.[28] Both are validated instruments for measurement of functional status and degree of disability, and are highly correlated with one another.[28] The Phase III studies, IM101102, IM101029, and IM101031, utilized the HAQ-DI; the mHAQ was used in the Phase II studies, IM101100 and IM101101. Clinically meaningful improvement was prospectively defined as at least a 0.3 unit reduction in HAQ/mHAQ score from baseline at the end of the double-blind period; this is a more stringent definition than the minimum clinically important difference (MCID), a 0.22 unit reduction in HAQ/mHAQ score.[29] Improvement in physical function measured as the proportion of patients with a clinically meaningful change in HAQ-DI was a co-primary objective in IM101102 and IM101029. In the Phase II study IM101100, improvement in physical function (mHAQ) was assessed as a secondary objective at 1 year during the double-blind period, and an additional 2 years of data were captured during the open-label period of the study.

The efficacy of abatacept in the inhibition of the progression of structural damage was assessed radiographically using the Genant-modified Sharp scoring system in Study IM101102.[30] The Genant-modified Sharp scoring system evaluates erosion, joint space

narrowing (JSN), and a combination of erosion and joint space narrowing, referred to as the total score. All radiographs were sent to a central reading facility where they were tracked, assessed for readability, digitized, and scored independently by 2 experienced and trained radiologists in a blinded manner. Images were evaluated in a side-by-side comparison blinded to treatment and sequence. An adjudicator resolved differences between reviewing radiologists that exceeded a specific threshold, without knowledge of the scores determined by the individual readers. Change in erosion score at 12 months was a co-primary measure in Study IM101102. Changes in JSN and total score were secondary measures.

The efficacy of abatacept in inhibiting the progression of structural damage was also explored as a tertiary objective in the Phase II dose ranging study IM101100. The results of this preliminary assessment were used to design the definitive assessment conducted in IM101102. In accordance with the exploratory nature of this assessment, the radiographs were initially scored using a simplified procedure, with only 1 blinded reader, and follow-up radiographs were not obtained on subjects who discontinued treatment. In order to ensure the results of this assessment would be relevant to the design of the definitive assessment in IM101102, the radiographs were subsequently re-scored using a more thorough procedure that incorporated many of the methodologic enhancements planned for the definitive assessment, including independent assessment by 2 blinded readers, balanced weighting of scores for hands and feet, and more stringent quality control. Results from this more rigorous assessment of data from IM101100 are reported in Section 5.4.2.4 (Efficacy Results).

For improvement in health-related quality of life, the validated Medical Outcomes Study Short Form (MOS SF-36 or SF-36) was used.[31] The SF-36 was validated for use in RA patients.[32,33]

Table 5.2 summarizes the primary and secondary efficacy endpoints in IM101100, IM101102, and IM101029.

Table 5.2: Primary and Secondary Efficacy Endpoints in the 3 Principal Efficacy Studies: Patients with an Inadequate Response to Methotrexate or TNF-Blocking Agents

Analysis Endpoints	IM101100	IM101102	IM101029
Primary Endpoint			
ACR 20 Responses, n (%)[a]	X	X	X
mHAQ/HAQ Responses, n (%)		X[b]	X[a]
Change in Erosion Scores[b]		X	
Secondary Endpoint			
ACR 20 Responses, n (%)[b]	X	X	
ACR 50 Responses, n (%)[a,b]	X	X	X
ACR 70 Responses, n (%)[a,b]	X	X	X
Major Clinical Response, n (%)[b]	X	X	
mHAQ/HAQ Responses, n (%)	X[a,b]	X[a]	
DAS28 (ESR)[a,b]		X	X
DAS28 (CRP)[a,b]	X[c]	X	X
Change in Joint Space Narrowing Scores[b]		X	
Change in Total Genant-modified Sharp Scores[b]		X	
SF-36: Physical Component, Change from Baseline[a,b]	X	X	X
SF-36: Mental Component, Change from Baseline[a,b]	X	X	X

Source: Summary of Clinical Efficacy, Table 1.3

[a] 6 Months or Day 180 for IM101100; Day 169 for IM101102 and IM101029

[b] 12 Months or Day 360 for IM101100; Day 365 for IM101102

[c] Post-hoc analysis

5.3 Analytical Methods

All efficacy analyses were carried out on the intent-to-treat (ITT) population defined as all randomized subjects who received at least one dose of study medication. All available

assessments at each analysis time point were included in the primary analyses regardless of either study drug discontinuation or the addition of other DMARDs. All statistical tests were based on the 2-sided 0.05 level of significance.

For the co-primary analyses of ACR20 at 6 months and HAQ responses at 1 year, a 2-sided Cochran-Mantel-Haenszel (CMH) Chi square test was used to compare the responses for the abatacept group with the placebo group. For the ACR20 and HAQ primary responder analyses, all subjects who discontinued were considered as non-responders subsequent to their discontinuation. Additional sensitivity analyses were performed to assess the impact of imputation of missing data.

Progression of structural damage, characterized as changes from baseline in Genant-modified Sharp scores, was analyzed at 12 months within the framework of a non-parametric ANCOVA model. The primary radiographic analyses included all observed data at baseline and at 12 months. Missing annual radiographic data were imputed with linear extrapolation for discontinued subjects based on the baseline value and the on-treatment assessment at the time of discontinuation, provided both assessments were available. Additional sensitivity analyses were performed to assess the impact of imputation of missing data.

Mean changes from baseline in the disease activity score (DAS28), HAQ disability index and the physical (PCS) and mental (MCS) component summary of the SF-36 were compared between treatment groups using analysis of covariance (ANCOVA) models adjusting for the baseline assessments. For subjects who discontinued, the last observation obtained prior to their discontinuation was used (LOCF).

During BMS monitoring visits, compliance issues were noted for a single investigator in IM101102, IM101029, and IM101031. It was decided, prior to the unblinding of data, that data from this site would be excluded from all analyses of efficacy. Fourteen (14), 2 and 16 subjects were randomized and treated at this site in IM101102, IM101029, and IM101031, respectively.

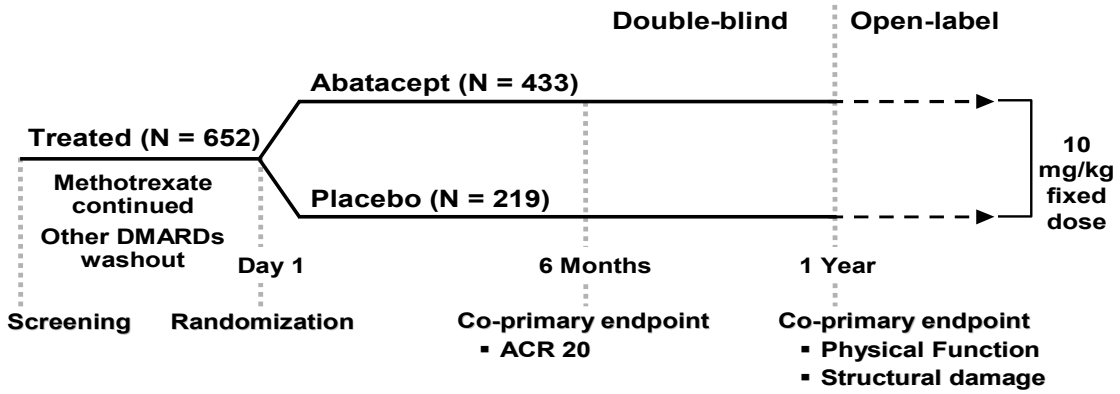
5.4 Principal Efficacy Studies

5.4.1 Phase III Study in RA Patients with Inadequate Response to Methotrexate (IM101102)

5.4.1.1 Overview

Study IM101102 was conducted in patients with RA and an inadequate response to MTX, defined as having active disease in spite of MTX treatment at a minimum of 15 mg/week for at least 3 months (Figure 5.4.1.1). Patients continued to receive MTX during the study.

Figure 5.4.1.1: Study IM101102: Patients with Inadequate Response to Methotrexate



No new DMARDs or increases in MTX were permitted during the first 6 months to standardize concomitant medication between treatment groups when the co-primary endpoint of ACR 20 was measured. Low-dose corticosteroids and/or NSAIDS were

allowed on a background of MTX. The addition of new DMARDs, courses of high-dose corticosteroids and increases in MTX were allowed, if needed, during Months 6 through 12.

5.4.1.2 Endpoints

There were 3 sequential, co-primary objectives in this study: ACR 20 response at 6 months; HAQ-DI response at 12 months; and change in joint erosion score at 12 months. The second and third co-primary analyses were only performed if the proceeding objective(s) had been met. Secondary objectives included assessment of ACR 50 and 70 responses, MCR, disease activity using the disease activity score (DAS)28 composite,[25] additional measures for HAQ-DI, and other aspects of radiographic progression including JSN and total scores. Improvement in health-related quality of life, measured by the SF-36, was also an important secondary objective.

5.4.1.3 Patient Disposition

A greater proportion of patients in the abatacept group (89%) completed 12 months of treatment compared with the placebo group (74%). Lack of efficacy and AEs were the most common reasons for discontinuation. Discontinuation due to lack of efficacy was greater in the placebo group (18%) than in the abatacept group (3%). Discontinuation due to AEs was higher in the abatacept group (4%) than in the placebo group (2%).

5.4.1.4 Demographic Characteristics

The treatment groups were well balanced with respect to demographic characteristics. The majority of patients were Caucasian (87.7%) and female (79.1%), with a mean age of 51.1 years. Patients were located in the following geographic regions: North America (21.3%), South America (40.8%), Europe (32.2%), and the rest of the world (5.7%).

5.4.1.5 Clinical Characteristics

Baseline clinical RA characteristics and baseline radiographic scores were well balanced for both treatment groups (Supplemental Table S.5.4.1.5). The mean duration of RA was approximately 9 years. A majority (79-82%) of patients were positive for rheumatoid

factor (RF). Despite concurrent treatment with MTX (mean doses of approximately 15 mg/week), patients in both groups had a high degree of baseline disease activity on the basis of the mean number of tender (31-32) and swollen (21-22 joints) and DAS28 (CRP) score (6.8). Baseline radiographic total scores for structural damage were consistent with moderate disease (31.65-33.35).

Corticosteroids were used by approximately 73 to 76% of patients and NSAIDS by approximately 85 to 88%, with similar rates across treatment groups.

5.4.1.6 Efficacy

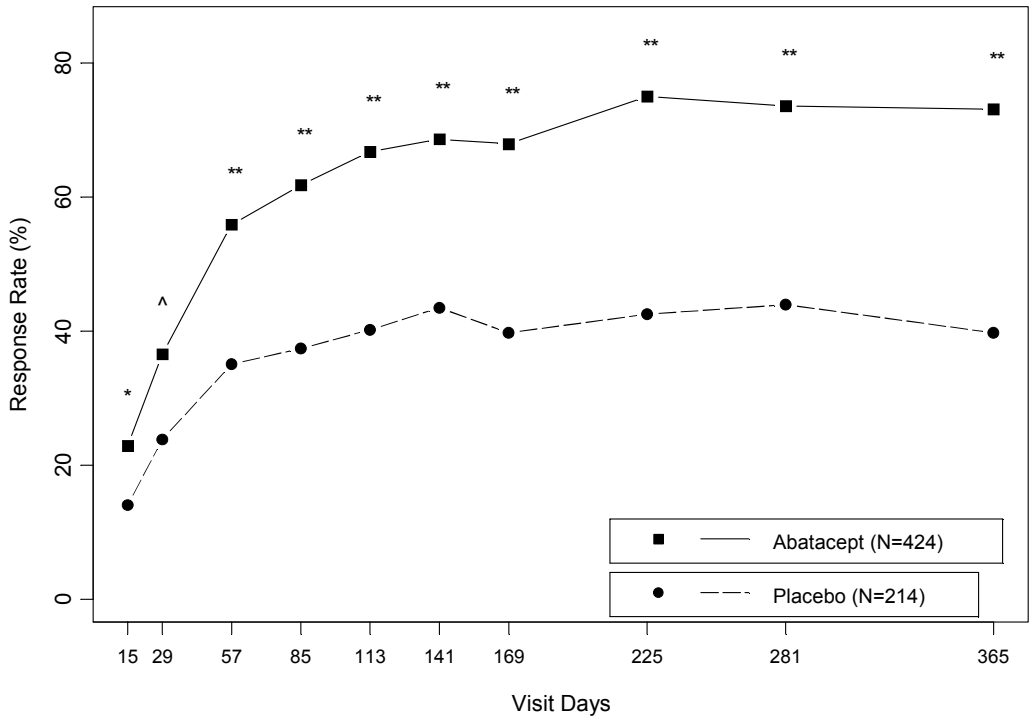
Signs and Symptoms

ACR20

Abatacept was more effective than placebo in reducing the signs and symptoms of active RA in patients with an inadequate response to MTX. Statistically significant differences in the ACR 20 response rate relative to placebo were observed by Day 15, the first visit after the initial dose, and were preserved through all subsequent study visits (Figure 5.4.1.6A). The number of subjects evaluated for efficacy was less than the number of subjects randomized due to the exclusion of 14 patients from one site, as described in Section 5.3 (Analytical Methods).

During Months 6 through 12 of the trial, when DMARDS could be added to control disease activity, 25 (14.4%) of placebo-treated patients received a DMARD other than methotrexate vs 15 (3.7%) of abatacept-treated patients.

Figure 5.4.1.6A: ACR 20 Response Rates Over Time (Study IM101102)

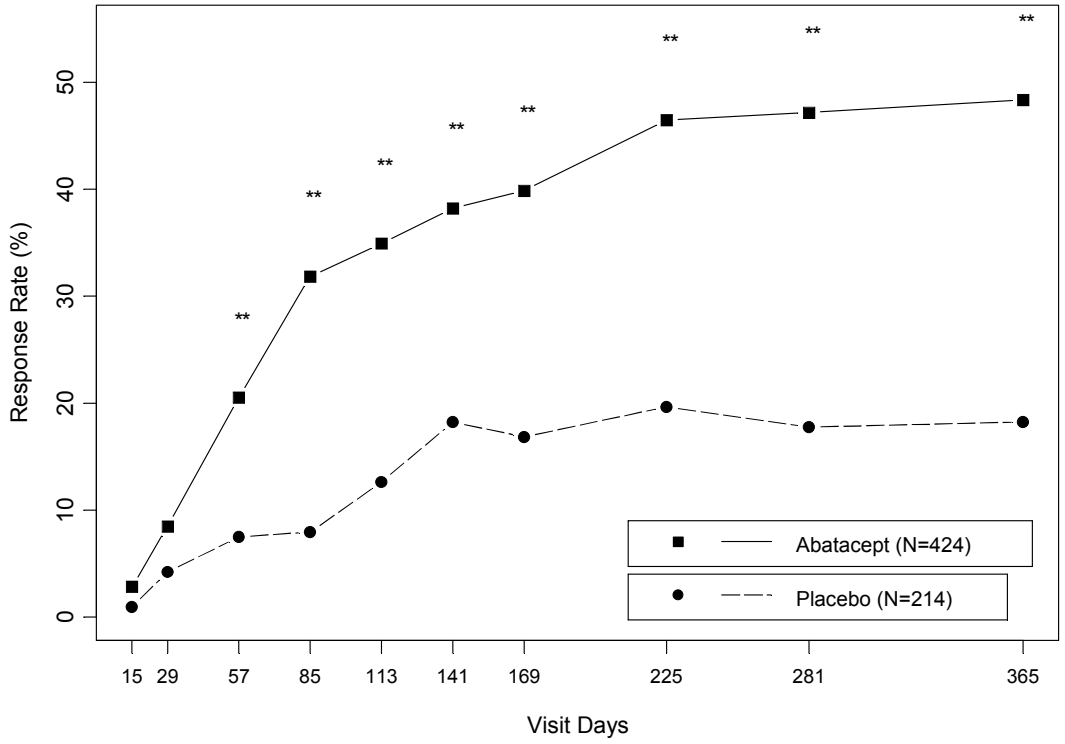


** - significant at the 0.001 level, ^ - significant at the 0.01 level; * - significant at the 0.05 level;
Population: All randomized and treated patients.
One additional non-biologic DMARD could be added on or after Day 169.

ACR 50 and 70

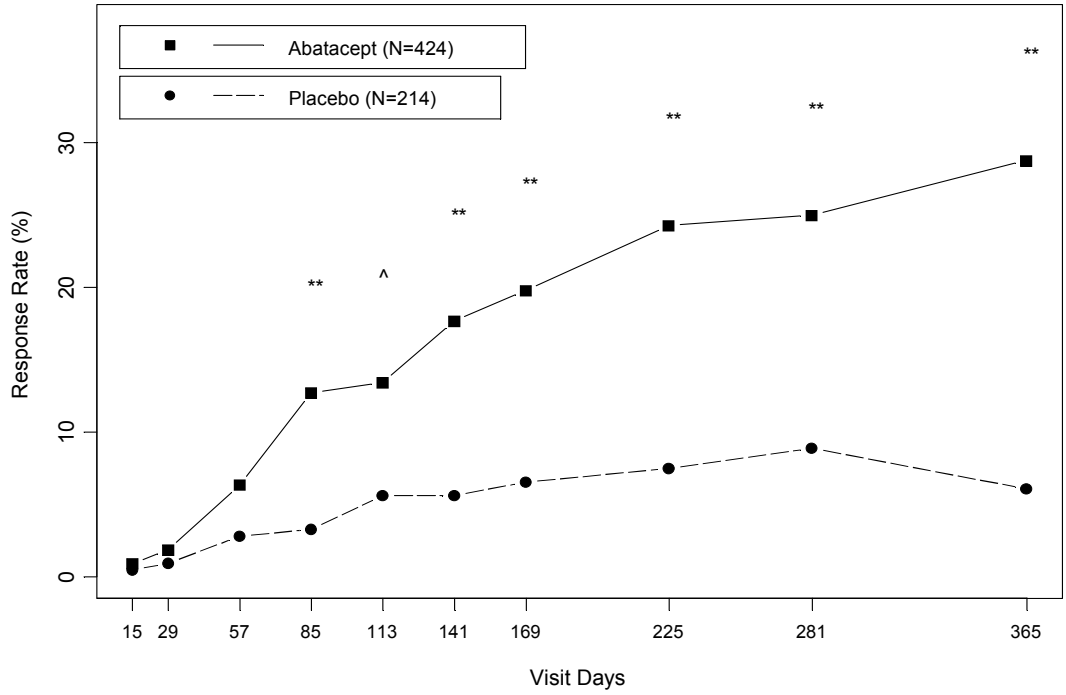
Similar to the results for the ACR 20, abatacept demonstrated consistently greater response rates than placebo for the ACR 50 and 70 outcomes. (Figure 5.4.1.6B and 5.4.1.6C)

Figure 5.4.1.6B: ACR 50 Response Rates Over Time (Study IM101102)



** - significant at the 0.001 level, ^ - significant at the 0.01 level; * - significant at the 0.05 level
Population: All randomized and treated patients.
One additional non-biologic DMARD could be added on or after Day 169.

Figure 5.4.1.6C: ACR 70 Response Rates Over Time (Study IM101102)



** - significant at the 0.001 level, ^ - significant at the 0.01 level; * - significant at the 0.05 level
Population: All randomized and treated patients.
One additional non-biologic DMARD could be added on or after Day 169.

MCR

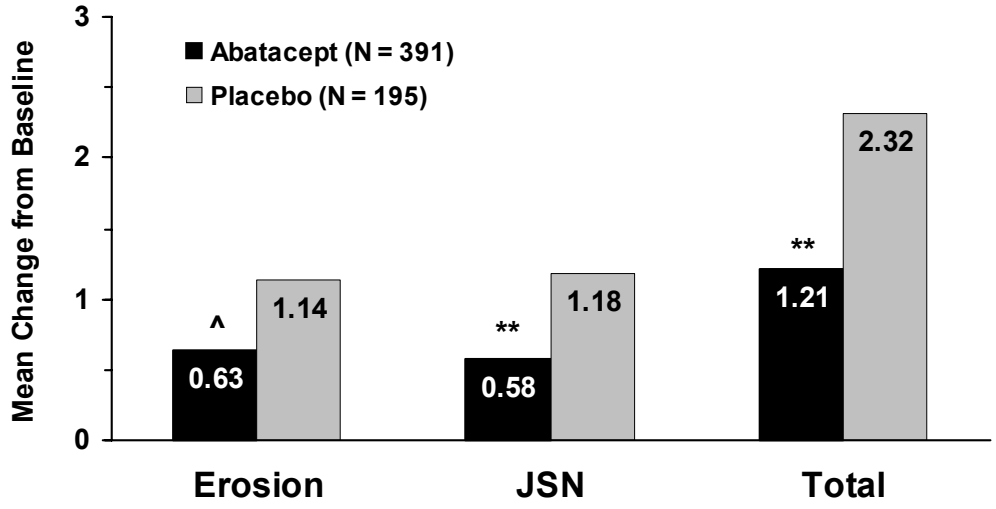
By Day 365 more patients treated with abatacept (14.2%) than patients treated with placebo (1.9%) achieved a MCR (maintenance of ACR 70 response over a continuous 6-month period, $p<0.001$).

Structural Damage

Paired radiographs were obtained for 586 (92%) of all randomized patients for the primary statistical analysis, and scored using the Genant-modified Sharp scoring system. Scores for erosion and JSN could range from 0 (no damage) to 145 (maximum damage). Total scores (the sum of erosion and JSN scores) could range from 0 to 290.

Comparison of mean changes from baseline in the total and component scores have been used to assess efficacy in inhibiting structural damage. The mean changes from baseline for the erosion, JSN and total scores were all significantly lower for the abatacept group (Figure 5.4.1.6D).

Figure 5.4.1.6D: Mean Change in Radiographic Scores in Patients with Inadequate Response to MTX



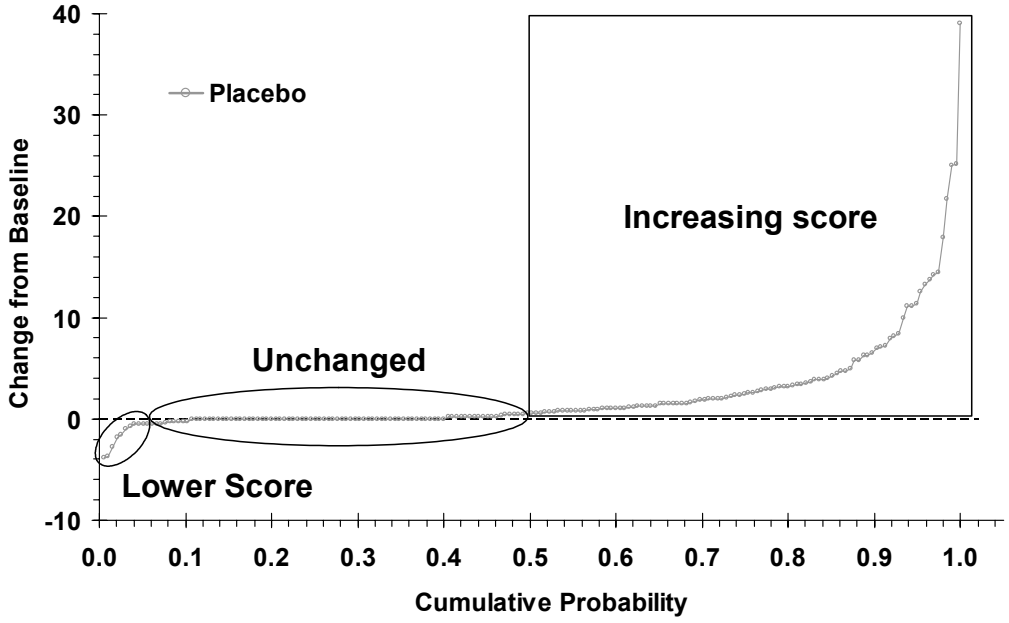
** $p < 0.001$
^ $p < 0.01$
JSN = Joint Space Narrowing
IM101-102

Due to the skewed distribution of data, however, a comparison of the distribution of radiographic changes between treatment groups, rather than a comparison of means, is the most appropriate method to assess the efficacy of a drug in inhibiting the progression of structural damage.[34] For this reason, non-parametric methods were used for the primary statistical comparisons of radiographic data. Using these non-parametric methods, the distribution of changes were shown to be significantly different between treatment groups in favor of abatacept for erosions (p = 0.029), JSN (p = 0.009), and total score (p = 0.012), thus meeting the co-primary objective and 2 key secondary radiographic objectives of the study.

To better understand the effect of abatacept on structural damage, a cumulative distribution plot was used. The plot depicts all data including outliers and allows precise assessment of where the differences between treatment groups exist. The plot is a visual representation of the cumulative proportion of patients with a particular degree of radiographic progression. For any given change in the total progression score shown on the x axis, the proportion of all patients with a change less than the specified magnitude on the can be determined by examination of the y axis.

The plot in Figure 5.4.1.6E shows the distribution of changes in total score from baseline for patients treated with placebo on background MTX in Study IM101102. Approximately 50% of patients had no radiographic progression, as indicated by a 0 change from baseline, suggesting that MTX is an effective disease modifying therapy. This is represented by the large, elliptical section labeled ‘unchanged.’ Approximately 45% of patients had increasing scores from baseline, suggesting progression, as represented by the square section labeled ‘increasing score.’ A much smaller proportion, approximately 5%, had lower scores on follow-up radiographs, represented by the small, elliptical section marked ‘lower score’ at the extreme left side of the chart. Collectively, the plot illustrates the skewed distribution of data.

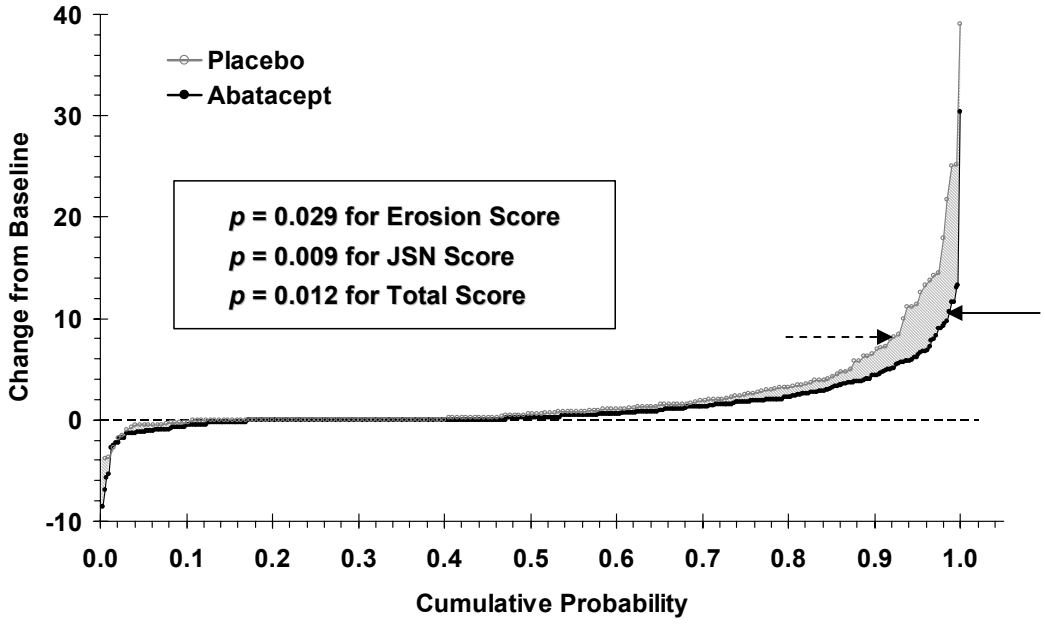
Figure 5.4.1.6E: Distribution of Radiographic Changes in Total Score at 1 Year in Placebo-Treated Patients with Inadequate Response to MTX (Study IM101102)



IM101-102

Distribution of changes in total score at 1 year in both treatment groups is presented in Figure 5.4.1.6F. The abatacept curve, marked by the solid arrow to the right of the curve, is shifted down and to the right, indicating a lower probability of an increase in total score from baseline as well as a smaller magnitude of increase. The placebo curve, marked by the dashed arrow to the left of the curve, is shifted up and to the left, indicating a higher probability of an increase in total score from baseline as well as a larger magnitude of increase. A small difference can also be appreciated in the left-hand portion of the curves, suggesting a higher probability of reduction from baseline in total score with abatacept treatment. The distribution of results was similar for the total score components, JSN and erosions.

Figure 5.4.1.6F: Distribution of Radiographic Changes in Total Score at 1 Year in All Patients with Inadequate Response to MTX (Study IM101102)



IM101-102

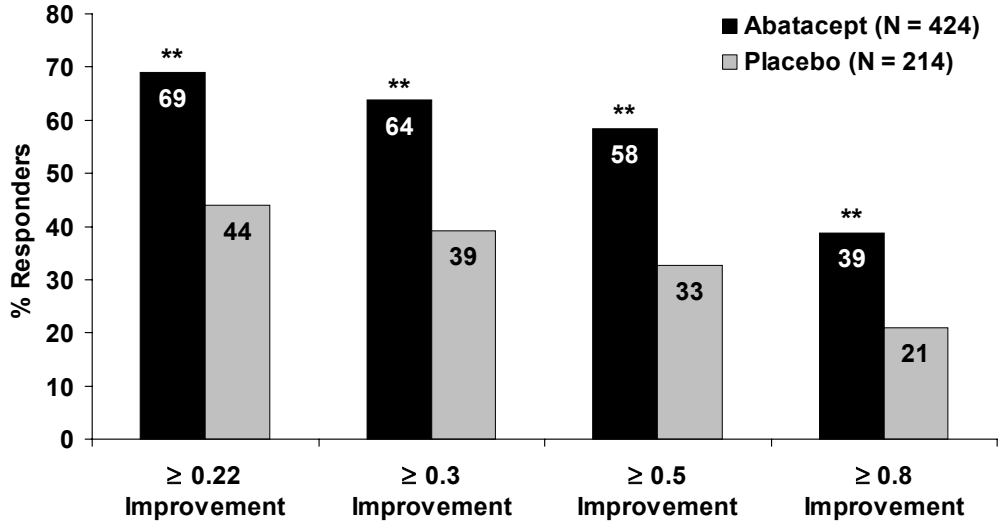
As previously noted, the distribution of changes were shown to be significantly different between treatment groups in favor of abatacept for erosions (p = 0.029), joint space narrowing (p = 0.009), and total score (p = 0.012). Collectively, these data demonstrate that abatacept combined with methotrexate effectively inhibits the progression of structural damage compared with MTX alone.

Physical Function (HAQ-DI)

The Health Assessment Questionnaire Disability Index (HAQ-DI) was used to assess changes in physical function. Both groups had a mean HAQ score of 1.7 at baseline, reflecting significant physical limitation. Clinically meaningful improvement in physical function (≥ 0.3 units) in HAQ-DI was achieved by a significantly greater proportion of patients treated with abatacept than with placebo (Figure 5.4.1.6G). Similarly, statistically significant improvements in HAQ-DI were observed using threshold values

of 0.22, 0.5, and 0.8. The adjusted mean improvement from baseline in HAQ-DI was also significantly higher ($p < 0.001$) with abatacept (-0.66) than with placebo (-0.37).

Figure 5.4.1.6G: Physical Function Responder Analysis (HAQ-DI) at 1 Year in Patients with Inadequate Response to MTX



** $p < 0.001$

IM101-102

ACR 20 Subgroup Analyses

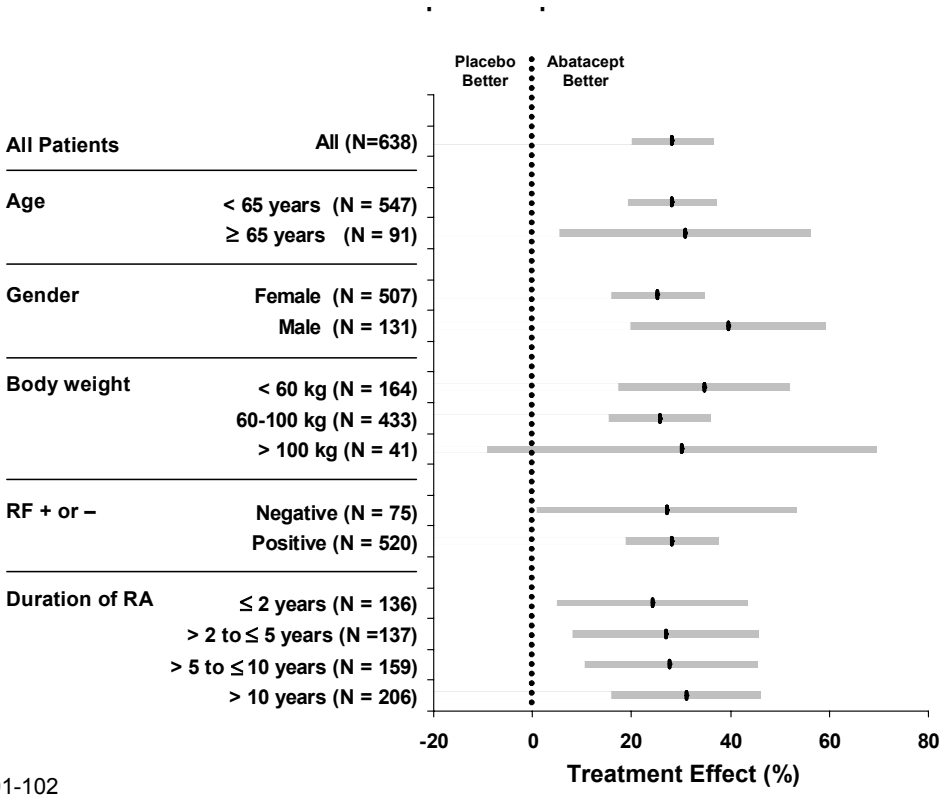
ACR response rates in major demographic and clinical subgroups were greater for abatacept than for placebo in all subgroups analyzed, including age, gender, body weight, duration of arthritis, and rheumatoid factor status. The small number of non-Caucasian patients precluded any analysis by race.

ACR 20 response rates (the first co-primary endpoint) in different subgroups are presented in Figure 5.4.1.6H. For each subgroup, the point estimate for the treatment effect (abatacept vs placebo) is indicated by the solid black line in the middle of the grey bar. The grey bar extending to either side of the black line represents the 95% CI around

the point estimate. The point of equivalence (no treatment effect) is illustrated by the dotted vertical line.

For ACR 20 response, the point estimates of treatment effect for the subgroups are distributed in a relatively narrow range around approximately 30%.

Figure 5.4.1.6H: Summary of ACR 20 Subgroup Analyses at 6 Months



IM101-102

Similarly, for the other co-primary endpoints in this study, a comparison between abatacept and placebo favored abatacept for all of the major demographic and clinical subgroups.

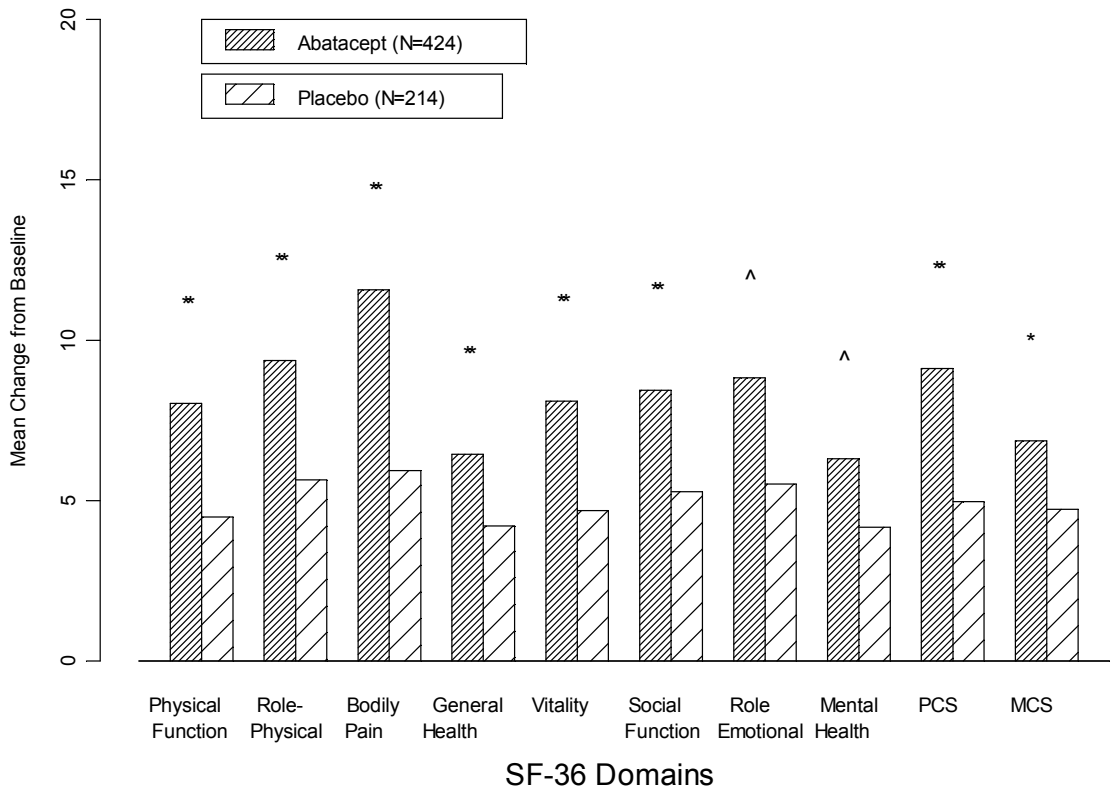
Quality of Life (SF-36)

The validated SF-36[33] was used to assess the impact of abatacept on health-related quality of life (HRQOL) in accordance with FDA guidance.[35] The SF-36 covers 8 health dimensions including 4 physical domains (physical function, role-physical, bodily pain,

and general health) and 4 mental domains (vitality, social function, role-emotional, and mental health). In addition, 2 summary scores, physical component summary (PCS) and mental component summary (MCS), were produced by taking a weighted linear combination of the 8 individual domains.

Abatacept was significantly more effective than placebo in improving each of the 4 mental and 4 physical dimensions of quality of life after 1 year of treatment (Figure 5.4.1.6I). Abatacept was also significantly more effective than placebo in improving the physical and mental health component summary scores.

Figure 5.4.1.6I: Improvement in Quality of Life (SF-36) at 1 Year (Study IM101102)



** - significant at the 0.001 level, ^ - significant at the 0.01 level; * - significant at the 0.05 level;
PCS: Physical Component Summary, MCS: Mental Component Summary
Population: All randomized and treated patients.
One additional non-biologic DMARD could be added on or after Day 169.

Disease Activity (DAS28)

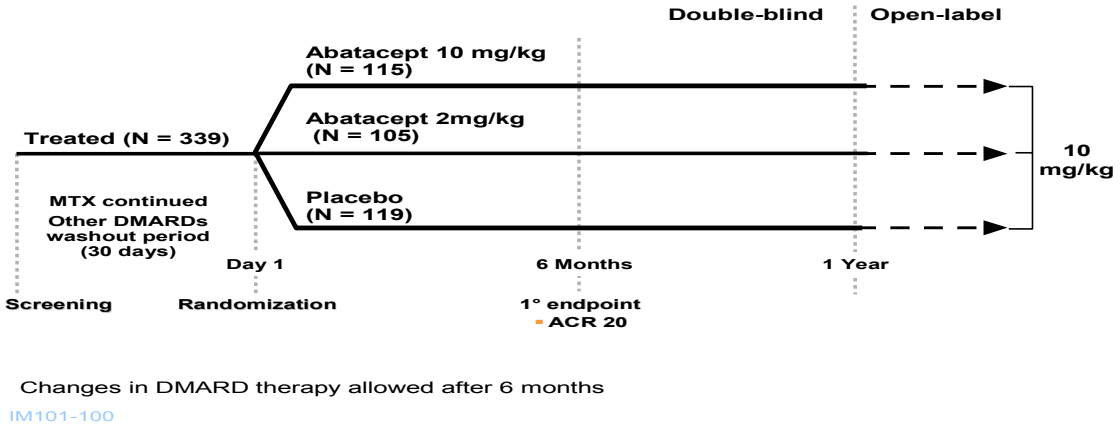
Improvements in disease activity were consistent with the symptomatic improvements assessed by the ACR variables. Clinically meaningful improvements (defined as change ≥ 1.2 in the DAS28 score by EULAR response criteria) in disease activity were observed at Day 169 in a greater proportion of subjects (81%) in the abatacept group compared with the placebo group (49%) using C-reactive protein (CRP) for the calculation of DAS28 score. Also at 6 months, a greater proportion of subjects in the abatacept group compared with the placebo group had low disease activity (DAS28 score ≤ 3.2) (30% vs 10%, respectively) and remission (DAS 28 score ≤ 2.6) (15% vs 3%, respectively).

Similar results were observed at 12 months, and at both 6 and 12 months when erythrocyte sedimentation rate (ESR), rather than CRP, was used to calculate DAS28.

5.4.2 Phase II Study in RA Patients with Inadequate Response to Methotrexate (IM101100)

IM101100 was a 12-month, multi-national, randomized, double-blind, placebo-controlled Phase IIb study designed to test the hypothesis that abatacept had greater clinical efficacy than placebo in patients with active RA despite treatment with MTX (Figure 5.4.2). Because Study IM101100 began before the Phase III studies (IM101102 and IM101029), it is the principal source of information about maintenance of efficacy with abatacept beyond 1 year.

Figure 5.4.2: Study IM101100: Patients with Inadequate Response to Methotrexate



Patients were eligible if they had active disease despite treatment with MTX (10 -30 mg/wk) for at least 6 months prior to randomization. Patients must have received a stable dose of MTX for 28 days prior to the first treatment day, and adjustments to background MTX during the first 6 months of study were not allowed, except for toxicity. Patients were required to have persistent disease activity, defined as a minimum of 10 swollen joints (66 joint count), ≥ 12 tender joints (68 joint count), and CRP ≥ 1.0 mg/dL at randomization.

No new DMARDs or increases in MTX were permitted during the first 6 months. Stable, low-dose corticosteroids and/or NSAIDs were allowed.

5.4.2.1 Patient Disposition

More patients completed 12 months of therapy with abatacept at 10 mg/kg (78.3%) than with placebo (59.7%). The most common reasons for discontinuation were lack of efficacy (11.3% for abatacept 10 mg/kg vs 25.2% for placebo) and adverse events (4.3% for abatacept vs 9.2% for placebo). The rates of discontinuation for lack of efficacy and adverse events were lower for the abatacept 10 mg/kg group than for the placebo group.

5.4.2.2 Demographics

Demographic characteristics were balanced across treatment groups. The majority of patients were Caucasian (87.7%) and female (66%), with a mean age of 54.7 years.

5.4.2.3 Clinical Characteristics

Baseline clinical characteristics were well balanced across treatment groups (Supplemental Table S.5.4.2.3). The mean duration of RA was 9 to 10 years. Patients had approximately 28 to 30 tender and 20 to 22 swollen joints. The majority of patients were RF positive (76-86%). Mean doses of MTX on Day 1 were 15 to 16 mg/wk. Corticosteroids were used at baseline by 59 to 66% of patients.

5.4.2.4 Efficacy Results

Signs and Symptoms

The percentage of subjects who had an ACR 20 response at 6 months was significantly higher in the 10 mg/kg group than in the placebo group (61% vs 35%, $p < 0.001$) (Table 5.4.2.4A; Figure 5.4.2.4). There was no significant difference in the rate of ACR 20 responses at Day 180 between the 2 mg/kg group and the placebo group. The ACR 50 and ACR 70 response rates at 6 months were significantly higher in both the 10 mg/kg and 2 mg/kg groups ($p \leq 0.05$) than in the placebo group (Table 5.4.2.4A).

Table 5.4.2.4A: ACR Responses at 6 Months (Study IM101100)

Parameter	Abatacept 10 mg/kg + MTX (N=115)	Abatacept 2 mg/kg + MTX (N=105)	Placebo + MTX (N=119)
ACR 20			
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
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

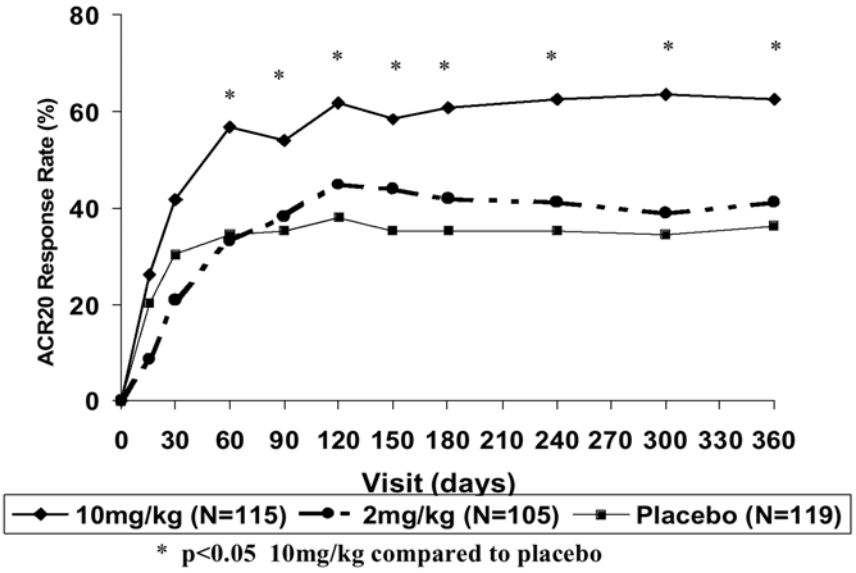
ITT Population

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.

[a] Comparison of abatacept vs placebo.

Figure 5.4.2.4: ACR 20 Response Rates Over Time (IM101100)



Source: IM101100 CSR, Table 10.1.4.1A.

At 12 months, ACR 20, ACR 50, and ACR 70 response rates in the 10 mg/kg group were significantly higher ($p \leq 0.005$) than in the placebo group (Table 5.4.2.4B). Although response rates in the 2 mg/kg group were numerically higher than in the placebo group, these differences were not statistically significant.

Table 5.4.2.4B: ACR Responses at 12 Months (Study IM101100)

Parameter	Abatacept 10 mg/kg + MTX (N=115)	Abatacept 2 mg/kg + MTX (N=105)	Placebo + MTX (N=119)
ACR 20			
n (%)	72 (62.6)	44 (41.9)	43 (36.1)
Estimate of the difference with respect to placebo (95% CI)	26.5 (13.7, 39.3)	5.8 (-7.0, 18.6)	N/A
p-value[a]	< 0.001	0.377	N/A
ACR 50			
n (%)	48 (41.7)	24 (22.9)	24 (20.2)
Estimate of the difference with respect to placebo (95% CI)	21.6 (9.7, 33.4)	2.7 (-8.1, 13.5)	N/A
p-value[a]	< 0.001	0.625	N/A
ACR 70			
n (%)	24 (20.9)	13 (12.4)	9 (7.6)
Estimate of the difference with respect to placebo (95% CI)	13.3 (4.4, 22.2)	4.8 (-3.0, 12.6)	N/A
p-value[a]	0.003	0.227	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.

[a] Comparison of abatacept vs placebo.

Physical Function (mHAQ-DI)

The proportion of patients achieving a clinically significant improvement in physical function (≥ 0.3 units) based on the modified HAQ-DI (mHAQ-DI) was significantly greater with abatacept 10 mg/kg than with placebo at Month 6 (47.7% vs 27.7%, respectively; p = 0.002). Abatacept also produced significant improvements in the proportion of patients achieving an improvement in mHAQ-DI of at least 0.22 or 0.5 units at Months 6 and 12.

Quality of Life (SF-36)

Statistically significant improvements in each of the 4 physical and 4 mental domains of the SF-36 as well as in the physical and mental component summaries were achieved with abatacept 10 mg/kg at Months 6 and 12.

Structural Damage

Interpretation of the radiographic assessment in this study was complicated by missing data. Follow-up radiographs were not obtained in 40% of placebo-treated and 22% of abatacept-treated patients. No radiographic data were imputed for these patients. The imbalance in missing data is due to an imbalance in the rate of discontinuation overall, including the rate of discontinuation due to lack of efficacy (25% of placebo-treated and 11% of abatacept-treated patients). Nevertheless, the mean change from baseline in the erosion score was significantly lower in the abatacept 10 mg/kg group than in the placebo group, and there was a non-significant trend towards a lower total score as well.

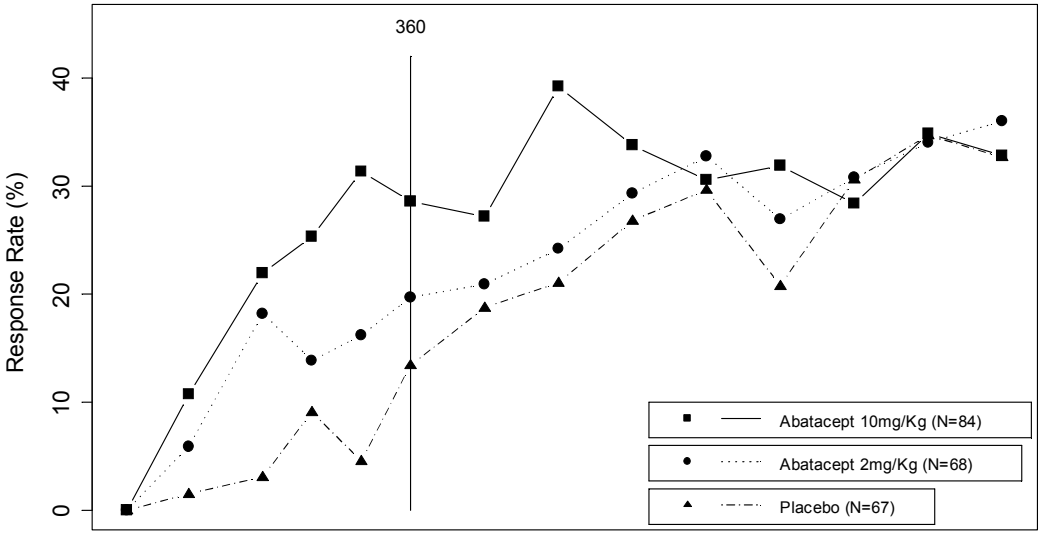
5.4.2.5 Sustained Efficacy

The IM101100 study was extended to an open-label period following the 12-month, double-blind period. Patients previously receiving placebo or 2 or 10 mg/kg abatacept were switched to the monthly, fixed-dose abatacept regimen approximating 10 mg/kg. Efficacy and safety data up to Day 1080 (since the start of double-blind period of treatment, and including up to 2 years of data from the open-label periods) are available through 22-Jun-2004. The majority of patients (165 [75.3%]) were exposed to abatacept for ≥ 24 months during the open-label period.

Sustained Improvement in Signs and Symptoms

ACR 20, 50, and 70 responses for the original 10 mg/kg group were maintained through Day 1080 of open-label therapy. ACR 70 responses are displayed in Figure 5.4.2.5A. Improvements in ACR 20, 50, and 70 were observed in the original abatacept 2 mg/kg and placebo groups over time.

Figure 5.4.2.5A: ACR 70 Response Over Time During Double-Blind (Up to Day 360) and Open-Label Periods (IM10100 LT)



10mg/Kg (n)	82	84	82	83	83	84	81	74	77	72	69	67	66	64
2mg/Kg (n)	67	68	66	65	68	66	67	62	58	55	52	52	50	50
Placebo	67	66	65	66	66	67	64	57	56	54	53	49	49	49

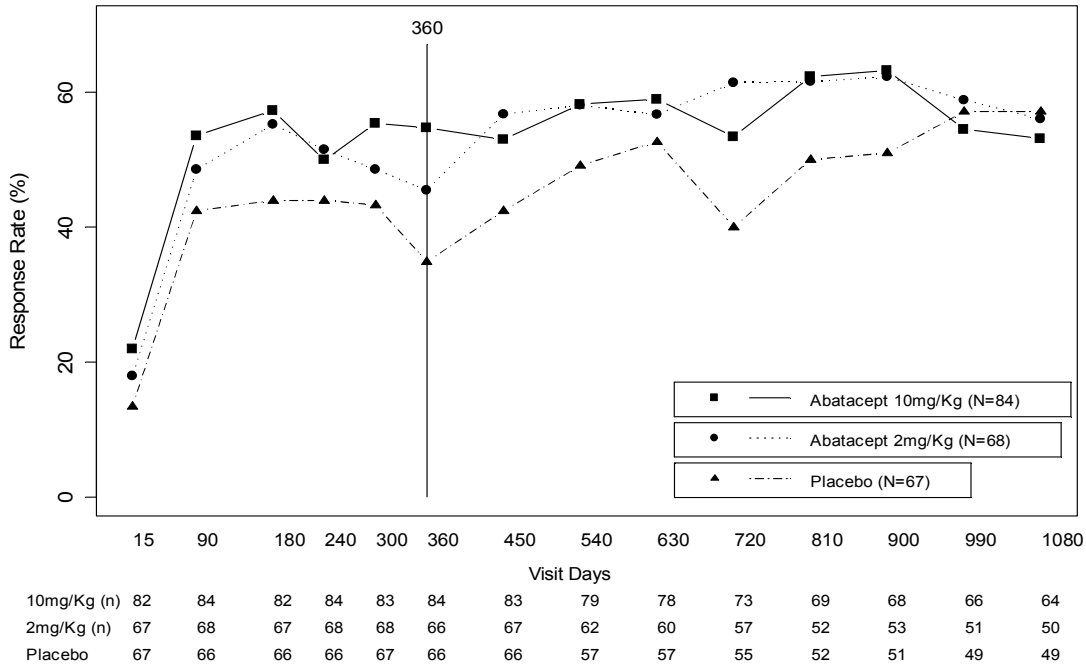
Population: All treated subjects; as-observed data.
Source: IM101100LT
Program Source: G:\IM_RA\Figures\SCE_pgm\F5.1.1C.ssc.

All patients received abatacept at a fixed dose approximating 10 mg/kg during the open-label period. Data presented as original treatment groups.
Source: Summary of Clinical Efficacy, Figure 5.1.1C

Sustained Improvement in Physical Function (mHAQ-DI)

Between 53 and 57% patients in each of the original abatacept treatment groups from the double-blind period of IM101100 had clinically significant improvement in physical function (≥ 0.3 units) in mHAQ-DI at 3 years (Figure 5.4.2.5B). The proportion of mHAQ responders in the original 10 mg/kg group was maintained over 1080 days of abatacept therapy. The mHAQ response rates in the original 2 mg/kg and placebo groups increased during the open-label period to levels comparable to the original 10 mg/kg cohort.

Figure 5.4.2.5B: Proportion of Patients with Clinically Meaningful HAQ Responses During Double-Blind (Up to Day 360) and Open-Label Periods (IM101100 LT)



10mg/Kg (n)	82	84	82	84	83	84	83	79	78	73	69	68	66	64
2mg/Kg (n)	67	68	67	68	68	66	67	62	60	57	52	53	51	50
Placebo	67	66	66	66	67	66	66	57	57	55	52	51	49	49

Population: All treated subjects; as-observed data.
Source: IM101100LT
Program Source: G:\IM_RA\Figures\SCE_pgm\F5.1.2.ssc.

All patients received abatacept at a fixed dose approximating 10 mg/kg during the open-label period. Data presented as original treatment groups.

5.4.3 Phase III Study in Patients with RA and Inadequate Efficacy Response to TNF-Blocking Agents (Study IM101029)

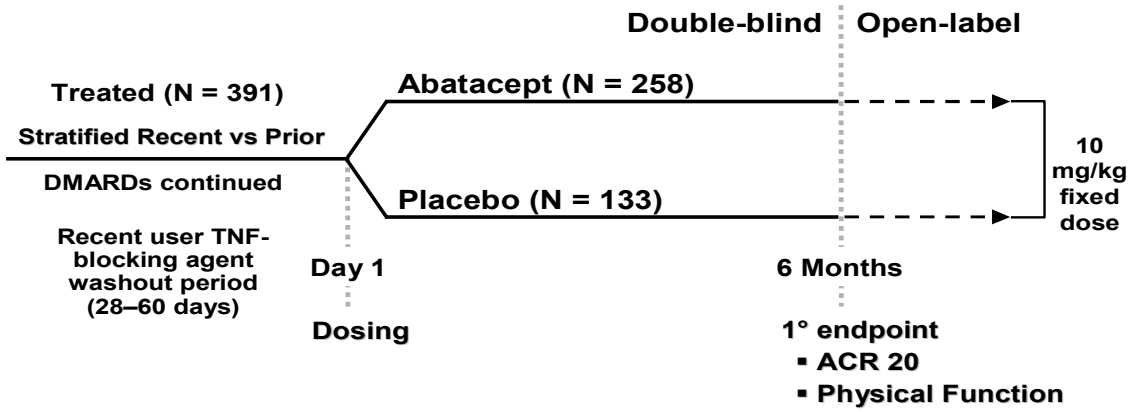
5.4.3.1 Overview

Currently, patients with RA who have active disease despite treatment with TNF-blocking agents have no alternate, approved therapeutic options and therefore represent a significant unmet medical need in RA therapy.

Study IM101029 was designed to test the hypothesis that abatacept will have greater clinical efficacy when compared with placebo in patients with RA who have experienced an inadequate efficacy response while receiving etanercept and/or infliximab therapy.

This was a multinational, randomized, double-blind, placebo-controlled study with a parallel-dosing design (Figure 5.4.3.1).

Figure 5.4.3.1: Study IM101029: Patients with an Inadequate Response to TNF-blocking Agents



IM101-029

Patients received a fixed dose of abatacept approximating 10 mg/kg, based on their body weight range or placebo. Patients were not allowed to continue on TNF-blocking agents during the study but were allowed to receive background DMARDs or anakinra.

Only patients with active RA who had had an inadequate response to etanercept or infliximab were eligible for this study. Adalimumab was not marketed in the United States at the time of study initiation. Patients who had discontinued a TNF-blocking agent primarily for toxicity or intolerability were not eligible. Patients were required to have a minimum of 10 swollen and 12 tender joints with an elevated CRP despite at least 3 months of therapy with a TNF-blocking agent at the time of enrollment. Lack of efficacy in patients still taking TNF-blocking agents must have been observed by the investigator immediately before enrollment; these patients were designated as 'recent

users' and their disease activity was directly recorded in the case report form (CRF). Other patients had discontinued TNF-blocking agents more distantly in the past due to lack of efficacy. These patients were designated as 'prior users' and source documentation attesting to the resistant nature of their disease was required. This could have been in the form of a chart note, referral letter or other suitable documentation. These eligibility criteria were monitored by BMS study personnel and high adherence to the protocol was documented. Randomization was stratified by TNF-blocking agent use at enrollment ('recent' or 'prior').

5.4.3.2 Patient Disposition

A greater proportion of patients in the abatacept group (86%) completed 6 months of treatment compared with the placebo group (74%). Lack of efficacy and AEs were the most common reasons for discontinuation. Discontinuation due to lack of efficacy was greater in the placebo group (20%) than in the abatacept group (5%). Discontinuation due to AEs was similar between the abatacept (4%) and placebo (4%) groups.

5.4.3.3 Demographic Characteristics

Treatment groups were well balanced with respect to demography. The majority of patients were Caucasian (95.1%) and female (78.0%), and the mean age was 53.2 years. Patients were located in North America (73.7%) or Europe (26.3%).

5.4.3.4 Clinical Characteristics

Baseline clinical RA characteristics were similar for both treatment groups (Supplemental Table S.5.4.3.4). Most had long standing RA with a mean duration of disease of 11 to 12 years. Approximately 73% were RF positive. Approximately 40% of patients in both treatment groups were considered to be recent users of TNF-blocking therapy. Approximately one-third of all patients in the study exhibited an inadequate response to etanercept therapy, while two-thirds were observed to have disease with an inadequate response to infliximab. The median duration of TNF-blocking therapy was approximately 8 months; 10% of patients had tried both etanercept and infliximab before being enrolled in the study.

Despite treatment with DMARDs, disease activity was high in both treatment groups at randomization, as determined by the mean number of tender joints (31-33), swollen joints (22), HAQ-DI scores of 1.8, CRP of ≥ 4.0 mg/dL, and DAS28 score of 6.9.

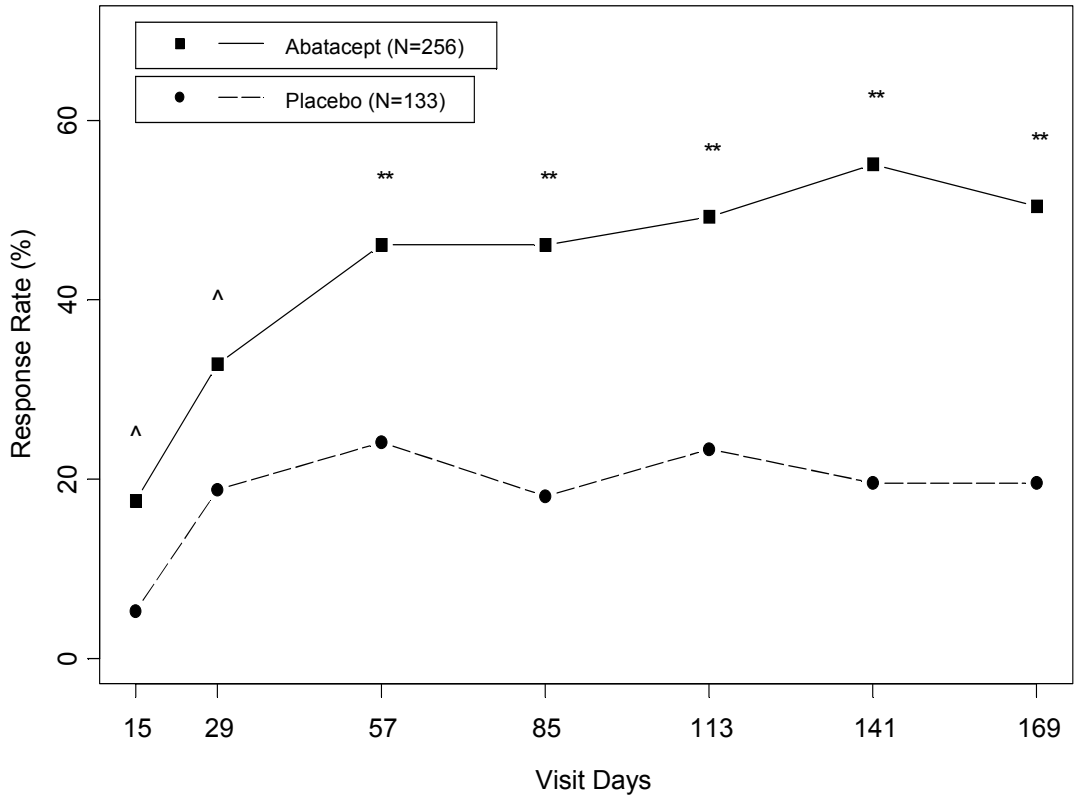
5.4.3.5 Efficacy

Signs and Symptoms

ACR 20

The proportion of patients achieving an ACR 20 response was significantly greater with abatacept than with placebo throughout the duration of double-blind therapy. Figure 5.4.3.5A presents ACR 20 response rates over time. The number of subjects evaluated for efficacy was less than the number of subjects randomized due to the exclusion of 2 patients from 1 site, as described in Section 5.3 (Analytical Methods).

Figure 5.4.3.5A: ACR 20 Response Rates Over Time (Study IM101029)

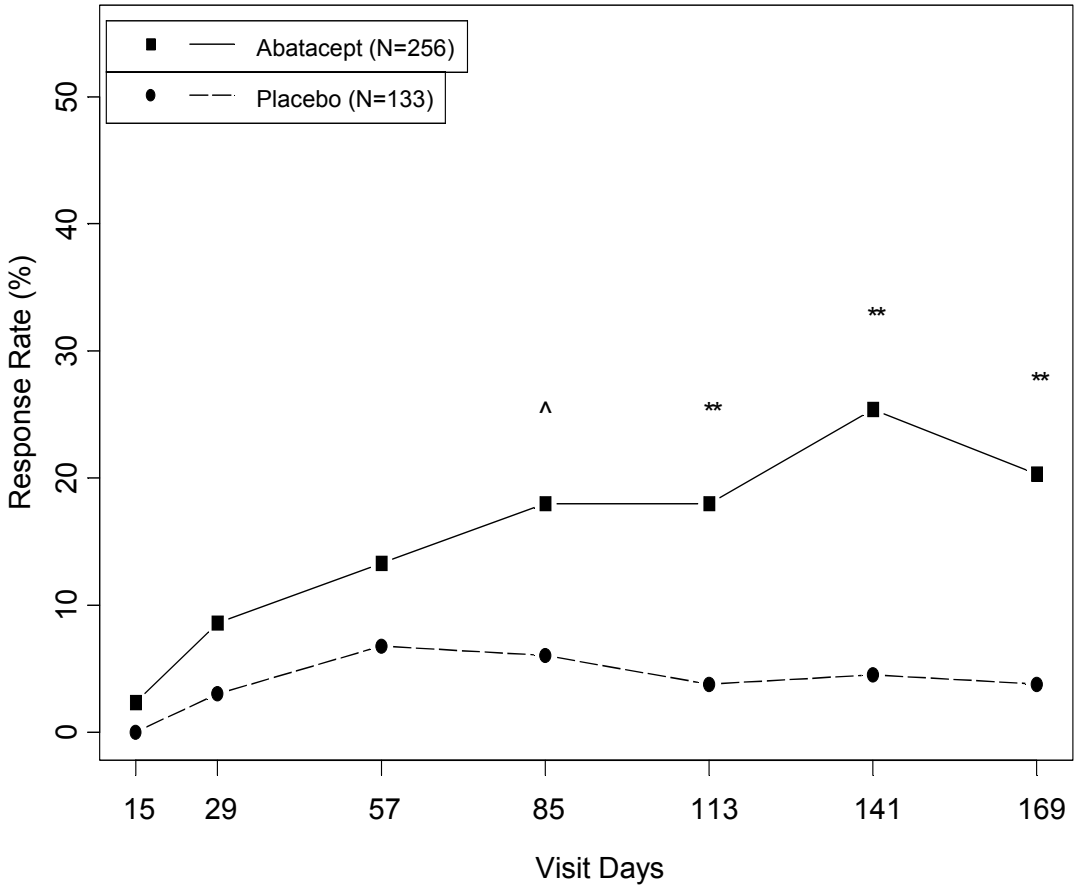


Population: All randomized and treated subjects.
*-significant at the 0.05 level; ^-significant at the 0.01 level; **-significant at the 0.001 level
Source: Appendix 10.0; Supplemental Table S10.1.
Program Source: G:\IM_RA\Figures\029_pgm\im101029_f.10.1.2.1a.ssc.

ACR 50 and 70

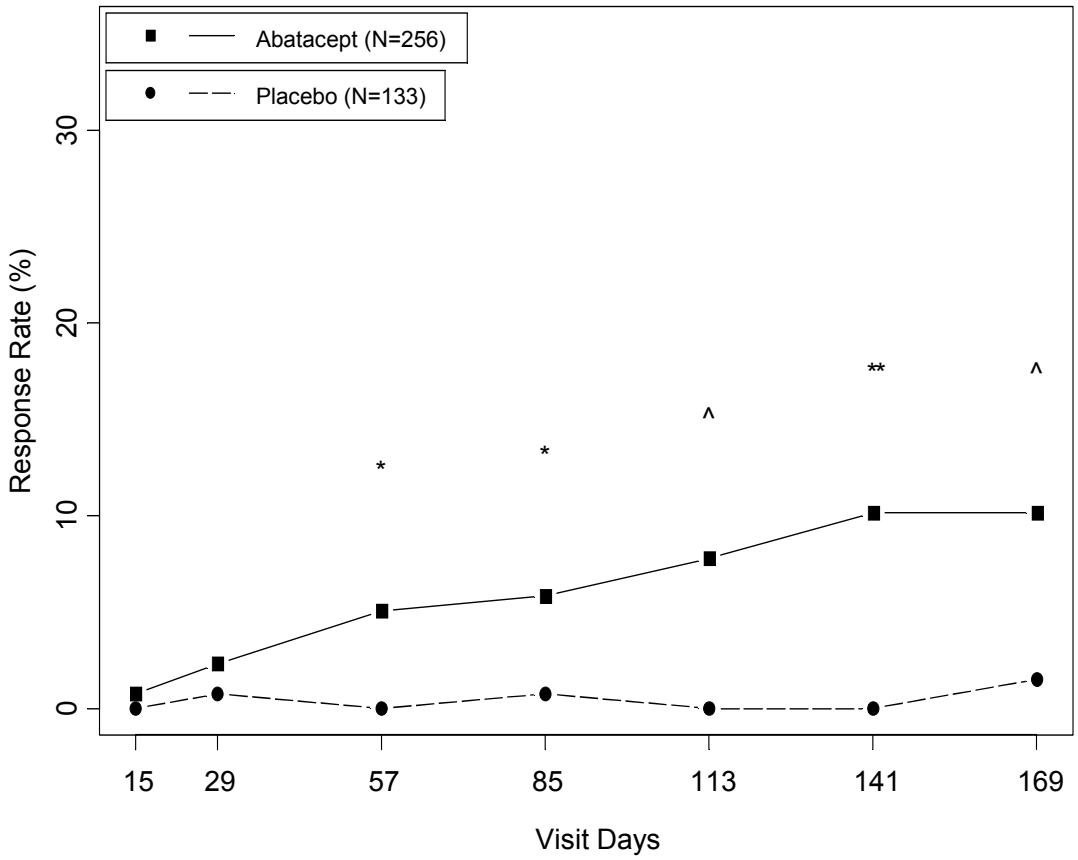
Statistically significant improvements in ACR 50 and ACR 70 response rates were achieved with abatacept relative to placebo (Figures 5.4.3.5B and 5.4.3.5C).

Figure 5.4.3.5B: ACR 50 Response Rates Over Time (Study IM101029)



Population: All randomized and treated subjects.
*-significant at the 0.05 level; ^-significant at the 0.01 level; **-significant at the 0.001 level
Source: Appendix 10.0; Supplemental Table S10.1.
Program Source: G:\IM_RA\Figures\029_pgm\im101029_f.10.1.2.1b.ssc.

Figure 5.4.3.5C: ACR 70 Response Rates Over Time (Study IM101029)

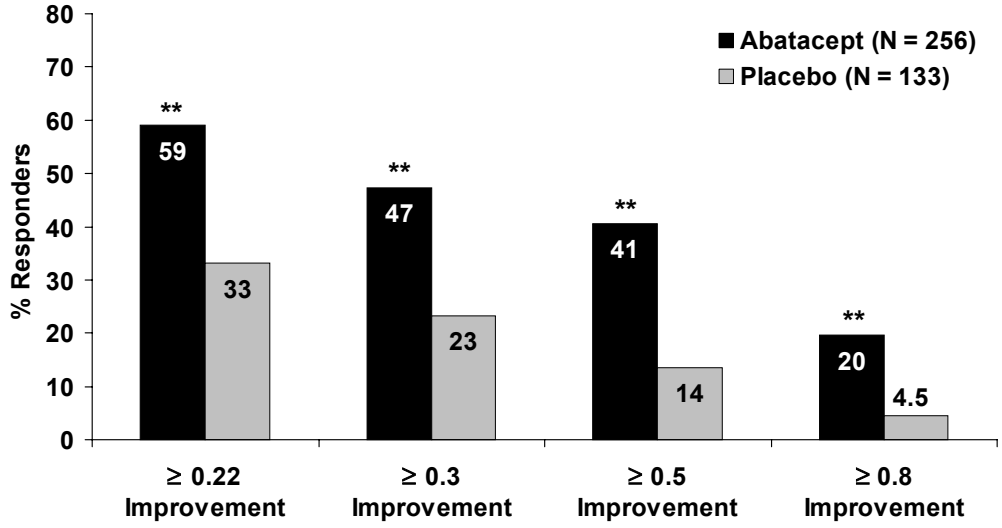


Population: All randomized and treated subjects.
*-significant at the 0.05 level; ^-significant at the 0.01 level; **-significant at the 0.001 level
Source: Appendix 10.0; Supplemental Table S10.1.
Program Source: G:\IM_RA\Figures\029_pgm\im101029_f.10.1.2.1c.ssc.

Physical Function (HAQ-DI)

Clinically significant improvement (≥ 0.3 units) in physical function as measured by the HAQ-DI was achieved by a significantly greater proportion of patients treated with abatacept than with placebo (Figure 5.4.3.5D). Similarly, statistically significant improvements in the HAQ-DI were observed using threshold values of 0.22, 0.5, and 0.8. The mean improvement in HAQ-DI values was significantly higher ($p < 0.001$) with abatacept (-0.45) than with placebo (-0.11).

Figure 5.4.3.5D: Improvement in Physical Function (HAQ) at 6 Months (Study IM101029)



** $p < 0.001$

IM101-029

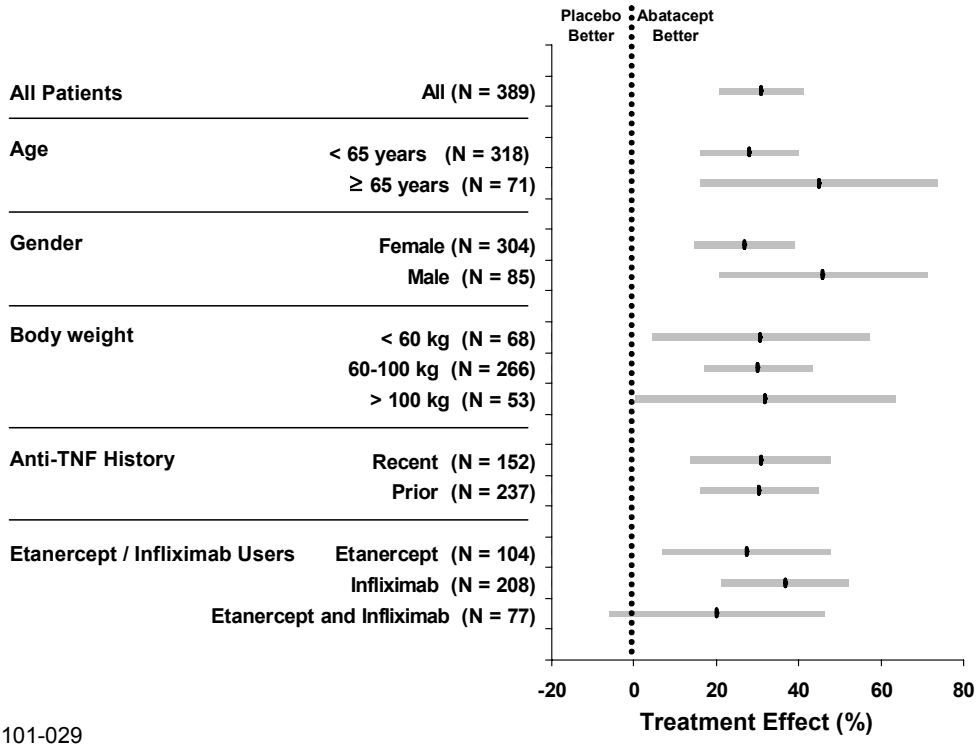
Subgroup Analyses

ACR response rates in major demographic and clinical subgroups were greater for abatacept than for placebo in all subgroups analyzed, including age, gender, body weight, duration of arthritis, and rheumatoid factor status. The small number of non-Caucasian patients precluded any analysis by race. ACR 20 response rates (the first co-primary endpoint) in different subgroups are presented in Figure 5.4.3.5E.

Two additional sub-group analyses were of particular clinical relevance in this study and are illustrated in the bottom of this figure. ACR 20 response rate was greater with abatacept than with placebo,

- whether the patient had persistent disease activity despite 'recent' or 'prior' TNF-blocking therapy, or
- whether they had tried etanercept, infliximab, or both drugs.

Figure 5.4.3.5E: Summary of ACR 20 Subgroup Analyses at 6 Months (Study IM101029)



IM101-029

Two (2) subjects did not have a baseline weight and as a result, could not be included in the subgroup analyses.

Similarly, for the other co-primary endpoint in this study (physical function), a comparison between abatacept and placebo favored abatacept for each of the major demographic and clinical subgroups.

Quality of Life (SF-36)

Abatacept was significantly more effective than placebo in improving each of the 4 mental and 4 physical dimensions of quality of life at 6 months in TNF-blocking agent inadequate responders. Abatacept was also significantly more effective than placebo in improving the physical and mental component summary scores.

Disease Activity (DAS28)

Improvements in the DAS28 score at 6 months were consistent with the improvements assessed by the ACR variables. Clinically meaningful improvement (defined as change ≥ 1.2 in the DAS 28 score) was observed in a greater proportion of the abatacept group (65%) compared with the placebo group (32%) using CRP for the calculation of DAS28 score. The proportion of subjects with low disease activity (DAS28 score ≤ 3.2) was also higher in subjects receiving abatacept (17%) compared with placebo (3%). Disease remission (DAS28 < 2.6) was achieved in 10% of subjects treated with abatacept compared with 1% of subjects receiving placebo.

Similar results were observed when ESR, rather than CRP, was used to calculate DAS.

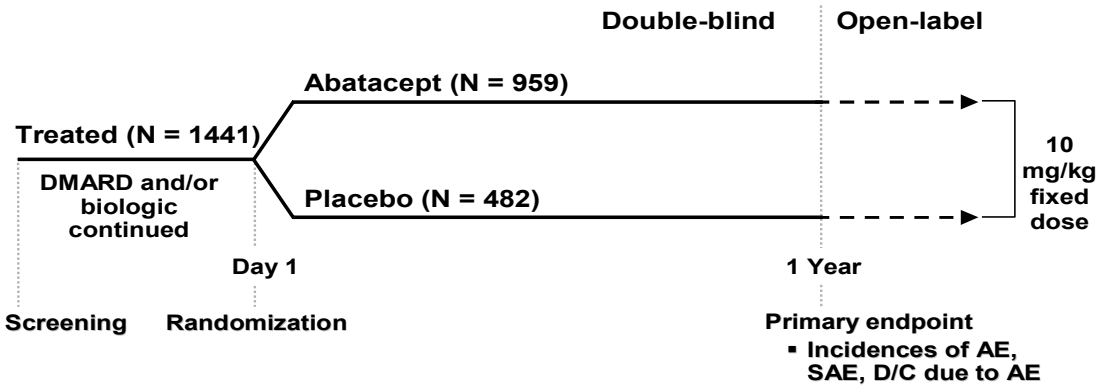
5.5 Other Studies Providing Efficacy Data

5.5.1 Safety and Tolerability in Patients with Active RA with or without Medical Co-Morbidities Receiving DMARDS and/or Biologics (IM101031)

5.5.1.1 Overview

Study IM101031 was a randomized, double-blind, placebo-controlled, parallel-dosing design study with a double-blind treatment period of 12 months (Figure 5.5.1.1). This study was designed with broad inclusion criteria and few exclusion criteria to capture a diverse study population representative of the general population with RA. Male or female patients at least 18 years old with active RA, with or without co-morbidities and currently treated with background non-biologic DMARDs and/or biologic therapy(ies) approved for RA, were eligible for participation. Background RA therapy refers to the regimen of non-biologic or biologic disease-modifying agents used by the patient for treatment of RA at enrollment. Eligible patients had to have an average patient global assessment of disease (VAS) at screening and Day 1 of ≥ 20 mm. Patients with stable renal, endocrine, hepatic, hematologic, gastrointestinal, pulmonary, cardiac, neurologic, or cerebral disease(s) were eligible for participation.

Figure 5.5.1.1: Study IM101031: Patients with or without Co-Morbidities and Currently Treated with Background Non-Biologic DMARDs and/or Biologic Therapy(ies) Approved For RA



Changes in DMARD therapy allowed after 3 months

IM101-031

Prior to study participation, patients must have been treated with a non-biologic DMARD, biologic RA therapy, or their combination for at least 3 months and with a stable regimen for 28 days prior to Day 1. Patients were maintained on their background RA therapy at the dose(s) they were receiving at the time of randomization. Stable, low-dose oral corticosteroids (10 mg/day or less for at least 25 of 28 days prior to Day 1)) and/or stable doses of non-steroidal anti-inflammatory drugs (NSAIDs) including aspirin (ASA) were allowed.

Adjustments in background RA therapy and corticosteroids were not permitted during the first 3 months of the double-blind period (unless due to toxicity).

5.5.1.2 Efficacy Endpoints

The main objective of this study was to measure safety and tolerability of abatacept in patients with active RA with or without medical co-morbidities and receiving DMARDS

and/or biologics. Exploratory efficacy endpoints in this study were change in physical function (HAQ-DI), Patient Global Assessment of Disease Activity, Patient Global Assessment of Pain, and Physician Global Assessment of Disease Activity. Assessments of these factors were made prior to dosing on Days 1 (baseline), 85, 169, 253, and 365. The number of subjects evaluated for efficacy was less than the number of subjects randomized due to the exclusion of 16 patients from the 1 site as described in Section 5.3 (Analytical Methods). Other ACR components (tender and swollen joints) were not assessed and ACR response rates were not determined.

5.5.1.3 Patient Disposition

A greater proportion of patients in the abatacept group (87%) completed 365 days of treatment compared with the placebo group (82%). More patients in the placebo group (9%) discontinued for lack of efficacy compared with the abatacept group (3%). Adverse events led to discontinuation for 5% of patients in the abatacept group and 4% of patients in the placebo group.

5.5.1.4 Demographic Characteristics

Demographic characteristics were similar for the abatacept- and placebo-treatment groups. The majority of patients were Caucasian (85.0%) and female (82.4%), with a mean age of 52 years. Patients were located in the following geographic regions: North America (42.7%), South America (27.4%), Europe (19.5%), and the rest of the world (10.4%).

5.5.1.5 Clinical Characteristics

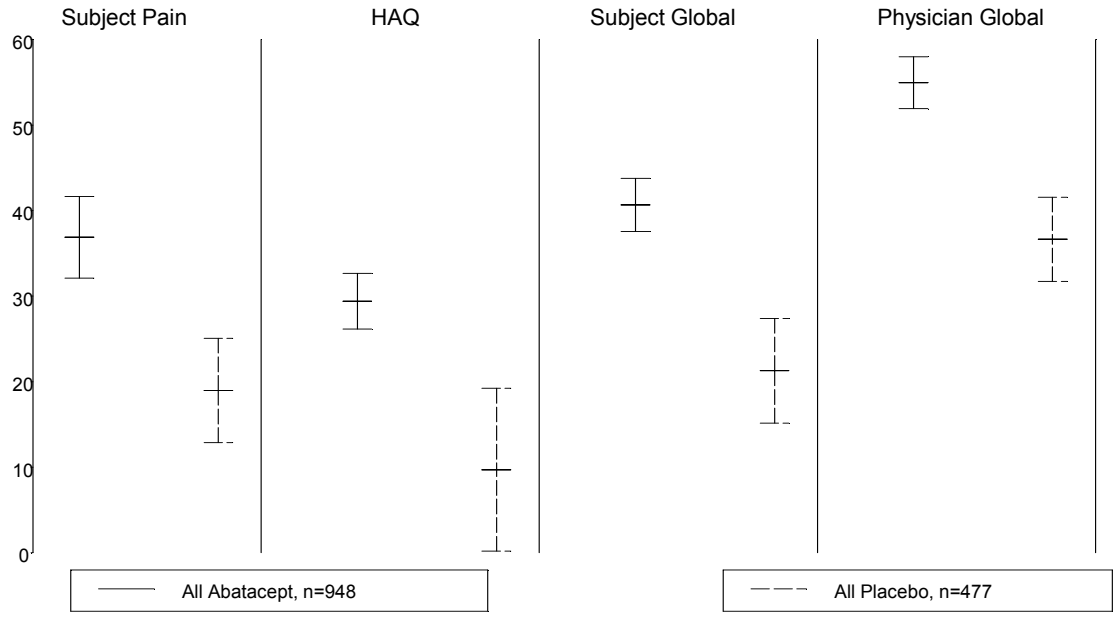
Baseline clinical characteristics also were similar for the abatacept- and placebo-treatment groups. Patients had a mean duration of RA of approximately 10 years. Mean patient pain, patient global, and physician global VAS scores for the entire study population were 61.3, 60.7, and 57.9, respectively, and the mean HAQ disability index was 1.5.

5.5.1.6 Efficacy

Percentage Improvement from Baseline of Efficacy Measures in All Patients at Day 365

Mean percent improvements for each of these variables were numerically larger in the abatacept group than in the placebo group. While statistical significance testing was not performed, the 95% CIs for the abatacept group and the placebo group do not overlap, suggesting that the differences between the groups are robust. Figure 5.5.1.6A summarizes the mean percent improvement from baseline with corresponding 95% CIs at Day 365 for each of the 4 disease outcome variables.

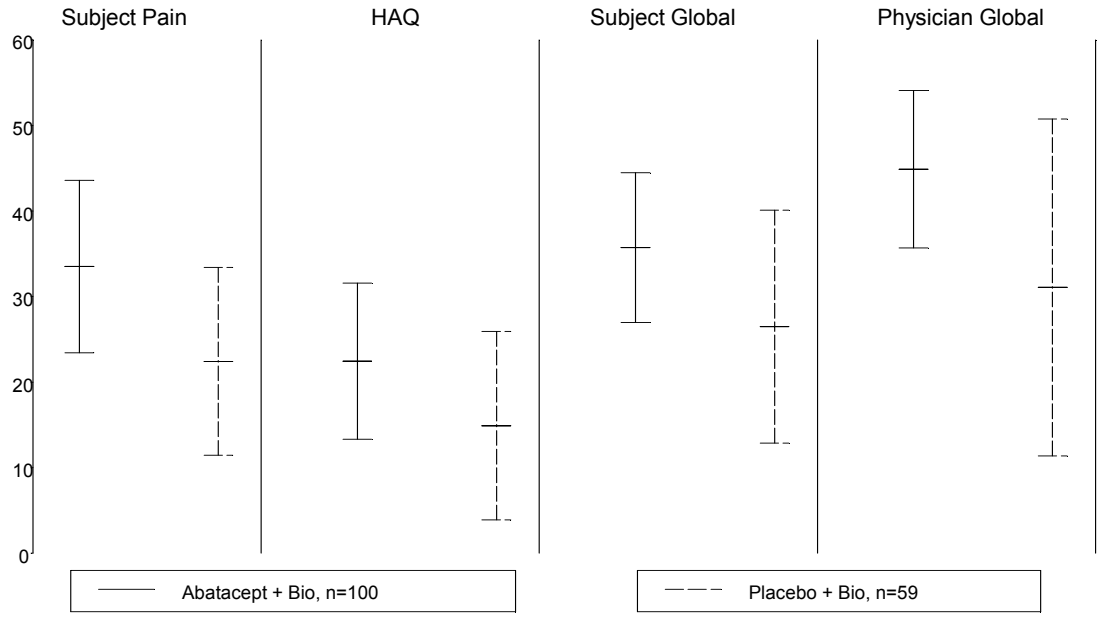
Figure 5.5.1.6A: Mean Percent Improvement from Baseline in ACR Core Components in All Patients on Day 365 with 95% Confidence Intervals (IM101031)



Percentage Improvement from Baseline in Patients Receiving Background Biologic Therapy for RA

Approximately 10% of patients were receiving biologic therapy for RA at the time of randomization, and most continued to receive these agents during the double-blind period. Improvements in efficacy measures with abatacept, relative to placebo, were relatively small in these patients (Figures 5.5.1.6B).

Figure 5.5.1.6B: Mean Percent Improvement from Baseline in Select ACR Core Components in Patients on a Background of Biologics on Day 365 with 95% Confidence Intervals (IM101031)



5.5.2 Study in RA Patients with Inadequate Response to Etanercept (IM101101)

Study IM101101 provided preliminary clinical efficacy data on the combination of abatacept 2 mg/kg and etanercept in a different patient population than those in Studies IM103002 and IM101100. Because this was an initial pilot study combining the use of 2 biologics, only the 2 mg/kg dose was used.

Administration of abatacept (2 mg/kg) with etanercept in patients with an inadequate response to etanercept treatment resulted in trends in improvement in modified ACR response rates, mHAQ and SF-36 compared with the placebo group although the results were not statistically significant. There was no consistent evidence of efficacy with this dose of abatacept in combination with etanercept in this population. The magnitude of the changes was similar to that observed in the abatacept 2 mg/kg group in Study IM101100. Modified ACR 20 responses at 6 months are presented in Supplemental Table S.5.5.2.

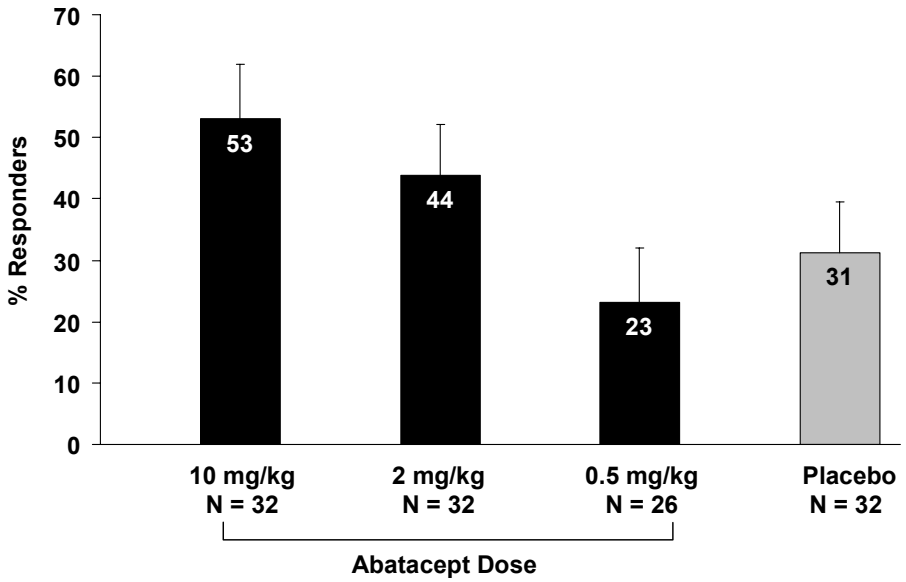
5.5.3 Study in Patients with Active RA Who Failed at Least One DMARD (IM103002)

IM103002 was a pilot, multi-center, randomized, double-blind, placebo-controlled, Phase II, dose-finding study evaluating the safety, clinical activity and immunogenicity of multiple doses of abatacept. Abatacept was administered during Weeks 0, 2, 4, and 8 at doses of 0.5, 2, and 10 mg/kg IV to patients with active RA, who had all other DMARDs discontinued prior to the first dose of study medication. A total of 122 patients were randomized and treated with either abatacept (n = 90) or placebo (n = 32).

The primary outcome measure was the proportion of patients achieving an ACR 20 response at Month 3. A greater proportion of abatacept patients achieved an ACR 20, 50, and 70 response with 2 and 10 mg/kg abatacept compared with 0.5 mg/kg abatacept and placebo. There were modest trends for increasing response with increasing dose. No significance testing was performed in this pilot study.

By Month 6, 112 days after the last dose of study medication, there were no differences in the ACR response rates in patients treated with abatacept or placebo. Notably, after discontinuation of abatacept there was no sign of rebound in RA activity, by both clinical and laboratory assessments, at Month 6. As discussed in Section 4.3 (Dose Selection), both the 2 and 10 mg/kg doses were carried forward into a definitive dose-ranging study (IM101100).

Figure 5.5.3: ACR 20 Response at Month 3



SEM shown; LOCF analysis for ACR responses

IM103-002

5.6 Consistency of Efficacy Results Across Patient Populations

Efficacy outcomes were evaluated across the 3 principal efficacy trials (IM101100, IM101102, IM101029) and the large safety study (IM101031). For the IM101100 trial, only the abatacept 10 mg/kg and placebo group were compared with the treatment arms of the other trials. These trials were conducted in patients with similar demographic but different disease characteristics and medical history, and located in different geographic regions. The study populations differed in that:

1) the severity and duration of RA disease was greater in IM101029 compared with the other 3 trials;
2) all patients in IM101029 and approximately 10% of patients in IM101031 had a history of TNF-blocking agent use whereas few patients had used TNF-blocking agents in IM101100 and IM101102;
3) IM101031 was designed to be more representative of patients with RA in clinical practice, and enrolled patients with or without co-morbid conditions using a greater

number of both non-biologic and biologic background DMARDs at randomization than the other 3 trials;

4) patients in IM101100, IM101102, and IM101029 were not allowed to make adjustments or modifications to background DMARDs during the first 6 months of the double-blind period whereas patients in IM101031 were allowed to make such adjustments after 85 days; and
5) more patients were recruited from North America in IM101029 compared with patients in the other 3 trials.

Despite the differences in study populations noted above, abatacept was effective in all 4 trials, the magnitude of improvement in efficacy measures for abatacept-treated patients was similar across the studies, and robust efficacy was observed as measured by the ACR core components and all domains of the HAQ/mHAQ-DI and SF-36, including the physical and mental component summary scores. Consistent efficacy of abatacept in improving signs and symptoms of RA as well as physical function was seen in patients with active RA who had an inadequate response to MTX or TNF-blocking agents (IM101100, IM101102 and IM101029). Consistent efficacy of abatacept in improving health-related quality of life measures was also seen across study populations, where evaluated (IM101100, IM101102 and IM101029).

5.6.1 Consistency in Improvement of Signs and Symptoms of RA

ACR 20, 50 and 70 response rates are available at 6 and 12 months in patients with an inadequate response to MTX (Studies IM101100 and IM101102) and at 6 months in patients with an inadequate response to TNF-blocking agents (Study IM101029). Statistically significant differences in ACR response rates were observed between the abatacept and placebo arms of each study. The magnitude of improvement in ACR response rates was similar in these 3 studies, with the difference from placebo at 6 months ranging from about 26% to 31% (ACR 20), 17% to 25% (ACR 50), and 9% to 15% (ACR 70) (Table 5.6.1A). Similar consistency across studies was observed at 12 months.

Table 5.6.1A: Proportion of Patients with ACR 20, 50, and 70 Responses at 6 Months

	IM101102		IM101100		IM101029	
	Abatacept[a] (N = 424)	Placebo (N = 214)	Abatacept[a,b] (N = 115)	Placebo (N = 119)	Abatacept[a] (N = 256)	Placebo (N = 133)
ACR 20	67.9%	39.7%	60.9%	35.3%	50.4%	19.5%
ACR 50	39.9%	16.8%	36.5%	11.8%	20.3%	3.8%
ACR 70	19.8%	6.5%	16.5%	1.7%	10.2%	1.5%

Population: All randomized and treated patients.

[a] Differences between abatacept and placebo were statistically significant ($p < 0.05$).

[b] 10 mg/kg abatacept treatment group

Abatacept rapidly induced improvement in signs and symptoms, as measured by ACR response rates in all 3 studies. Statistically significant differences in ACR 20 responses compared with placebo were observed within 15 days of treatment with abatacept for Studies IM101102 and IM101029 (the time of the first efficacy assessment), and within 60 days of treatment (ie, following 3 infusions) for Study IM101100. The difference in ACR 20 response rates remained significant at all time points through 6 months (and through 12 months in IM101100 and IM101102).

Abatacept-induced improvements in signs and symptoms of disease, as assessed by DAS28 (CRP or ESR), were also similar where evaluated (IM101100, IM101102, and IM101029). Clinically meaningful improvement (defined as change in DAS28 ≥ 1.2) was observed in a greater proportion of patients in the abatacept groups compared with the placebo groups in all 3 studies (Table 5.6.1B). The magnitude of difference between the proportions of patients (abatacept vs placebo) with low disease activity and remission ranged from 14 to 21% and 9 to 19%, respectively.

Table 5.6.1B: Proportion of Patients with Clinically Meaningful Improvement, Low Disease, or in Remission (as Defined by DAS28 [CRP]) at 6 Months

	IM101102		IM101100[a]		IM101029	
	Abatacept[b] (N = 424)	Placebo (N = 214)	Abatacept[b] (N = 115)	Placebo (N = 119)	Abatacept[b] (N = 256)	Placebo (N = 133)
n	418	211	105	114	251	130
Improvement (Change DAS28 ≥ 1.2)	339 (81.1%)	103 (48.8%)	76 (72.4%)	53 (46.5%)	164 (65.3%)	41 (31.5%)
Low Disease (DAS28 ≤ 3.2)	126 (30.1%)	21 (10.0%)	44 (41.9%)	24 (21.1%)	43 (17.1%)	4 (3.1%)
Remission (DAS28 < 2.6)	62 (14.8%)	6 (2.8%)	29 (27.6%)	10 (8.8%)	25 (10.0%)	1 (0.8%)

N = number randomized and treated; n = number with baseline and 6 month values

[a] 10 mg/kg abatacept treatment group shown

[b] Difference between abatacept and placebo in change from baseline in DAS28 (CRP) was evaluated in IM101102 (6 and 12 Months) and IM101029 (6 months). The results were significant ($p<0.001$) for all comparisons.

5.6.2 Consistency in Improvement of Physical Function

Physical function was evaluated using the HAQ/mHAQ-DI at 6 and 12 months in Studies IM101100, IM101102, and IM101031. In IM101029, physical function was evaluated at 6 months (end of double-blind period). A larger proportion of patients receiving abatacept achieved a clinically meaningful HAQ/mHAQ response (reduction in baseline HAQ-DI ≥ 0.3) compared with placebo in all studies (Table 5.6.2). Statistically significant differences between the proportions of patients achieving a HAQ response in the abatacept vs placebo treatment arms were observed by 6 months in Studies IM101100, IM101102, IM101029, and IM101031 and were maintained at 12 months (IM101100, IM101102, and IM101031).

Table 5.6.2: Proportion of Patients with Clinically Meaningful Change from Baseline in HAQ/mHAQ (Reduction of ≥ 0.3) in Controlled Studies

Protocol	Time	Abatacept	Placebo	P value
IM101102		(N=424)	(N=214)	
	Day 169	61.1%	45.3%	<0.001
	Day 365	63.7%	39.3%	<0.001
IM101100		(N = 115)	(N = 119)	
	Day 180	47.0%[a]	27.7%	0.004
	Day 360	38.3%[a]	20.2%	0.004
IM101029		(N=256)	(N=133)	
	Day 169	47.3%	23.3%	<0.001
IM101031[b]		(N = 948)	(N = 477)	
	Day 169	50.0%	33.8%	<0.001
	Day 365	47.3%	34.6%	<0.001

Population: All randomized and treated patients.

[a] 10 mg/kg abatacept treatment group

[b] Post-hoc analysis, shown for comparison

5.6.3 Consistency in Quality of Life Outcomes

SF-36 data are available for Studies IM101100 and IM101102 at 6 and 12 months and for Study IM101029 at 6 months. In all 3 studies, there was a statistically significant improvement from baseline with abatacept (10 mg/kg or fixed dose) compared with placebo in all 4 mental and 4 physical domains of the SF-36, and both the mental and physical component summary scores at all time points. At 6 months, the difference from placebo in the adjusted mean change from baseline ranged from approximately 4 to 5.5 (PCS) and approximately 2.4 to 3.3 (MCS)

5.6.4 Conclusions

Abatacept demonstrated robust efficacy across studies for all measures studied, including reduction in the signs and symptoms of RA, improvement in physical function, inhibition of the progression of structural damage, and improvement in health-related quality of life.

Moreover, abatacept's effects demonstrated a high degree of internal consistency for each group of measures, regardless of endpoint definition or duration of treatment:

- Signs and Symptoms: Abatacept treatment resulted in improvements in ACR 20, 50, and 70 at 6 and 12 months, as well as positive results for MCR.
- Physical Function: Abatacept treatment resulted in improvement in the HAQ-DI for a greater proportion of patients regardless of the responder cut-off points (0.22, 0.3, 0.5, and 0.8 HAQ-DI units).
- Structural Damage: Abatacept treatment resulted in the inhibition of the progression of structural damage as evidenced by erosion, JSN and total scores.
- Quality of Life: Abatacept treatment resulted in improvement in each of the 4 mental and 4 physical domains of the SF-36, as well as positive results in the mental and physical component summaries.
- Subgroup Analysis: Abatacept's effects were also consistent in all subgroups of patients categorized by relevant intrinsic or extrinsic factors.
- Maintenance of Effect: Abatacept treatment resulted in improvement in physical function and signs and symptoms of RA that were sustained for up to 3 years of treatment.

6 CLINICAL SAFETY

Clinical safety data from the abatacept development program in RA are presented here in Section 6. The organization and content of this section, and the methods for safety assessment, are described in the following pages.

Organization and Content

The presentation of clinical safety in this section is divided into 3 parts:

- General safety, including adverse events, serious adverse events, adverse events resulting in discontinuation, and deaths;
- Adverse events of special interest, including infection, malignancy, autoimmunity, peri-infusional safety, and immunogenicity; and
- Safety in subpopulations or special settings, including use in combination with existing biologic RA therapy and use as monotherapy.

To simplify the presentation and interpretation of data, and assist in the assessment of uncommon events, data have been integrated from the double-blind, controlled portions

of the 5 RA studies (IM101100, IM101101, IM101102, IM101029, and IM101031) that were at least 6 months in duration, blinded and placebo controlled. Safety data collected during the open-label, uncontrolled periods of the above-mentioned 5 studies were also integrated in a separate data set. Safety data from the remaining RA trial, a 3-month study in patients treated with abatacept as monotherapy (IM103002), are presented separately as part of the discussion of safety in special settings.

The presentations of safety data in this section are based on information submitted to the US Food and Drug Administration (FDA) in the Clinical Module of the BLA in December 2004 or in the 4-Month Safety Update in April 2005. These presentations include data from both the double-blind, controlled study periods and the open-label, uncontrolled study periods. The presentation of data from the open-label study periods is focused on adverse events, such as deaths, serious infections, and malignancy that are serious, uncommon, and may have a long latency period.

The safety presentations generally include both patients treated with non-biologic DMARD background therapy, who represent approximately 90% of patients studied, as well as a smaller number treated with biologic background therapy. The safety experience in the latter group is also presented separately as part of the discussion of safety in special settings.

Methods for Safety Assessment

Safety and tolerability were assessed through the collection of adverse events (AEs) reported in clinical trials, measurement of vital signs, and laboratory monitoring. Infections, malignancies, potential autoimmune disorders, and infusion reactions were identified as AEs of special interest early in the development program and were the subject of additional prospective data collection, except for infusion reactions.

All AEs for the 5 principal RA studies were coded and grouped into Preferred Terms by System Organ Class (SOC), using the Medical Dictionary for Regulatory Activities (MedDRA). The SOCs correspond to body system (eg, vascular, gastrointestinal) or class of event (eg, infections and infestations, procedural complication).

The presentations of data from the double-blind study period generally include comparisons of abatacept and placebo. When interpreting these comparisons, it should be

remembered that roughly twice as many patients were treated with abatacept as with placebo.

Several methods were used to distinguish more severe or important adverse events:

- Events were classified as serious or non-serious by the investigator based on regulatory criteria. A serious adverse event (SAE) was defined as any AE that met any of the following criteria: was fatal, was life threatening, resulted in or prolonged hospitalization, resulted in persistent or significant disability or incapacity, was cancer, was a congenital anomaly/birth defect, resulted in an overdose, resulted in the development of drug dependency or drug abuse, or was an important medical event.
- Events were classified as mild, moderate, severe, or very severe by the investigator according to the following pre-specified definitions of intensity:
  - Mild (Grade I): Awareness of event but easily tolerated;
  - Moderate (Grade II): Discomfort enough to cause some interference with usual activity;
  - Severe (Grade III): Inability to carry out usual activity; and
  - Very Severe (Grade IV): Debilitating, significantly incapacitates subject despite symptomatic therapy.

Tabulations of AEs included events occurring up to 56 days following the last dose of study medication. The follow-up period is approximately 5 half-lives of the drug in the peripheral blood.

6.1 Extent of Exposure

A total of 1955 patients were treated with abatacept during the double-blind study periods. Approximately 90% of these patients (1765/1955) were treated with 10 mg/kg or a dose approximating 10 mg/kg. The remainder (190 patients) were treated with 2 mg/kg.

The mean duration of exposure during the double-blind study period was 10.5 months; 68% of patients were exposed to abatacept for at least 12 months. The total abatacept population in the double-blind period was 1688 person-years.

For the 2688 patients exposed in the cumulative double-blind and open label experience, the total exposure is 3827 person-years. In this data set, 55% of patients were exposed for

18 months or more, and 6% were exposed for 3 years or more. The mean cumulative exposure was 17.3 months.

6.2 General Safety Profile in Double-blind Studies of Abatacept vs Placebo

Most patients experienced at least one AE during the double-blind study periods, but few of these events resulted in discontinuation from the studies. A small increase in the proportion of patients experiencing AEs, SAEs, and discontinuation due to AEs was observed with abatacept relative to placebo (Table 6.2). This difference was largely due to a small increase in the frequency of infectious adverse events with abatacept. Infectious AEs are discussed further in Section 6.2.6.1 of this document. Deaths were infrequent and occurred in similar frequency in patients treated with abatacept (9/1955; 0.5%) and placebo (6/989; 0.6%). One additional death was reported after the database lock for the double-blind period (see Table 6.2.4) and is not reflected in Table 6.2.

Table 6.2: Overview of Adverse Events in Double-Blind, Controlled Study Periods: All Patients

	Number (%) of Patients		
Adverse Events	Abatacept (N=1955)	Placebo (N=989)	Total (N=2944)
Deaths	9 (0.5)	6 (0.6)	15 (0.5)
SAEs	266 (13.6)	122 (12.3)	388 (13.2)
Discontinuation due to SAEs	53 (2.7)	16 (1.6)	69 (2.3)
Related SAEs	58 (3.0)	17 (1.7)	75 (2.5)
AEs	1736 (88.8)	840 (84.9)	2576 (87.5)
Discontinuation due to AEs	107 (5.5)	39 (3.9)	146 (5.0)
Related AEs	1013 (51.8)	456 (46.1)	1469 (49.9)

Population: Treated patients.
SAEs include hospitalizations for elective surgical procedures.
Related events defined as Certain, Probable, Possible, or Missing.
MEDDRA VERSION: 7.0

6.2.1 Common Adverse Events

The most frequently reported AEs were headache (abatacept: 18.2%; placebo: 12.6%), upper respiratory tract infection (abatacept: 12.7%; placebo: 12.0%), and nasopharyngitis (abatacept: 11.5%; placebo: 9.1%) (Table 6.2.1). In addition to headache and nasopharyngitis, dizziness (abatacept: 9.4%; placebo: 7.0%), dyspepsia (abatacept: 6.4%;

placebo: 4.2%), and hypertension (abatacept: 6.6%; placebo: 4.3%) were reported ≥ 2.0% more commonly with abatacept than with placebo. Measured blood pressures were similar for abatacept- and placebo-treated patients throughout the double-blind study periods.

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Table 6.2.1:
Most Frequently Reported (At Least 5% of Patients in Any Therapy Group) Adverse Events in Double-Blind, Controlled Study Periods: All Patients

SYSTEM ORGAN CLASS (SOC) (%) PREFERRED TERM (PT) (%)	Abatacept N = 1955	Placebo N = 989
TOTAL PATIENTS WITH AE	1736 (88.8)	840 (84.9)
INFECTIONS AND INFESTATIONS	1051 (53.8)	478 (48.3)
UPPER RESPIRATORY TRACT INFECTION	248 (12.7)	119 (12.0)
NASOPHARYNGITIS	225 (11.5)	90 (9.1)
SINUSITIS	125 (6.4)	68 (6.9)
URINARY TRACT INFECTION	113 (5.8)	45 (4.6)
INFLUENZA	111 (5.7)	52 (5.3)
BRONCHITIS	101 (5.2)	45 (4.6)
GASTROINTESTINAL DISORDERS	750 (38.4)	351 (35.5)
NAUSEA	224 (11.5)	105 (10.6)
DIARRHOEA	189 (9.7)	93 (9.4)
DYSPEPSIA	126 (6.4)	42 (4.2)
NERVOUS SYSTEM DISORDERS	623 (31.9)	268 (27.1)
HEADACHE	356 (18.2)	125 (12.6)
DIZZINESS	183 (9.4)	69 (7.0)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	589 (30.1)	304 (30.7)
RHEUMATOID ARTHRITIS	157 (8.0)	87 (8.8)
BACK PAIN	144 (7.4)	58 (5.9)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	443 (22.7)	192 (19.4)
COUGH	162 (8.3)	71 (7.2)

Population: Treated patients.
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Table 6.2.1:
Most Frequently Reported (At Least 5% of Patients in Any Therapy Group) Adverse Events in Double-Blind, Controlled Study Periods: All Patients

SYSTEM ORGAN CLASS (SOC) (%) PREFERRED TERM (PT) (%)	Abatacept N = 1955	Placebo N = 989
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	430 (22.0)	240 (24.3)
FATIGUE	126 (6.4)	68 (6.9)
VASCULAR DISORDERS	252 (12.9)	93 (9.4)
HYPERTENSION	129 (6.6)	43 (4.3)

Population: Treated patients.
MEDDRA VERSION: 7
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6.2.2 Serious Adverse Events

SAEs were reported by more abatacept-treated patients (13.6%) than placebo-treated patients (12.3%) (Table 6.2.2). SAEs in the infections and infestations SOC were reported in 3.0% of abatacept-treated patients and 1.9% of placebo-treated patients. Infections are discussed further in Section 6.2.6.1 (Infections). There were no appreciable differences between abatacept- and placebo-treated patients in the frequency of SAEs coding to other SOCs.

The most common SAEs (≥ 0.5%) by preferred term for both abatacept- and placebo-treated patients, respectively, were RA (1.9% in both groups), pneumonia (0.5% in both groups), chest pain (0.6% vs 0.4%), basal cell carcinoma (0.5% vs 0.3%), and congestive cardiac failure (0.2% vs 0.5%). Most other SAEs were reported by 1 or 2 patients in either treatment group.

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Table 6.2.2:
Most Frequently Reported (At Least 0.3% of Patients in Any Therapy Group) Serious Adverse Events in Double-Blind, Controlled Study Periods: All Patients

SYSTEM ORGAN CLASS (SOC) (%) PREFERRED TERM (PT) (%)	Abatacept N = 1955	Placebo N = 989
TOTAL PATIENTS WITH SAE	266 (13.6)	122 (12.3)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	59 (3.0)	37 (3.7)
RHEUMATOID ARTHRITIS	37 (1.9)	19 (1.9)
LOCALISED OSTEOARTHRITIS	3 (0.2)	3 (0.3)
ARTHROPATHY	1 (<0.1)	3 (0.3)
INFECTIONS AND INFESTATIONS	58 (3.0)	19 (1.9)
PNEUMONIA	9 (0.5)	5 (0.5)
SEPSIS	1 (<0.1)	3 (0.3)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	28 (1.4)	11 (1.1)
BASAL CELL CARCINOMA	9 (0.5)	3 (0.3)
GASTROINTESTINAL DISORDERS	23 (1.2)	13 (1.3)
GASTROINTESTINAL HAEMORRHAGE	0	3 (0.3)
CARDIAC DISORDERS	18 (0.9)	17 (1.7)
CARDIAC FAILURE CONGESTIVE	4 (0.2)	5 (0.5)
ATRIAL FIBRILLATION	1 (<0.1)	3 (0.3)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	16 (0.8)	9 (0.9)
CHEST PAIN	11 (0.6)	4 (0.4)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	16 (0.8)	6 (0.6)
DYSPNOEA	3 (0.2)	3 (0.3)

Population: Treated patients.
MEDDRA VERSION: 7
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Table 6.2.2:
Most Frequently Reported (At Least 0.3% of Patients in Any Therapy Group) Serious Adverse Events in Double-Blind, Controlled Study Periods: All Patients

SYSTEM ORGAN CLASS (SOC) (%) PREFERRED TERM (PT) (%)	Abatacept N = 1955	Placebo N = 989
HEPATOBILIARY DISORDERS	6 (0.3)	3 (0.3)
CHOLELITHIASIS	5 (0.3)	3 (0.3)
EYE DISORDERS	2 (0.1)	3 (0.3)
CATARACT	1 (<0.1)	3 (0.3)

Population: Treated patients.

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6.2.3 Adverse Events that Led to Discontinuation of Study Treatment

Adverse events resulting in discontinuation of study treatment occurred in 5.5% of abatacept-treated patients and 3.9% of placebo-treated patients during the double-blind study periods (Table 6.2.3). No specific AE led to discontinuation in more than 0.2% of patients, with the exception of back pain in 0.3% of placebo-treated patients. Infections were the most common reason for study discontinuation and were reported by similar proportions of patients in both treatment groups (1.2% vs 1.0%).

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Table 6.2.3
Adverse Events that Led to Discontinuation in Two or More Patients in Double-Blind, Controlled Study Periods: All Patients

SYSTEM ORGAN CLASS (SOC) (%) PREFERRED TERM (PT) (%)	Abatacept N = 1955	Placebo N = 989
TOTAL PATIENTS WITH AE	107 (5.5)	39 (3.9)
INFECTIONS AND INFESTATIONS	24 (1.2)	10 (1.0)
PNEUMONIA	4 (0.2)	1 (0.1)
LOCALISED INFECTION	3 (0.2)	0
BRONCHITIS	2 (0.1)	2 (0.2)
SEPSIS	1 (<0.1)	2 (0.2)
NERVOUS SYSTEM DISORDERS	14 (0.7)	4 (0.4)
DIZZINESS	3 (0.2)	0
HEADACHE	2 (0.1)	1 (0.1)
TRANSIENT ISCHAEMIC ATTACK	2 (0.1)	1 (0.1)
CARDIAC DISORDERS	13 (0.7)	2 (0.2)
CARDIAC FAILURE CONGESTIVE	3 (0.2)	0
CORONARY ARTERY DISEASE	2 (0.1)	0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	10 (0.5)	6 (0.6)
ASTHENIA	3 (0.2)	0
CHEST PAIN	2 (0.1)	1 (0.1)
PYREXIA	2 (0.1)	1 (0.1)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	10 (0.5)	4 (0.4)
RASH	3 (0.2)	1 (0.1)
PSORIASIS	2 (0.1)	0

Population: Treated patients.
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Table 6.2.3:
Adverse Events that Led to Discontinuation in Two or More Patients in Double-Blind, Controlled Study Periods

SYSTEM ORGAN CLASS (SOC) (%) PREFERRED TERM (PT) (%)	Abatacept N = 1955	Placebo N = 989
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	10 (0.5)	3 (0.3)
LUNG NEOPLASM MALIGNANT	2 (0.1)	0
ENDOMETRIAL CANCER	0	2 (0.2)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	10 (0.5)	3 (0.3)
COUGH	3 (0.2)	0
DYSPNOEA	2 (0.1)	2 (0.2)
PLEURISY	2 (0.1)	0
INVESTIGATIONS	7 (0.4)	2 (0.2)
GAMMA-GLUTAMYLTRANSFERASE INCREASED	2 (0.1)	0
BLOOD AND LYMPHATIC SYSTEM DISORDERS	7 (0.4)	0
LEUKOPENIA	3 (0.2)	0
VASCULAR DISORDERS	6 (0.3)	1 (0.1)
HYPOTENSION	2 (0.1)	0
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	5 (0.3)	6 (0.6)
MYALGIA	2 (0.1)	0
BACK PAIN	1 (<0.1)	3 (0.3)
IMMUNE SYSTEM DISORDERS	3 (0.2)	1 (0.1)
HYPERSENSITIVITY	2 (0.1)	1 (0.1)
PSYCHIATRIC DISORDERS	3 (0.2)	1 (0.1)
DEPRESSION	2 (0.1)	0

Population: Treated patients.
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6.2.4 Deaths

The frequency of death was comparable in the abatacept and placebo groups during the double-blind study periods (0.5% and 0.6%, respectively) (Table 6.2.4). The causes of death were similar, with cardiovascular disease predominating in both treatment groups.

Table 6.2.4: Deaths in the Double-Blind, Controlled Study Periods

Patient Number (Age/Gender)	Onset Day	Cause of Death (Preferred Term)	Relationship (Investigator Assessment)
Abatacept (N = 1955)			
IM101031-21-9 (58/F)	17	Hypertensive heart disease	Unlikely related
IM101029-102-3 (67/M)	30	Cardiac failure congestive	Unrelated
IM101031-150-10 (77/F)	101	Sudden death	Unlikely related
IM101029-124-10 (70/F)[a]	198[b]	Bile duct cancer	Possibly related
IM101031-118-21 (49/M)	262	Death (cause unknown)	Unrelated
IM101031-99-18 (56/F)	294	Coronary artery atherosclerosis, Myocardial ischemia	Unrelated Unrelated
IM101100-28-2 (61/F)	259 271	Chest pain Death	Unlikely related Unrelated
IM101031-197-6 (49/M)	306	Burns third degree Cardiac arrest	Unrelated Unrelated
IM101100-35-2 (83/M)	332	Lung neoplasm malignant	Unrelated
IM101102-136-5 (53/M)	346	Bronchopulmonary aspergillosis	Possibly related
Placebo (N = 989)			
IM101031-38-3 (60/F)	195	Death (cause unknown)	Unrelated
IM101100-24-6 (55/F)	231	Endometrial cancer	Unrelated
IM101031-108-16 (61/F)	321 339	Candidiasis Pneumocystis carinii HIV test positive	Possibly related Possibly related Unrelated

Table 6.2.4: Deaths in the Double-Blind, Controlled Study Periods

Patient Number (Age/Gender)	Onset Day	Cause of Death (Preferred Term)	Relationship (Investigator Assessment)
IM101102-96-11		Multiorgan failure	Unlikely related
(77/M)	342	Pneumonia	Unlikely related
		Sepsis	Unlikely related
IM101031-109-36	364	Cerebrovascular accident	
(36/M)	365	Cardiac arrest	Unlikely related
IM101031-78-30			
(58/F)	376	Myocardial infarction	Unrelated

F = female, M = male

[a] Reported after double-blind database lock

[b] 4 months after discontinuation of study drug, which was outside of the data counting rules. Therefore, the subject does not show up on summary data listings.

6.2.5 General Safety Profile in Open-Label, Uncontrolled Periods

The most common AEs reported during open-label, uncontrolled treatment with abatacept were similar to those reported in the double-blind period (RA, upper respiratory tract infection, nasopharyngitis, headache, and bronchitis). No new or unexpected AEs were observed.

The incidence rates of serious adverse events remained stable during the open-label, uncontrolled study periods (Table 6.2.5A). Details about infections and malignancies during the open-label study periods are provided in Section 6.2.6 (Adverse Events of Special Interest).

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Table 6.2.5A:
Incidence Rates by Six-Month Intervals for SAEs by All Abatacept Exposure with CIs:
All Subjects

PREFERRED TERM (PT) (95% Poisson CI on Incidence Rate)	All Abatacept Exposure: Subjects With Event (Rate: Incidence/100 person-yrs) Days 1-180	Days 181-360	Days 361-540	Days 541-720	Days 721-900	Days 901-last
TOTAL EXPOSURE (PERSON-YEARS)	1285.28	1031.85	795.09	399.37	117.18	198.46
ALL SAEs	229 (18.6) (16.2, 21.1)	201 (20.3) (17.6, 23.3)	124 (16.2) (13.4, 19.3)	45 (11.6) (8.45, 15.5)	21 (18.7) (11.6, 28.6)	33 (18.5) (12.7, 26.0)

Population: Treated subjects.
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Ten (10) of 2285 patients in the open-label period died (0.4%). As in the double-blind period, cardiovascular disease was the most common cause of death.

Table 6.2.5B: Deaths in Open-Label, Uncontrolled Study Periods Through the 4-Month Safety Update

Patient Number (Age/Gender)	Onset Day	Cause of Death (Preferred Term)	Relationship (Investigator Assessment)
IM101031-71-6 62/F	404	Small cell lung cancer	Unlikely related
IM101031-58-11 61/M	429	Cardiac arrest	Unlikely related
IM101031-102-18 73/F	454	Victim of homicide	Unrelated
IM101100-21-1 61/F	484	Lung adenocarcinoma	Unlikely related
IM101031-176-2 78/F	505	Leukopenia, Death	Possibly related
IM101031-104-14 43/F	526	Cardiac failure congestive, valve suture complication	Unrelated
IM101102-81-1 65 / F	572	Myocardial ischaemia	Unrelated
IM101100-76-4 81/M	649	Cardiopulmonary failure	Unrelated
IM101100-41-8 65/M	1051	Dyspnea	Unlikely related
IM101101-14-2 61/F	1100	Diffuse large B-cell lymphoma	Possibly related

6.2.6 Adverse Events of Special Interest

RA patients are more likely to develop infections, malignancies, and other autoimmune diseases. Numerous studies have shown an increased risk of infection and cancer, specifically lymphomas and other hematologic neoplasms, in patients with RA.[36,37,38,39] Overall, it seems that the risk for the development of any malignancy in patients with RA is not significantly different from that seen in the general population.[40,41,42,43,44] However, patients with RA appear to have increased risks for lung cancer[42,43,44] and lymphoproliferative disorders,[40,41,42,43,44,45,46] and a decreased risk for intestinal

cancers.[42,43,44] Most studies have shown that, on average, the risk for patients with RA to develop lymphoma is between 2 and 4 times greater than the risk in the general population.[40,42,43,44,45,46]

This section reviews and discusses AEs and SAEs of particular interest in understanding the safety of abatacept in the target population of patients with RA. These AEs and SAEs are a subset of the overall safety experience that has been presented in Sections 6.2.1 and 6.2.2, and are highlighted here since they may be more common with an agent that modulates the immune response and/or have been observed with existing biologic therapies for RA. The events of interest presented here include infections, malignancies, autoimmune disorders, AEs following infusion of abatacept, and development of anti-abatacept antibodies.

6.2.6.1 Infections

Frequency

A higher proportion of patients treated with abatacept, compared with patients treated with placebo, reported events in the System Organ Class 'infections/infestations' in the double-blind periods (53.8% vs 48.3%). Respiratory tract infections and urinary tract infections were the most common type of infections in both groups (Table 6.2.6.1A).

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Table 6.2.6.1A:
Most Frequently Reported (At Least 1% of Patients in Any Therapy Group) Infections (within SOC) in Double-Blind, Controlled Study Periods: All Patients

PREFERRED TERM (PT) (%)	All Abatacept N = 1955	All Placebo N = 989
TOTAL PATIENTS WITH AE	1051 (53.8)	478 (48.3)
UPPER RESPIRATORY TRACT INFECTION	248 (12.7)	119 (12.0)
NASOPHARYNGITIS	225 (11.5)	90 (9.1)
SINUSITIS	125 (6.4)	68 (6.9)
URINARY TRACT INFECTION	113 (5.8)	45 (4.6)
INFLUENZA	111 (5.7)	52 (5.3)
BRONCHITIS	101 (5.2)	45 (4.6)
PHARYNGITIS	59 (3.0)	27 (2.7)
RHINITIS	53 (2.7)	17 (1.7)
HERPES SIMPLEX	37 (1.9)	10 (1.0)
PNEUMONIA	33 (1.7)	8 (0.8)
GASTROENTERITIS	31 (1.6)	19 (1.9)
HERPES ZOSTER	30 (1.5)	16 (1.6)
TOOTH ABSCESS	28 (1.4)	14 (1.4)
BRONCHITIS ACUTE	28 (1.4)	10 (1.0)
EAR INFECTION	23 (1.2)	8 (0.8)
FUNGAL INFECTION	22 (1.1)	11 (1.1)
CELLULITIS	21 (1.1)	9 (0.9)
CYSTITIS	16 (0.8)	11 (1.1)
FUNGAL SKIN INFECTION	16 (0.8)	10 (1.0)

Population: Treated patients.

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Severity

The severity of infections was assessed using several measures:

- the proportion of patients experiencing an infection reported as serious, by regulatory criteria;
- the proportion of patients experiencing infections of severe or very severe intensity, as determined by the investigator;
- the proportion of patients requiring antibiotic therapy, including IV antibiotics; and
- the proportion of patients discontinued from study therapy due to infection.

The results of these analyses are summarized in Table 6.2.6.1B. Infections satisfying regulatory criteria for reporting as serious adverse events were more common in abatacept than in placebo treated patients (3.0% vs 1.9%). Approximately 90% of these infections satisfied regulatory criteria for reporting as serious because they resulted in hospitalization; the remaining 10% were considered to be 'important medical events.' Few (3) resulted in death: 1 in the abatacept group and 2 in the placebo group. In contrast, infections reported as severe/very severe or resulting in discontinuation of study therapy occurred with similar frequency in abatacept- and placebo-treated patients. Moreover, use of antibiotics (including IV antibiotics) was similar in abatacept- and placebo-treated patients.

Table 6.2.6.1B: Overview of Infections During Double-Blind Study Periods

	Number (%) of Patients	
Infection Characteristics	**Abatacept**	**Placebo**
Serious infections N = 1955	58 (3.0)	19 (1.9)
Severe infections N = 1955	58 (3.0)	24 (2.4)
Very severe infections N= 1955	4 (0.2)	4 (0.7)
Treated with Antibiotics		
IM101102: 0–6 months N = 433	112 (25.9)	70 (32.0)
IM101102: 6–12 months N = 401	132 (32.9)	59 (33.9)
IM101029: 0–6 months N = 258	83 (32.2)	32 (24.1)
IM101031: 0–12 months N = 959	428 (44.6)	204 (42.3)
Treated with IV Antibiotics		
IM101102: 0–6 months N = 433	9 (2.1)	5 (2.3)
IM101102: 6–12 months N = 401	15 (3.7)	7 (4.0)
IM101029: 0–6 months N = 258	3 (1.2)	4 (3.0)
IM101031: 0–12 months N = 959	38 (4.0)	18 (3.7)
Discontinuation Due to AEs of Infection N = 1955	24 (1.2)	10 (1.0)

N = Number treated with abatacept; IV = intravenous

Deaths Due to Infections

In the double-blind study periods, one patient in the abatacept group died due to bronchopulmonary aspergillosis. This 53-year-old patient's medical history was remarkable for chronic underlying lung disease, a history of miliary TB with residual scarring of the lungs, hypertension, history of smoking, and suspicion of exposure to asbestos. In contrast, 1 patient in the placebo group died due to Pneumocystis carinii pneumonia, and 1 died due to sepsis. No deaths due to infection were reported during the open-label period.

Cumulative Incidence of Serious Infections (Double-Blind and Open-Label Study Periods up to the 4-Month Safety Update)

The incidence by patient of serious infections as a function of duration of exposure to abatacept is summarized in Table 6.2.6.1C. As a relatively common and clinically important infection, the incidence of pneumonia is summarized in a similar manner. The incidence rate of serious infection and serious pneumonia did not appear to increase with increasing duration of exposure to abatacept.

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Table 6.2.6.1C:
Incidence Rates by Six-Month Intervals for Infection SAEs by All Abatacept Exposure:
All Patients

PREFERRED TERM (PT) (95% Poisson CI on Incidence Rate)	---- All Abatacept Exposure---- Patients With Event (Rate: Incidence/100 person-yrs) Days 1-180	Days 181-360	Days 361-540	Days 541-720	Days 721-900	Days 901-last
TOTAL EXPOSURE (PERSON-YEARS)	1285.28	1031.85	795.09	399.37	117.18	198.46
ALL SERIOUS INFECTIONS	50 (3.92) (2.91, 5.17)	39 (3.81) (2.71, 5.20)	22 (2.78) (1.74, 4.21)	9 (2.26) (1.03, 4.29)	4 (3.45) (0.94, 8.83)	3 (1.53) (0.31, 4.46)
PNEUMONIA (COMBINED)	8 (0.62) (0.27, 1.23)	11 (1.07) (0.53, 1.91)	2 (0.25) (0.03, 0.91)	3 (0.75) (0.16, 2.20)	1 (0.85) (0.02, 4.76)	1 (0.51) (0.01, 2.82)

PNEUMONIA (COMBINED) includes events assigned to the preferred term ‘pneumonia’and events assigned to other, closely related preferred terms, such as bronchopneumonia’ or ‘lobar’ pneumonia.
Population: Treated patients.
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Infections by Category

Serious Bacterial Infections

A review of primary terms assigned to serious infections (Table 6.2.6.1D) suggests they were likely to be bacterial in origin. No individual serious infection was reported in more than 0.5% of patients in either group. The most common serious infections reported by abatacept-treated patients were: pneumonia (0.5%), cellulitis (0.3%), urinary tract infection (0.2%), bronchitis (0.2%), diverticulitis, and acute pyelonephritis (0.2%). The most common serious infections reported by placebo-treated patients were: pneumonia (0.5%), sepsis (0.3%), and cellulitis (0.2%). All other serious infections were reported by < 0.2% of patients. Other than pneumonia (0.5% in each group), there was no predominant type of serious infection in either treatment group. There were no differences in frequency of 0.3% or more between groups in any individual serious infection.

Table 6.2.6.1D: Number (%) of Patients with Serious Bacterial Infections (≥ 0.2%) in Double-Blind, Controlled Study Periods

Event by Preferred Term	All Abatacept N = 1955	All Placebo N = 989
Total Patients with SAE of Infection	58 (3.0)	19 (1.9)
Pneumonia	9 (0.5)	5 (0.5)
Cellulitis	5 (0.3)	2 (0.2)
Urinary tract infection	4 (0.2)	1 (0.1)
Bronchitis	4 (0.2)	0
Diverticulitis	3 (0.2)	0
Pyelonephritis acute	3 (0.2)	0
Sepsis	1 (<0.1)	3 (0.3)

Tuberculosis (TB)

Two cases of suspected TB were reported during the double-blind study periods: 1 by a patient in the abatacept group and 1 by a patient in the placebo group.

A 55-year-old white woman in the abatacept group was noted to have a neck mass on Day 54. She underwent resection of an enlarged lymph node and the histology

was negative for malignancy. On Day 293, the lymph node biopsy was noted to have findings compatible with TB, although a Ziehl-Neelson stain was negative for TB and no acid fast bacilli were identified. The patient remained asymptomatic for TB throughout this time. The patient discontinued abatacept treatment on Day 306. Treatment for TB (4 drugs) was started on Day 320.

In addition, one case of suspected TB was reported during the open-label study period.

A 39-year-old white female was treated with abatacept and methotrexate for 580 days. Tuberculosis was diagnosed presumptively on the basis of constitutional symptoms and bibasilar infiltrates that did not respond to broad spectrum antibiotic therapy. She exhibited a response to 4-drug therapy for tuberculosis, although bronchial lavage and biopsy did not identify TB. Study drug was discontinued.

It should be noted that patients with a history of active TB during the previous 3 years before entry into the study were excluded from the Phase II and III studies. In addition, patients were screened for latent TB using skin testing in the Phase III studies, and patients with evidence of possible latent TB who had not received adequate chemoprophylaxis were excluded from the studies.

Herpes Family Infections

Viruses in the herpesvirus family (herpes simplex, varicella-zoster, cytomegalovirus, and Epstein-Barr) are of particular interest in immunocompromised patients, as they have been associated with severe and/or disseminated infection and malignancy. The frequency of infections caused by viruses in the herpesvirus family is summarized in Table 6.2.6.1E.

Table 6.2.6.1E: Frequency of Infections in Herpesvirus Family During the Double-Blind Controlled Study Periods

	Number (%) of Patients			
Preferred Term	**Abatacept N = 1955**		**Placebo N = 989**	
Total herpetic infections	75	(3.8)	28	(2.8)
Herpes simplex	37	(1.9)	10	(1.0)
Herpes zoster	30	(1.5)	16	(1.6)
Herpes viral infection	5	(0.3)	2	(0.2)
Varicella	3	(0.2)	0	–
Epstein-Barr virus	0	–	0	–
Cytomegalovirus	0	–	0	–

Herpes simplex virus infections occurred approximately twice as frequently in abatacept-treated patients as in placebo-treated patients (1.9 vs 1.0%). Herpes zoster virus infections occurred with similar frequency in abatacept- and placebo-treated patients. No cytomegalovirus or Epstein-Barr virus infections were reported. In general, few herpesvirus infections satisfied regulatory criteria for reporting as serious, were considered by the investigator to be severe or very severe in intensity, or required discontinuation of therapy.

Three (3) episodes of disseminated zoster were reported in abatacept-treated patients during the double-blind study periods. All occurred in patients receiving concomitant prednisone for RA, were treated with antiviral therapy, and resolved satisfactorily. None were reported as serious or resulted in discontinuation of abatacept.

A fourth episode of disseminated zoster, reported as serious, occurred during the open-label study period.

> The patient was a 51-year-old white female with a history of diabetes and herpes zoster. She received a total of 5 open-label abatacept infusions with background methotrexate and prednisone, prior to developing lesions on the face, right breast, and eye. The lesions were cultured and determined to be herpes simplex virus I and II, and herpes zoster. She was treated with intravenous acyclovir before being switched to oral acyclovir; the event resolved with sequelae (skin scars and scarring keratitis). Study medication was interrupted.

Opportunistic Infections

In addition to the infections discussed above, 1 episode of fatal pneumocystis pneumonia occurred in a placebo-treated patient during the double-blind study periods.

One opportunistic infection was reported in an abatacept-treated patient during the open-label study periods.

> The patient was a 59-year-old white male with a 9-year history of RA. After receiving approximately 10 months therapy with abatacept, methotrexate, and methylprednisolone, he developed iritis of the right eye following surgery for a pre-existing retinal condition. He was treated with tobramycin/dexamethasone eyedrops, with resolution. Thirty-six (36) days later, the patient developed severe necrotic scleritis, which was treated with an increase in his oral steroid dose. Thirty (30) days following the development of necrotic scleritis, he developed an aspergillus infection of the eye. This was treated with systemic antifungal therapy, and resolved, but with complete and irreversible loss of vision. Abatacept treatment was discontinued.

Conclusions

The incidence of infections, including serious infections, was slightly increased with abatacept relative to placebo during the double-blind study periods. The type, severity, treatment, and outcome of infections did not differ between abatacept- and placebo-treated patients. Most serious infections were likely to be bacterial in origin and responded appropriately to therapy. Mycobacterial, disseminated viral, invasive fungal, or other infections of special interest were rare. The incidence, type, and outcome of infections did not change in patients followed during the open-label study periods.

6.2.6.2 Malignancy

Introduction

Malignancy is a known risk of immunosuppressive therapy. Non-clinical findings about the potential for malignancy with abatacept were discussed in Section 3.7.3 (Carcinogenicity). Relevant clinical data are presented in 2 sections that follow.

The first section describes the incidence and type of malignancies observed during double-blind and open-label treatment periods. This section includes a summary of

incidence of malignancy in patients exposed to abatacept for up to 3 years. The data summaries in this section are based on data included in the original BLA filing as well as the 4-Month Safety Update.

The second section provides detailed information on 2 malignancies of special interest. Lymphoma is of special interest because of its increased incidence in patients with rheumatoid arthritis and its possible association with existing therapies for RA, including the TNF-blocking agents. Lung cancer is of special interest because it was the most commonly observed solid cancer (excluding skin cancer) in abatacept-treated patients. Clinical data on the individual cases of lymphoma and lung cancer are provided, as well as a summary of the incidence of these malignancies in patients exposed to abatacept for up to 3 years.

Because lymphoma and lung cancer are uncommon AEs, and randomized clinical trials have limited power to detect differences in incidence rates between abatacept- and placebo-treated patients, the expected rates from epidemiological data are also summarized in this section to assist in interpretation of the observed incidence rates. Reference incidence rates in RA patients have been developed based on analyses of RA observational cohorts in North America and Europe. These cohorts are appropriate sources of reference incidence rates for the abatacept program given the observation that cancer, specifically lymphoma, is more common in patients with rheumatoid arthritis than in the general population.[40,41,42,43,44,45,46] The characteristics of the RA cohorts are summarized in Table 6.2.6.2A.

Table 6.2.6.2A: Populations Evaluated in Epidemiology Studies of RA Subjects

	Canada	United Kingdom[a]	United States
Registry name	British Columbia Registry (BC)	Norfolk Arthritis Registry (NOAR)	National Data Bank for Rheumatic Diseases (NDB)
Data type	Medical and outpatient pharmacy claims	Patient questionnaire and assessment	Patient questionnaire
Time covered	Jan 96-Dec 2001	1990-1999	1998-2003
Population	27,710	2,153 Early RA/IP	21,229
Sampling method	Population-based	Population-based	Physician referral

[a] Early RA cohorts.

IP = inflammatory polyarthritis

For completeness, malignancy rates for the general US population are also provided, based on the Surveillance, Epidemiology, and End Results (SEER) Cancer Statistics Review database.[47]

It should be noted that the individual RA cohorts used to develop reference incidence rates differ in their size, sampling, disease characteristics, case ascertainment, and verification. No individual cohort should be regarded as providing definitive information. Collectively, the cohorts provide a range of estimates within which the true value is likely to be found.

It should also be noted that the cohorts include only patients treated with non-biologic DMARDs and with no history of treatment with biologic RA therapy. In contrast, the abatacept clinical development program included patients who had received or were currently receiving biologic RA therapy. These patients may therefore have had more severe disease and/or a greater lifetime burden of immunosuppression than the patients represented in the RA cohorts.

Clinical Findings

Double-Blind, Controlled Study Periods

The overall frequency of all neoplasms (benign, malignant, or unspecified) in the double-blind controlled study periods was similar between abatacept- and placebo-treated patients (3.4% vs 3.1%). The majority of these events were benign. A similar proportion of patients in both groups reported malignant neoplasms (1.3% and 1.1% of abatacept and placebo patients, respectively).

Malignant neoplasms were further divided into 3 categories: non-melanoma skin cancers, solid tumors, and hematologic/lymphatic cancers. Within each category, the proportion of patients with malignancies was similar (see Table 6.2.6.2B).

Non-melanoma skin cancers were reported in 15 (0.8%) abatacept-treated patients and 6 (0.6%) placebo-treated patients. Basal cell carcinoma occurred more frequently than squamous cell carcinoma in both treatment groups. Solid cancers were reported in 9 abatacept-treated and 5 placebo-treated patients, representing 0.5% of both treatment groups. The most commonly reported solid tumor was lung cancer, which occurred in 4 abatacept-treated and no placebo-treated patient. Lung cancer is discussed in more detail in the Section *Malignancies of Special Interest: Lung Cancer*. Other solid tumors occurred in 1 or 2 patients, with no clear pattern across treatment groups. Lymphoma was reported in 1 abatacept-treated patient, and is discussed in more detail in the Section *Malignancies of Special Interest: Lymphoma*.

Table 6.2.6.2B: Malignant Neoplasms in Abatacept-Treated Patients During the Double-Blind, Controlled Study Periods

	Number (%) of Patients	
	All abatacept (N=1955)	**Placebo (N=989)**
Non-Melanoma Skin Cancers	**15 (0.8)**	**6 (0.6)**
Basal Cell Carcinoma	10 (0.5)	4 (0.4)
Squamous Cell Carcinoma	6 (0.3)	2 (0.2)
Solid Cancers	**9 (0.5)**	**5 (0.5)**
Lung Neoplasm Malignant	4 (0.2)	0
Thyroid	2 (0.1)	0
Breast	1 (<0.1)	2 (0.2)
Prostate	1 (<0.1)	0
Bladder	1 (<0.1)	0
Renal	1 (<0.1)	0
Endometrial	0	2 (0.2)
Melanoma	0	1 (0.1)
Hematologic/Lymphatic Cancers	**2 (<0.1)**	**0**
Lymphoma	1 (<0.1)	0
Myelodysplastic Syndrome	1 (<01)	0

Cumulative Experience (Including Open-Label, Uncontrolled Study Periods)

The malignancies reported during the cumulative experience with abatacept (including the double-blind, controlled study periods and the open-label, uncontrolled study periods through the data locks for the 4-Month Safety Update) are summarized in Table 6.2.6.2C as the number and incidence per 100 person-years. Because there was no comparator during the open label study periods, these data are presented only for abatacept. As a reference, the number and incidence rates per 100 person-years are also presented for abatacept for the double-blind period alone.

The type and pattern of malignancies reported cumulatively, including both double-blind and subsequent open-label treatment periods, were similar to that observed during the double-blind study periods alone. There was no increase in the incidence per 100 person-

years of non-melanoma skin cancers or solid tumors, both overall and for individual tumor types, including lung. There was also no increase in the overall incidence of hematologic malignancies, although there were 3 additional reported cases of lymphoma, and an increase in the incidence of lymphoma from 0.06 to 0.10 per 100 person-years.

Table 6.2.6.2C: Malignant Neoplasms Observed in Abatacept-Treated Patients During Double-Blind and Cumulative Study Periods

Malignancy	Double-Blind Period N = 1955 (P-Y=1688) n (per 100 p-y)	Cumulative[a] N = 2688 (P-Y=3827) n (per 100 p-y)
Non-Melanoma Skin Cancers	**15 (0.89)**	**24 (0.63)**
Basal Cell Carcinoma	10 (0.59)	16 (0.42)
Squamous Cell Carcinoma	6 (0.36)	9 (0.24)
Other (Neoplasm skin)	0	1 (0.03)
Solid Cancers	**9 (0.53)**	**21 (0.55)**
Lung	4 (0.24)	8 (0.21)
Breast	1 (0.06)	2 (0.05)
Prostate	1 (0.06)	2 (0.05)
Thyroid	2 (0.12)	2 (0.05)
Bladder	1 (0.06)	1 (0.03)
Ovarian	0	2 (0.05)
Renal	1 (0.06)	1 (0.03)
Melanoma	0	1 (0.03)
Endometrial / Uterine	0	2 (0.05)
Cervix	0	1 (0.03)
Hematologic/Lymphatic Cancers	2 (0.12)	5 (0.13)
Lymphoma	1 (0.06)	4 (0.10)
Myelodysplastic Syndrome	1 (0.06)	1 (0.03)

P-Y = person-years

[a] Cumulative = double-blind plus open-label periods through the 4-Month Safety Update data locks.

To further characterize the relationship between duration of exposure to abatacept and the risk of malignancy, the incidence rates by patient for all neoplasms (malignant and benign), all malignancies, and all malignancies excluding non-melanomatous skin cancer were analyzed within 180-day exposure windows up to the 4-Month Safety Update (Table 6.2.6.2D). No increase in the incidence of neoplasms or malignancies was apparent up to 3 years of exposure, although data were limited beyond 2 years.

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Table 6.2.6.2D:
Incidence Rates by Six-Month Intervals for Neoplasm AEs by All Abatacept Exposure: All Patients

PREFERRED TERM (PT) (95% Poisson CI on Incidence Rate)	All Abatacept Exposure: Patients With Event (Rate: Incidence/100 person-yrs) Days 1-180	Days 181-360	Days 361-540	Days 541-720	Days 721-900	Days 901-last
TOTAL EXPOSURE (PERSON-YEARS)	1285.28	1031.85	795.09	399.37	117.18	198.46
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	44 (3.45) (2.51, 4.64)	43 (4.20) (3.04, 5.66)	33 (4.19) (2.88, 5.89)	11 (2.77) (1.38, 4.96)	7 (6.04) (2.43, 12.4)	7 (3.61) (1.45, 7.44)
TOTAL MALIGNANCIES	15 (1.17) (0.65, 1.93)	17 (1.65) (0.96, 2.65)	11 (1.39) (0.69, 2.48)	3 (0.75) (0.16, 2.20)	3 (2.57) (0.53, 7.52)	3 (1.52) (0.31, 4.45)
TOTAL MALIGNANCIES EXCLUDING NMSC	6 (0.47) (0.17, 1.02)	8 (0.78) (0.34, 1.53)	7 (0.88) (0.35, 1.82)	1 (0.25) (0.01, 1.40)	2 (1.71) (0.21, 6.18)	2 (1.01) (0.12, 3.64)

Population: Treated patients.
NMSC = non-melanomatous skin cancer
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Comparison to Reference Databases

Expected numbers of malignancies in the US general population and standard incidence ratios (SIRs) were calculated for the most frequent malignancies observed in subjects treated with abatacept during the cumulative period, with the 'most frequent' being defined as an incidence in 2 or more subjects treated with abatacept. Calculations were made based on accepted epidemiologic practices.[48] SIRs for non-melanoma skin malignancies were not computed because the SEER database does not provide incidence rates of non-melanoma skin malignancies. All SIRs were age- and gender-adjusted to the US population incidence rates.

Table 6.2.6.2E provides a summary of the cumulative observed number of malignancies, expected number of malignancies (based on the SEER[47] reference incidence rate and exposure to abatacept), and the SIR (observed/expected number of events) with 95% confidence intervals.

Table 6.2.6.2E: Most Frequently Observed vs Expected Cumulative Number of Events, and Standardized Incidence Ratios with 95% Confidence Intervals by Malignancy Type

Malignancy[a]	Observed	Expected[b]	SIR	95%CIs
Overall	26	30.159	0.862	(0.563, 1.263)
Lung	8	3.966	2.017	(0.869, 3.975)
Lymphoma	4	1.082	3.698	(0.995, 9.467)
Breast	2	7.742	0.258	(0.029, 0.933)
Prostate	2	3.236	0.618	(0.069, 2.231)
Thyroid	2	0.576	3.473	(0.390, 12.541)
Ovarian	2	0.743	2.691	(0.302, 9.717)
Endometrial	2	1.485	1.347	(0.151, 4.864)

SIR = standardized incidence ratio; CI = confidence intervals

[a] Excludes non-melanoma skin malignancies

[b] Age- and gender-adjusted to the US population, 1998 to 2002. Calculations are based on 15 age groups at 5-year intervals.

The total number of malignancies observed in the abatacept clinical trials was slightly lower than expected based on US general population reference rates. The numbers of lung, lymphoma, thyroid, ovarian and endometrial malignancies were more than expected, while the numbers of breast and prostate malignancies were less than expected. Malignancies that occurred in fewer than 2 abatacept-treated subjects are not represented in this analysis. No cases of colorectal cancer were reported.

The total numbers of malignancies observed in the abatacept trials were also lower than expected based on age- and gender-adjusted reference rates in US general population and the RA cohorts (Table 6.2.6.2F). The incidence of specific malignancies observed in the abatacept trials relative to the RA cohorts is described in the specific sections for lymphoma and lung cancer that follow.

Table 6.2.6.2F: Malignancies in Abatacept-Treated Patients and RA Populations During the Cumulative Double-Blind and Open-Label Study Periods

Malignancy	Observed Events	Expected Events in RA Cohorts and SEER		
		SEER[a]	BC	NOAR
Overall excluding NMSC 95% CI[b]	26 (17.0, 38.1)	28.8 (20.0, 41.5)	68.8 (54.4, 87.2)	30.2 (21.1, 43.1)

[a] Calculations are based on 8 age groups at 10-year intervals.

[b] Poisson confidence intervals

RA = rheumatoid arthritis; SEER = Surveillance, Epidemiology, and End Results; NMSC = non-melanomatous skin cancer; BC = British Columbia; NOAR = Norfolk Arthritis Registry (NOAR).
Source: Calculated from values in abatacept safety database and the reference databases.

Malignancies of Special Interest: Lymphoma

One lymphoma was reported in an abatacept-treated patient during the double-blind, controlled study periods. Three (3) lymphomas were reported in abatacept-treated patients during the open-label, uncontrolled study periods. These 4 cases are summarized in Table 6.2.6.2.G.

Two (2) patients had diffuse B-cell lymphoma, which has been known to occur with increased frequency in patients with RA.[40,41,42,43,44,45,46] One patient had a thyroid lymphoma associated with Hashimoto's thyroiditis, the latter a known risk factor for lymphoid malignancies of the thyroid.[49,50] Additionally, 1 patient was receiving concomitant therapy with etanercept and 2 patients had received prior treatment with inflixamab.

Table 6.2.6.2G: Patients Reporting Lymphoma during Double-Blind and Open-Label Study Periods

Patient No. Age/Race/Gender/ Country	Study Period	Adverse Event	Dose # Infusions PT Dx (Days)	Concomitant Medication
IM101102-39-9 81 / W / F USA	Double-Blind	Lymphoma (B-cell) associated with Hashimoto's Thyroiditis	750 mg 10 inf 241 D	Methotrexate [Infliximab][a]
IM101102-136-15 48 / W / M Belgium	Open-Label (Double-Blind = Placebo)	Lymphoma (Diffuse Large B-cell Non-Hodgkins, CD20+, Stage Ia)	750 mg 8 inf 203 D	Methotrexate
IM101029-26-9 58 / W / M USA	Open-Label (Double-Blind = Abatacept)	T-cell Lymphoma (Non-Hodgkins Large Cell, Stage IIb)	750 mg 19 inf 505 D	Methotrexate Leflunamide [Infliximab][a]
IM101101-14-2 61 / W / F USA	Open-Label (Double-Blind = Abatacept)	Diffuse Large B-Cell Lymphoma (Stage IVb)	750 mg 38 inf 1086 D	Etanercept

[a] Treatment prior to enrollment.

PT = prior to; Dx = diagnosis; inf = infusions; D = day

Comparison to RA Reference Databases for Lymphoma

Table 6.2.6.2H summarizes the observed number of lymphoma events in the abatacept cumulative experience (including both double-blind and open-label study periods) and the expected number of events in the US general population and the DMARD-treated patients in the rheumatoid arthritis cohorts. The expected events for the reference databases have been adjusted for exposure and to reflect the age and gender distribution of the abatacept clinical trial population.

The observed number of lymphoma events in the abatacept cumulative experience was 4. This is approximately 4 times higher than what would be expected based on the US general population incidence rates (SEER). The expected number of events of lymphoma in the rheumatoid arthritis cohorts ranged from 2.4 to 3.1. The observed number of events for abatacept-treated patients is similar to the range of expected events in the RA cohorts.

Table 6.2.6.2H: Events of Lymphoma in Abatacept-Treated Patients and RA Populations During the Cumulative Double-Blind and Open-Label Study Periods

		Expected Events in RA Cohorts and SEER			
Malignancy	**Observed Events**	**SEER**	**BC**	**NDB**	**NOAR**
Lymphoma 95% CI[a]	4 (1.1, 10.2)	1.1 (0.2, 7.1)	2.4 (0.7, 8.5)	3.1 (1.0, 9.5)	3.0 (1.0, 9.3)

Source: Calculated from values in abatacept safety database and the reference databases.
RA = rheumatoid arthritis; SEER = Surveillance, Epidemiology, and End Results; BC = British Columbia; NDB = National Data Bank for Rheumatic Diseases; NOAR = Norfolk Arthritis Registry (NOAR).
[a] Poisson confidence intervals

Incidence of Lymphoma over Time

To further evaluate the relationship between duration of exposure to abatacept and the risk of lymphoma, the incidence rate by patient for lymphoma was analyzed within 180-day exposure windows (Table 6.2.6.2I). No increase in the incidence of lymphoma was apparent up to 3 years of exposure, although data were limited beyond 2 years.

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Table 6.2.6.2I:
Incidence Rates by Six-Month Period for Lymphomas Over All Abatacept Exposure:
All Patients Through February 2005 Datalock

	---- All Abatacept Exposure----					
	Patients With Event (Rate: Incidence/100 pt-yrs)					
PREFERRED TERM (PT)	Days 1-180	Days 181-360	Days 361-540	Days 541-720	Days 721-900	Days 901-last
TOTAL EXPOSURE (PERSON-YEARS)	1285.28	1031.85	795.09	399.37	117.18	198.46
LYMPHOMAS (COMBINED)	0 (0.00)	2 (0.19)	1 (0.13)	0 (0.00)	0 (0.00)	1 (0.50)

Population: Treated patients.
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Malignancies of Special Interest: Lung Cancer

Lung cancer was the most commonly reported solid tumor in the cumulative experience with abatacept. Four (4) abatacept-treated patients were reported to develop lung cancer during the double-blind, controlled study periods, and an additional 4 abatacept-treated patients were reported to develop lung cancer during the open-label, uncontrolled study periods. Clinical features of these events are summarized in Table 6.2.6.2J.

Table 6.2.6.2J: Patients Reporting Lung Cancer in Double-Blind and Open-Label Study Periods

Patient No. Age/Race/Gender/ Country	Adverse Event	Dose # Infusions PT Dx (Days)	Concomitant Medication	Pre-treatment Chest Radiograph
Double-Blind Period				
IM101031-203-10[a] 69 / W / F Hungary	Lung Neoplasm Malignant (Squamous Cell Carcinoma, Stage II)	500 mg 3 inf 29 D	Methotrexate Azathioprine Chloroquine	Abnormal at Screening
IM101031-161-5 68 / W / M USA	Non-small Cell Lung Cancer (Squamous Cell Carcinoma, Stage IIb)	750 mg 5 inf 100 D	Methotrexate Azathioprine Sulfasalazine	Hyperinflated Chest, COPD
IM101102-97-25 72 / W / F[b] Brazil	Lung Neoplasm Malignant (Squamous Cell Carcinoma)	500 mg 13 inf 320 D	Methotrexate Chloroquine	Small Lesion in Left Pulmonary Apex
IM101100-35-2 83 / W / M USA	Lung Neoplasm Malignant (Non-small Cell Lung Cancer)	10 mg/kg 13 inf 332 D	Methotrexate	Normal

Table 6.2.6.2J: Patients Reporting Lung Cancer in Double-Blind and Open-Label Study Periods

Patient No. Age/Race/Gender/ Country	Adverse Event	Dose # Infusions PT Dx (Days)	Concomitant Medication	Pre-treatment Chest Radiograph
Open-Label Period				
IM101-102-14-5[c] 72 / W / F USA	Lung Neoplasm (Carcinoid Tumor, Stage I)	750 mg 14 inf 397 D	Methotrexate	Apical Dorsal Consolidation of Left Superior Lobe
IM101-031-71-6 62 / W / F USA	Small Cell Lung Cancer (Carcinoma, Extensive)	750 mg 16 inf 404 D	Methotrexate Leflunamide Sulfasalazine Chloroquine	Prominence of Interstitium and Minimal Pleural Reaction at Left Base
IM101-102-98-12 64 / W / M Argentina	Lung Neoplasm Malignant (Adenocarcinoma, Stage IIIb)	500 mg 16 inf 415 D	Methotrexate	Bibasilar Reticular Nodular Changes in Right Subhilar Region
IM101-100-21-1 61 / W / F Belgium	Lung Adenocarcinoma (+ Pleural Metastasis)	10 mg/kg 16 inf 484 D	Methotrexate	Interstitial Fibrosis

[a] This subject experienced passive exposure to smoking.

[b] Pre-treatment chest radiograph had evidence of a small, left apical spiculated pulmonary nodule of 1.1 cm in maximal diameter.

[c] Evidence of a pre-existing tumor based on abnormal, pre-treatment chest-radiographs.

PT = prior to; Dx = diagnosis; inf = infusions; D = day

Lung cancer occurred in older patients, with an age range of 61 to 83 years of age. All but 1 patient (7/8) had an extensive smoking history. The remaining patient was the spouse of a smoker. The severity of rheumatoid arthritis in these patients is reflected in their concomitant medications. Three (3) were receiving 3 DMARDS, one 2 DMARDS, and 4 one DMARD.

The time on study treatment prior to diagnosis of lung cancer ranged from 29 to 484 days. Two (2) patients (Patient Numbers IM101031-203-10 and IM101031-161-5) had only a short period of study therapy during the double-blind period prior to diagnosis (29 and 100 days). Whenever possible, baseline and follow-up radiographs and diagnostic pathologic material were obtained by the sponsor for independent review.

These reviews indicated that 2 other patients (Patient Numbers IM101102-97-25 in the double-blind period and IM101102-14-5 in the open-label period) had baseline radiographic abnormalities suggestive of malignancy.

No predominant cell type was reported for the malignancies. There were 3 squamous cell, 2 adenocarcinoma, 1 small cell, 1 carcinoid, and 1 non-small cell lung cancers.

Comparison to RA Reference Databases for Lung Cancer

Table 6.2.6.2K summarizes the observed number of lung cancer events in the abatacept cumulative experience (including both double-blind and open-label study periods) and the expected events in the US general population and the rheumatoid arthritis cohorts. The reference databases were previously defined in the Section *Comparison to Reference Databases for Lymphoma.* The expected events for the reference databases have been adjusted to reflect the age and gender distribution of the abatacept clinical trial population.

The observed number of lung cancer events in the abatacept cumulative experience was 8. This is approximately twice what would be expected based on the US general population incidence rates (SEER). The expected number of lung cancer events in the rheumatoid arthritis cohorts ranged from 3.6 to 9.9. The observed number of lung cancer events in the abatacept-treated patients fall within the range of expected events in the RA cohorts.

Table 6.2.6.2K: Events of Lung Cancer in Abatacept-Treated Patients and RA Populations During the Cumulative Double-Blind and Open-Label Study Periods

		Expected Events in RA Cohorts and SEER			
Malignancy	**Observed Events**	**SEER**	**BC**	**NDB**	**NOAR**
Lung Cancer 95 % CI[a]	8 (3.5, 15.8)	4.0 (1.5, 10.7)	9.9 (5.3, 18.5)	3.6 (1.3, 10.1)	4.8 (1.9, 11.7)

RA = rheumatoid arthritis; SEER = Surveillance, Epidemiology, and End Results; BC = British Columbia; NDB = National Data Bank for Rheumatic Diseases; NOAR = Norfolk Arthritis Registry (NOAR).

[a] Poisson confidence intervals

Incidence of Lung Cancer over Time

To further characterize the relationship between duration of exposure to abatacept and the risk of lung cancer, the incidence rate by patient for lung cancer was analyzed within 180-day exposure windows (Table 6.2.6.2L). No increase in the incidence of lung cancer was apparent up to 3 years of exposure, although data were limited beyond 2 years.

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Table 6.2.6.2L:
Incidence Rates by Six-Month Period for Lung Cancers Over All Abatacept Exposure:
All Patients Through February 2005 Datalock

	---- All Abatacept Exposure----					
	Patients With Event (Rate: Incidence/100 pt-yrs)					
PREFERRED TERM (PT)	Days 1-180	Days 181-360	Days 361-540	Days 541-720	Days 721-900	Days 901-last
TOTAL EXPOSURE (PERSON-YEARS)	1285.28	1031.85	795.09	399.37	117.18	198.46
ALL LUNG CANCERS (COMBINED)	2 (0.16)	2 (0.19)	4 (0.50)	0 (0.00)	0 (0.00)	0 (0.00)

Population: Treated patients.
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Interpretation of the Incidence of Malignancies

An assessment of the risk of malignancy is essential in the development of an immunodulatory agent. A traditional mouse carcinogenicity study was conducted with abatacept. This type of study is infrequently performed with human therapeutic proteins because these agents usually induce an antibody response in rodents that prevents sufficient exposure from being achieved over the duration of the study. However, in the non-clinical studies of abatacept, suppression of the antibody response permitted sustained exposure to be achieved. Sustained immunomodulation appeared to result in the development of tumors (lymphoma and mammary gland) associated with reactivation of latent oncogenic viruses specific to the mouse. The species-specific nature of these findings was underscored by the absence of neoplastic findings or other findings associated with viral reactivation in monkeys treated with abatacept for 1 year, at up to 9 times the human exposure.

The relevance of these findings was explored in the clinical development program. Overall, malignancies occurred with similar frequencies in abatacept- and placebo-treated patients during the double-blind, controlled study periods. Non-melanomatous skin cancers were the most frequently reported malignancies. While squamous cell carcinoma of the skin has been noted to occur with increased frequency in immunosuppressed populations, the most commonly reported skin cancer in abatacept-treated patients, as in the general population, was basal cell carcinoma. Solid tumors occurred in approximately 0.5% of patients in both the abatacept- and placebo-treatment groups. Lymphoma was reported in only 1 abatacept-treated patient during the double-blind period.

During the open-label, uncontrolled study periods, the incidence rate of malignancy did not increase. The incidence rate for non-melanomatous skin cancer declined, while the incidence rate for solid tumors and hematologic malignancies remained stable. No increase in the incidence of malignancy was observed with increasing duration of exposure to abatacept, although data beyond 2 years were relatively limited. Overall, the number of malignancies observed with abatacept was lower than that expected based on reference data from the US general population and RA cohorts.

Thus, there does not appear to be an increase in the overall risk of malignancy with abatacept in humans. It should be noted that there are inherent limitations to the abatacept

clinical data set with respect to the overall assessment of cancer risk. The duration of observation is limited relative to the recognized latency periods for most human cancers. Despite being a relatively large clinical development program compared to that of other biologic RA therapies, the number of treated patients remains small in the context of assessment for infrequent events.

The frequency of individual tumor types should be interpreted with particular caution given the very low event rates. Only 13 solid tumors were reported during the double-blind study periods. These tumors occurred in 8 different anatomic sites. Even the most frequently reported solid organ malignancy, lung cancer, was only reported in 4 abatacept-treated patients during double-blind treatment. Of the most common solid organ malignancies in the US general population, one (lung cancer) occurred more frequently in abatacept-treated patients than expected (based on reference rates in the US population), while two (breast and prostate cancer) occurred less frequently than expected. The fourth, colorectal cancer, did not occur at all. All other tumor types occurred in only 1 or 2 patients. It should also be noted that approximately twice as many patients were treated with abatacept as with placebo. This 2:1 ratio creates a corresponding 2:1 ratio in the number of events expected for abatacept and placebo.

With these considerations in mind, 2 malignancies of special interest (lymphoma and lung cancer) were examined in particular detail. Lymphoma has been noted to occur 2 to 4 times more commonly in patients with rheumatoid arthritis than in the general population, and more commonly in patients with severe rheumatoid arthritis than in patients with milder disease.[40,42,43,44,45,46,51] Four (4) lymphomas occurred during the cumulative double-blind and open-label experience with abatacept. Two (2) of these were diffuse B-cell lymphomas, a type that has been associated with rheumatoid arthritis. A third, a thyroid B-cell lymphoma occurred concurrently with Hashimoto's thyroiditis, a known risk factor for thyroid lymphoma.[49,50] Three (3) of the 4 lymphomas occurred in patients with prior or concurrent TNF-blocking agent use. The observed number of events for abatacept is similar to the range of expected events in the RA cohorts, which do not include patients treated with TNF-blocking agents. Therefore, the experience with lymphoma in abatacept-treated patients appears to be typical for patients with rheumatoid arthritis, and there is no apparent signal for increased risk of lymphoma due to abatacept

at the present time. Nevertheless, the data are too limited to permit a definitive conclusion and further study will be undertaken (see Section 7 [Pharmacovigilance Plan]).

Lung cancer was the most commonly reported solid tumor in abatacept-treated patients. Four (4) cases were reported during the double-blind period, and an additional 4 cases during the open-label period. These cases had a typical clinical presentation with a variety of tumor types (squamous, adenocarcinoma, small cell, and carcinoid). All but one were associated with a history of cigarette smoking.

The total observed number of lung cancer events (8) in the abatacept cumulative experience is approximately twice what would be expected based on the US general population incidence rates (SEER). It should be noted, however, that 2 of the reported cases were determined by independent review to have baseline radiographic abnormalities suggestive of undiagnosed lung cancer. An additional 2 cases had their onset within a very short period of time after starting treatment with abatacept (29 and 100 days). Thus, it is likely that 4 of the 8 reported cases were unrelated to study drug. The observed number of lung cancer events (which includes these 4 cases) in the abatacept-treated patients falls within the range of expected events in the RA cohorts. Thus, there does not appear to be evidence of increased risk of lung cancer with abatacept. As with lymphoma, the data are too limited to permit a definitive conclusion to be made and further study will be undertaken (see Section 7 [Pharmacovigilance Plan]).

6.2.6.3 Autoimmune Symptoms and Disorders

Special analyses were performed to identify potential clinical and laboratory autoimmune adverse events. A set of pre-specified MedDRA codes representing symptoms or diseases that could be related to autoimmunity were used to facilitate this analysis.

In the double-blind period, the overall frequency of patients reporting symptoms potentially related to autoimmunity was low but modestly higher in abatacept-treated vs placebo-treated patients: 2.9% vs 1.8%. The most common autoimmune symptoms reported were symptoms often associated with RA, including keratoconjunctivitis sicca, vasculitis, and Sjogren's syndrome.

Aside from events associated with RA itself, psoriasis was the only AE that was appreciably more frequent in abatacept-treated patients during the double-blind period (0.5% vs 0.1%). The intensity was generally mild or moderate. Discontinuation was infrequent. When treatment for psoriasis was given, topical therapy was often sufficient and systemic corticosteroids were infrequently given. Early studies conducted in patients with psoriasis did not suggest that abatacept was associated with worsening disease.

In the open-label period, autoimmune symptoms/disorders were rare. The most common events were those seen in the double-blind period (keratoconjunctivitis sicca and psoriasis).

Antinuclear antibodies (ANA) and antibodies to double-stranded DNA (dsDNA) were measured in the double-blind studies to assess potential autoimmune reactions due to abatacept treatment. Seroconversion from antibody negative status at 6 or 12 months was less common with abatacept than with placebo (Table 6.2.6.3).

Table 6.2.6.3: Seroconversion: Anti-Nuclear and DS-DNA Antibodies, Baseline Negative Patients

	Anti-nuclear antibody (ANA)		Anti-dsDNA antibody	
	6 Months n (%)	12 months n (%)	6 Months n (%)	12 Months n (%)
Abatacept	N = 1137 47 (4.1)	N = 962 93 (9.7)	N = 1272 14 (1.1)	N = 1062 29 (2.7)
Placebo	N = 575 36 (6.3)	N = 443 48 (10.8)	N = 629 15 (2.4)	N = 490 23 (4.7)

In summary, the safety data do not suggest that the use of abatacept is associated with a medically important risk of developing autoimmune disorders.

Demyelinating Disorders

Demyelinating disorders have been reported in patients treated with marketed biologic therapy for RA. During the double-blind, controlled study periods, no cases of demyelinating disease or MS were reported in abatacept-treated patients. During the open-label, uncontrolled study periods, 1 case of MS was reported in an abatacept-treated patient.

> The patient was a 60-year-old woman treated with abatacept in the uncontrolled, open-label portion of Study IM101100. Toward the end of 2004, after approximately 33 months of abatacept treatment, she presented for neurologic examination with complaints of 10 years of slowly progressive urinary incontinence, and several years of right leg heaviness, weakness, discomfort, and difficulty with balance. Primary MS was diagnosed on the basis of oligoclonal bands in the CSF, although no enhancing lesions were present on MRI. Given the long symptom history, the investigator considered MS to be unrelated to abatacept treatment.

Additional information on the safety of abatacept in MS was provided by a study conducted with abatacept in patients with relapsing-remitting multiple sclerosis. Study IM101200 was a randomized, double-blind, placebo-controlled, parallel-group dose-ranging study. Patients were randomized to either 2 mg/kg abatacept, 10 mg/kg abatacept, or placebo, using a cohort recruitment schedule.

The study was terminated when a total of 128 of a planned 219 patients had been randomized. A Data Safety Monitoring Board (DSMB) review detected an increase in 1 of the randomized groups in enhancing T1 lesions and MS exacerbations. Therefore, the DSMB recommended truncating that arm of the study.

Following this recommendation, an internal review at BMS revealed significant imbalances in baseline prognostic characteristics, apparently as a result of the cohort design, in which early study enrollees, whose prognostic characteristics were more unfavorable than those enrolled later, were randomized disproportionately to the 2 mg/kg group. The study was subsequently terminated by BMS because these baseline imbalances would render the efficacy comparisons uninterpretable.

A descriptive analysis of the primary efficacy endpoint, cumulative new or recurrent T1-enhancing lesions, revealed that the 2 mg/kg group (median number of lesions = 8.0) was numerically inferior to placebo (median number of lesions = 5.5), while the 10 mg/kg group (median number of lesions = 1.5) was numerically superior to placebo. A similar pattern was observed for other efficacy endpoints.

The safety experience in this trial was unremarkable. Adverse events, other than those related to MS, were uncommon and occurred with similar frequency in all treatment groups.

6.2.6.4 Infusion Reactions

In the core RA studies, abatacept was administered intravenously as a 30-minute infusion without a protocol requirement or recommendation for pretreatment for potential hypersensitivity reactions. As is true for any protein therapeutic, infusional AEs were a potential concern. To focus on the most clinically relevant events, a list of pre-specified AEs (using MedDRA terms) considered most likely associated with infusion of therapeutic proteins was created by the Sponsor (eg, allergic-type reactions and hemodynamic events). Any AE reported within 24 hours of infusion was categorized as a 'peri-infusional AE.' Peri-infusional AEs were sub-divided into acute pre-specified AEs (with an onset time within 1 hour of the start infusion), all pre-specified AEs (reported within 24 hours), and other peri-infusional AEs. All AEs of special interest are subsets of all AEs; they are not additional events.

Overall, the peri-infusional tolerability profile of abatacept was excellent. Allergic-type reactions were infrequent and generally balanced between treatment groups.

Acute, pre-specified infusion events were reported more frequently in abatacept-treated patients (8.9%) compared with placebo-treated patients (5.6%). The most commonly reported events were dizziness (2.1% vs 1.3%, respectively) and headache (1.8% vs 1.2%, respectively). These infusion reactions were usually mild or moderate in intensity. Severe events in abatacept-treated patients, while rare, included clinically important events of hypersensitivity in 2 patients, and hypotension and 'drug hypersensitivity' in 1 patient each. None of these occurred with the initial abatacept dose.

Pre-specified peri-infusional AEs (reported within 24 hours of infusion), were reported by higher proportions of patients in both groups (22.8% vs 18.5%). These consisted mainly of headache, dizziness, and nausea. Few of these AEs were severe.

The frequency of treatment discontinuation due to a pre-specified infusion reaction was low (0.6% of abatacept-treated patients vs 0.2% of placebo-treated patients). Further, few patients (≤ 0.5% in each group) had a pre-specified infusional event either within 1 hour or 24 hours following the first infusion after a dose interruption.

In the open-label period, acute infusion events were similar to those in the double-blind period. One patient who received placebo during the double-blind period had a very severe and serious anaphylactic/anaphylactoid reaction with hypotension and dyspnea on Day 373 after the first dose of abatacept.

Thus, the infusion tolerability profile of abatacept was excellent even though study protocols did not require premedication. Severe events and events requiring discontinuation of therapy were uncommon as were anaphylactic-type reactions. As with all biologic therapies, there is a potential risk of anaphylaxis and/or hypersensitivity reactions and infusions should be given under medically controlled conditions, with medications for the treatment of hypersensitivity reactions available for immediate use.

6.2.6.5 Immunogenicity

The immunogenicity of abatacept was assessed using a direct-format ELISA to determine serum levels of anti-abatacept antibodies. Samples were assayed from 1993 evaluable, treated patients in phase II and III. Anti-abatacept antibodies were detected in:

- 1.7% (34/1993) of patients overall;
- 2.6% (10/387) of patients who missed one or two doses of abatacept;
- 2.3% (2/88) of patients who went more than 30 days without drug between double-blind and open-label; and
- 5.8% (9/154) of patients who discontinued drug for up to 85 days.

To determine the effect of development of anti-abatacept antibodies on exposure to abatacept, population PK analysis was performed on data from patients with confirmed antibody development. Estimates of PK parameters (clearance, central compartment volume, steady-state AUC, and steady state Cmin) were comparable in antibody-positive patients and the larger population of patients who did not develop anti-abatacept antibodies.

To assess the effect of development of anti-abatacept antibodies on the efficacy and safety of abatacept, the ACR response and adverse event profiles were examined in patients who developed anti-abatacept antibodies. Due to the small number of patients that developed an immune response and the difficulty in precisely establishing the time of onset of antibody development, no definitive conclusions can be made concerning the

impact of immunogenicity on safety and efficacy; however, the development of immunogenicity in patients did not appear to be associated with loss of efficacy or adverse safety outcomes.

Neutralizing antibody activity was studied in an in vitro T cell-activation bioassay, which assessed the ability of serum to inhibit the activity of abatacept. Because abatacept interfered with this assay, only samples with abatacept concentration of ≤ 1 μg/mL could be studied. Neutralizing antibody was documented in 7 of 10 evaluable samples (6 of 9 patients).

Overall, these data support that abatacept is associated with very low immunogenic potential.

6.3 Adverse Events by Subgroup

6.3.1 Demographics

The safety experience was similar when analyzed by gender, race and geographic region. An increase in the frequency of SAEs was observed in older (≥ 65 years) patients (24% for abatacept vs 16% for placebo). Approximately two-thirds of this difference was accounted for by differences in the rate of serious infection (5.6 vs 2.5%) and malignancy (5.3 vs 2.7%). Both serious infection and malignancy were more common in the elderly than in younger patients, regardless of treatment group. There was no discernible pattern in the occurrence of other serious adverse events.

A total of 21 serious infections was reported in 18 abatacept-treated elderly patients. One was viral (influenza), while the others were either confirmed or presumed to be bacterial. The most common type of infection was respiratory (10 patients, 11 infections, predominantly pneumonia or bronchitis) followed by soft tissue (4 patients, 5 infections) and urinary tract (3 patients, 3 infections) infections. Of the 10 patients with respiratory infections, 8 were receiving concomitant steroids and 7 had underlying cardiopulmonary disease such as heart failure or chronic obstructive pulmonary disease (COPD).

No elderly patients died due to serious infection. Of the 21 cases, 18 were reported to resolve. Study therapy was continued in 15 of the 18 elderly patients with serious infection.

Abatacept-treated elderly patients reported 17 cases of malignancy. The most common types were non-melanoma skin (9) and lung (4). As noted earlier, 2 cases of lung cancer were reported within 100 days of initiating study therapy and a third case had pre-existing radiographic abnormalities suggestive of malignancy. These cases are unlikely to be related to abatacept. In the open-label study periods, 9 elderly subjects (2.6%) reported a total of 11 malignancies. Nine (9) of these were skin cancers, including 1 melanoma in situ.

6.3.2 Disease Characteristics

No clinically notable findings were observed when AEs and SAEs were evaluated by baseline ANA, baseline ACR functional class, baseline HAQ score, baseline CRP, and baseline RF status. There was an overall pattern of increased frequency of SAEs, particularly RA-related SAEs and infections, observed in patients with more severe RA (ACR functional Class III, baseline HAQ scores > 2.0, baseline CRP > 2.5, and seropositive RF). This was observed equally for both treatment groups and is consistent with the natural pattern of disease complications observed in the general RA population.

6.3.3 Co-morbidity

In Study IM101031, the safety of abatacept in patients with comorbid conditions (asthma, COPD, CHF, diabetes mellitus type 1 and type 2) was collected and analyzed. The number of these patients was small and results should therefore be interpreted cautiously. There was an apparent trend for more respiratory AEs (16/37 [43.2%] vs 4/17 [23.5%]) and more overall SAEs (10/37 [27.0%] vs 1/17 [5.9%]) in patients with COPD and treated with abatacept vs placebo. There was no apparent increased risk of AEs in patients with asthma or CHF. There were no clear differences in the overall frequency of AEs, infections or loss of diabetes control in patients with diabetes mellitus. The number of diabetic patients in the abatacept group reporting SAEs was higher (21.5%) than those in the placebo group (12.9%); the difference was primarily driven by more musculoskeletal disorders and injuries.

6.3.4 Conclusions

Overall, subgroup analysis results are generally consistent with main safety analysis results. The frequency of SAEs was higher for abatacept than for placebo in patients ≥ 65 years of age. Because there is a higher frequency of infections and malignancies in the elderly in general, caution should be used when treating the elderly with abatacept.

6.4 Safety of Abatacept in Combination with Biologic Therapy

The data set for abatacept used chronically in combination with another biologic RA therapy is limited to 338 patients, primarily from 2 studies (IM101101 and IM101031). Overall, the risk of infection appeared higher in abatacept-treated patients on concomitant biologic anti-RA therapies, including TNF-blocking therapy and an IL-1 antagonist, than in patients receiving non-biologic DMARDs.

A summary of the safety profile of abatacept in patients who received both abatacept and a biologic RA therapy (N = 204) or placebo plus biologic therapy (N = 134) is presented in Table 6.4. Abatacept was given at 2 mg/kg in Study IM101101 (ie, to approximately half of the patients in this data set) and at a fixed dose approximating 10 mg/kg in IM101031.

Table 6.4: Summary of Safety in Double-blind, Controlled Study Periods: Biologic Background Therapies

Event	Number (%) of Patients	
	Abatacept + Biologic (N=204)	Placebo + Biologic (N=134)
Deaths	0	0
SAEs	40 (19.6)	12 (9.0)
Discontinuation due to SAEs	9 (4.4)	3 (2.2)
AEs	192 (94.1)	113 (84.3)
Discontinuations due to AEs	19 (9.3)	6 (4.5)
Infections	130 (63.7)	58 (43.3)
Serious Infections	9 (4.4)	2 (1.5)
Neoplasms (benign and malignant)	10 (4.9)	2 (1.5)

SAEs and study discontinuations due to AEs were more frequent for abatacept-treated patients with background biologic therapy than for placebo-treated patients with background biologic therapy. The proportion of patients reporting infections was higher in the abatacept plus biologic group than the placebo plus biologic group (63.7% vs 43.3%). These infections were mainly mild to moderate respiratory tract infections (upper respiratory tract infection, sinusitis, bronchitis, and influenza). Serious infections were reported in 4.4% and 1.5% of abatacept plus biologic vs placebo plus biologic patients, respectively. These were all localized bacterial infections that responded appropriately to therapy. None were disseminated, unusual, or fatal.

The frequency of neoplasms (benign, malignant, or unspecified) during double-blind treatment was low but higher in the abatacept plus biologic group than in the placebo plus biologic group (4.9% vs 1.5%). Three (3) patients (1.5%) treated with abatacept and biologic RA therapy had 4 malignant non-melanoma skin neoplasms compared with 0 patients in the placebo plus biologic group.

Thus, data from this relatively small subset of patients receiving abatacept on a background of biologic RA therapy suggest that the combination of 2 biologic therapies with different mechanisms of action increases the frequency of infection, including serious infections. The impact of 2 biologic therapies on the risk for developing neoplasms is difficult to evaluate because of the small numbers of patients and the low frequency of these events. Because the efficacy of abatacept in conjunction with another

biologic agent has not been established (see Section 5), concurrent therapy with abatacept and another biologic RA therapy is not recommended. While transitioning from a biologic RA therapy to abatacept, patients should be monitored carefully for signs of infection.

6.5 Safety of Abatacept Monotherapy (Study IM103002)

Abatacept administered as monotherapy (without concomitant non-biologic DMARDs or biologic RA therapy) was studied in Study IM103002. The frequencies of AEs reported by subjects receiving 3 dose levels of abatacept (0.5, 2 and 10 mg/kg) were similar, therefore the data was pooled. The majority of subjects in the abatacept group and the placebo group reported AEs (81.0% vs 75.0%). The most frequently reported AEs (in at least 10% of subjects) for subjects treated with abatacept or placebo were: arthritis (21% vs 38%), musculoskeletal pain (19% vs 19%), headache (17% vs 6%), and upper respiratory infection (10% vs 6%).

There were no deaths in Study IM103002. SAEs were reported by a slightly higher proportion of subjects in the placebo group than the abatacept group (18.8% vs 14.4%). SAEs reported by the abatacept group (N=90) included: RA (flare or worsening arthritis, 8 cases, 8.9%) and 1 subject each of malignant breast cancer, rectal bleeding, osteoporosis, gastrointestinal bleeding, orthopedic surgery, infection bone/joint, dyspnea, and peptic ulcer. SAEs reported by the placebo group (N=32) included RA (flare or worsening arthritis, 5 cases, 15.6%) and 1 case of memory impairment.

Discontinuation due to worsening RA was not classified as discontinuation due to an AE, but as a lack of efficacy in this study. Ten (10) of the 32 subjects in the placebo group discontinued for worsening RA (31%) compared with 12 of 90 subjects in the abatacept group (13%).

6.6 Summary of Safety Findings

The following is a summary of the key safety findings from the RA studies:

Double-Blind Controlled Study Periods

- For the overall RA population, the frequency of SAEs (13.6% vs 12.3%), discontinuations due to SAEs (2.7% vs 1.6%), and discontinuations due to AEs (5.5% vs 3.9%) were slightly higher in the abatacept group compared with placebo. Death was infrequent and comparable between treatment groups (0.5% for abatacept vs 0.6% for placebo)
- The most commonly reported AEs in the abatacept and placebo groups were headache (18.2% vs 12.6%), upper respiratory tract infection (12.7% vs 12.0%), nausea (11.5% vs 10.6%), and nasopharyngitis (11.5% vs 9.1%). The majority of these AEs were mild to moderate in severity.
- There were small differences in the overall frequencies of infection (53.8% vs 48.3%) and serious infections (3.0% vs 1.9%) in the abatacept group compared with the placebo group. There were no differences in the severity of infections or the use of IV antibiotics, and the proportion of patients discontinuing due to an infection was similar (1.2% vs 1.0%). Most infections were caused by typical pathogens, and responded to appropriate antibiotic treatment with resolution.
- Malignant neoplasms were reported in a similar proportion of patients in the abatacept and placebo groups (1.3% vs 1.1%). The risk of lymphoma appears to be similar to that associated with rheumatoid arthritis itself, and there is no clear evidence of an increased risk for other tumor types, including lung cancer. However, given the low event rate, a potential risk for individual tumor types cannot be excluded based on relatively limited sample size and short observation period in clinical trials. Malignancies during abatacept use should continue to be monitored to accumulate broader safety experience, and provide a better estimate of the malignancy incidence with abatacept treatment relative to the broader RA patient population.
- Safety data from the double-blind periods do not suggest that use of abatacept is associated with an increased risk of developing medically important autoimmune disorders.
- Abatacept infusions were well tolerated, and allergic-type reactions were infrequent and generally balanced between treatment groups.
- Analysis of the safety data from the small subset of patients receiving abatacept or placebo on a background of biologic RA therapy indicate that the risk of infection is higher in abatacept-treated patients receiving concomitant biologic RA therapy. The efficacy of abatacept in conjunction with another biologic agent has not been

established. Therefore, concurrent therapy with abatacept and another biologic RA therapy is not recommended. While transitioning from a biologic RA therapy to abatacept, patients should be monitored carefully for signs of infection.

- The frequencies and types of AEs and SAEs did not vary substantially between subgroups, with the exception of SAEs in patients > 65 years of age (abatacept 24.1% vs placebo 16.2%). No individual SAE or group of SAEs were identified that would prevent the use of abatacept in appropriate elderly patients.

Open-Label, Uncontrolled Study Periods

- Abatacept exhibited a safety profile in the open-label periods similar to that observed in the double-blind periods, with no apparent increase in the risk of malignancy or serious infections.

Cumulative Double-Blind and Open-Label Periods

- Abatacept treatment resulted in a low frequency of host anti-abatacept antibody responses (1.7%).

7 PHARMACOVIGILANCE PLAN

The clinical trials to date demonstrate a small increase in the risk of serious infection with abatacept compared with placebo. Compared with placebo, the overall risk of malignancy is comparable and consistent with the background incidence rates of malignancy in RA patients treated with DMARDs. However, the clinical trials neither contain sufficient numbers of patients nor follow up of sufficient duration to assess long-term treatment or to rule out increases in the risk of AEs of long latency such as malignancy.

BMS proposes 3 actions to address these questions:

1) Enhanced safety monitoring;
2) Long-term follow-up of ongoing studies; and
3) Pharmacoepidemiology studies.

7.1 Enhanced Safety Monitoring

BMS will conduct a real-time review of all AE reports collected from all sources (spontaneous and literature reports, and safety information from the ongoing clinical and

non-clinical studies), with particular emphasis on the adequacy of the information, biological plausibility, and whether additional information is required to evaluate the event(s) in the context of the disease under treatment, concurrent disease, and concomitant medications.

For AEs of special interest, such as infections and malignancy, follow-up questionnaires have been designed to collect targeted clinical information. In addition to routine follow up procedures, a safety scientist or safety physician will telephone the reporting health care professional to obtain additional information for selected AEs of special interest or potential new important safety signals.

7.2 Long-term Follow-Up of Ongoing Studies

Five (5) studies are available for long-term follow-up of abatacept-treated patients to assess for potential risk of malignant neoplasms and other potential adverse events. These studies are the uncontrolled study periods of clinical protocols IM101100, IM101101, IM101102, IM101029, and IM101031. At present, over 2000 patients are enrolled in these long-term, open-label periods. Data (AEs, SAEs and discontinuations due to AEs) from these studies will be collected and periodically analyzed. BMS plans to follow the patients in these studies for at least 5 years.

7.3 Pharmacoepidemiology Studies

The main objective of the post-approval studies is to estimate the incidence rates of targeted infections and malignancies in patients treated with abatacept compared with those treated with DMARDs or with other biologic RA therapies. The studies will accrue data that can also be used to evaluate potential signals for unanticipated but medically important adverse events. In addition, the studies will provide data useful to assess treatment patterns and appropriateness of abatacept use.

At the present time, the following 2 studies are proposed to accomplish these objectives:

1) A cohort study utilizing a medical and pharmacy claims database. This study is planned to be conducted using the United Health Care database, which has claims data and the ability to access medical records on 11 million patients and accrues 2% of prescription fills in the United States. Patients will be identified based on a combination of International Classification of Diseases version 9 (ICD-9) diagnosis

codes, current procedural terminology (CPT) codes and National Drug Codes (NDC) for pharmaceuticals. DMARD and biologic use, concurrent prescription medications, and co-morbidities will be identified from ICD-9 diagnosis or procedure codes and from NDC codes. Malignancies and infections will be identified by patterns of ICD-9 codes. The study will characterize prescribing patterns of abatacept (eg, patient characteristics, co-prescriptions, co-morbidities, etc) and assess the short-term risk of adverse events such as hospitalized infections associated with abatacept use in clinical practice. It is anticipated that, after 3 years the study will have 80% power to detect relative risks of approximately 2.0 for uncommon events such as hospitalized pneumonia. The study will be able to detect smaller increases in risk for more common events.

2) A cohort study utilizing an RA registry. This study is planned to include a total of 5000 abatacept-treated patients and 15,000 otherwise treated RA patients (RA patients taking a DMARD or biologic RA therapy). Patients will be enrolled at initiation of treatment with abatacept or other biologic RA therapy, adding or switching a DMARD to an existing regimen. These patients will be followed for 5 years after the last patient has been enrolled. The study sample size has been determined in order to detect an approximate doubling of lymphoma incidence rates compared with DMARD treatment. The study will be able to detect smaller increases in more common events such total malignancies and as hospitalized infections. Based on an assumed background lymphoma rate of 0.128 per 100 person-years exposure and 80% evaluable patients, the study would have 80% power to rule out a relative risk of approximately 1.75 for rare events such as non-Hodgkin's lymphoma.

Follow-up will be conducted semi-annually through patient contact to determine intercurrent malignancies, infections, and survival. Patient-reported events will be confirmed by physician interview and medical record review. Interim reports of incidence rates of malignancies will be computed after 5000, 10,000, and 15,000 person-years of abatacept treatment have accrued. The final analysis and report will be completed after the last patient enrolled has completed follow-up.

8 BENEFIT-RISK CONCLUSIONS

Abatacept has a mechanism of action that is different from that of existing therapies for RA. Abatacept inhibits, without totally blocking, multiple aspects of T cell-driven autoimmunity and inflammation. While abatacept directly modulates T-cell function, it also secondarily inhibits the production of pro-inflammatory cytokines, such as IL-6 and TNF-α and autoantibodies, such as RF. The development of abatacept was driven by the

potential for its unique mechanism of action to provide clinically meaningful benefits to RA patients who have not had an adequate response to existing therapies.

The potential benefit of abatacept was confirmed in the clinical development program. Abatacept demonstrated consistent and statistically robust effects on all primary and secondary endpoints in each of the 3 principal efficacy trials. Collectively, these data demonstrated clear efficacy in treating the signs and symptoms of RA, inducing a major clinical response, improving physical function, inhibiting the progression of structural damage, and improving the quality of life in patients with moderate to severe RA.

More importantly, treatment with abatacept led to clinically meaningful benefits to patients. Of particular note are the substantial numbers of patients achieving higher order ACR responses (ACR 50, ACR70, and major clinical response), which reflect highly meaningful improvements in signs and symptoms, and the consistency of effects on patient-reported quality of life. In the Phase III trial in methotrexate inadequate responders, the proportion of patients achieving an ACR 70 response, representing an improvement of at least 70% in signs and symptoms, was 20% at Day 169, the primary time point, and reached 29% at Day 365. Similar results were observed for ACR 50 and for MCR. With regard to quality of life, abatacept demonstrated remarkably consistent effects, with statistically significant improvement in each of the 8 domains of the SF-36, as well as the physical and mental component summaries, in each of the 3 principal efficacy studies.

Abatacept also demonstrated consistent efficacy in patients with an inadequate response to existing therapeutic agents, including both non-biologic DMARDS and TNF-blocking agents. These data confirm that abatacept's mechanism of action is distinct from existing RA therapies, and demonstrates abatacept's potential to offer a significant medical benefit to patients with unmet need, particularly those with an inadequate response to TNF-blocking agents.

Abatacept was generally safe with an excellent tolerability profile. Because abatacept acts on the immune system, infection and malignancy were identified prospectively as particular concerns and examined carefully in the clinical program. The overall frequency of infections was slightly increased in abatacept-treated patients, but the severity, treatment, and outcome was similar to that in placebo-treated patients. Serious viral,

fungal, or mycobacterial infections were uncommon. Considering the demonstrated efficacy of abatacept, the risk of infection is relatively modest and acceptable.

The overall incidence of malignancies with abatacept was comparable to placebo. However, there are inherent limitations to the assessment of infrequent adverse events in a registrational clinical program. To better define the risk of malignancy and serious infection, BMS proposes a post-marketing pharmacovigilance plan which includes 2 large observational studies. These studies, together with other elements of the pharmacovigilance plan, will provide additional important information to confirm the current clinical observations in the marketplace.

In summary, the overall benefit/risk assessment of abatacept in patients with RA is clearly favorable. As the first selective costimulation modulator for use in RA, abatacept provides a new therapeutic option for patients with moderately to severely active rheumatoid arthritis and an inadequate response to 1 or more non-biologic DMARDS as well as TNF-blocking agents.

9 LIST OF ABBREVIATIONS

Term	Definition
ACR	American College of Rheumatology
ACR 20/50/70	ACR criteria for 20%/50%/70% improvement
AE	adverse event
ANA	antinuclear antibodies
APC	antigen presenting cell
BMS	Bristol-Myers Squibb
BMS-188667	abatacept
CHF	congestive heart failure
CI	confidence interval
COPD	chronic obstructive pulmonary disease
CRF	case report form
CRP	C-reactive protein
CSR	clinical study report
CTLA4Ig	cytotoxic T-lymphocyte antigen 4 immunoglobulin fusion protein
DAS	disease activity score
DI	disability index
DMARD	disease modifying anti-rheumatic drug
ECG	electrocardiogram
ELISA	enzyme-linked immunosorbent assay
ESR	erythrocyte sedimentation rate
ETAN	etanercept
HAQ	health assessment questionnaire
KLH	keyhole limpet hemocyanin
IFN-γ	gamma interferon
IL	interleukin

Term	Definition
IV	intravenous
IVRS	Interactive Voice Randomization System
JSN	joint space narrowing
LPS	lipopolysaccharide
LT	open-label extension
mACR	modified ACR
MCID	minimum clinically important difference
MCR	major clinical response
MedDRA	Medical Dictionary for Regulatory Activities
mHAQ	modified Health Assessment Questionnaire
mHAQ-DI	modified Health Assessment Questionnaire with disability index
MMP-3	matrix metalloproteinase-3
MTX	methotrexate
NSAID	non-steroidal anti-inflammatory drug
PD	pharmacodynamics
PK	pharmacokinetics
RA	rheumatoid arthritis
RF	rheumatoid factor
SAE	serious adverse event
SC	subcutaneous
SD	standard deviation
SE	standard error
SF-36	Health Outcomes Short Form Questionnaire
SIR	Standardized incidence ration
TNF	tumor necrosis factor
VAS	visual analog scale

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11 SUPPLEMENTAL REPORT AND TABLES

Note to Reviewers: A uniform system of report and table numbering has been used in final study reports for this project to ensure consistency in the location of data across these reports. Report and tables are numbered in accordance with the report section numbers that they support. Thus, gaps appear in the sequential numbering of supplemental report and tables for this report.

Bristol-Myers Squibb Company

SUPPLEMENTAL REPORT 3.7.3
OVERVIEW OF NON-CLINICAL CARCINOGENICITY STUDIES

1 NON-CLINICAL CARCINOGENICITY

A rodent carcinogenicity study was deemed pertinent to the overall safety evaluation of abatacept since the drug is biologically active and not immunogenic in rodents when maintained at biologically active levels. Additionally, it is being developed for long-term use as a selective immunomodulator, and long-term immunosuppression has been associated with an increased incidence of neoplasia in humans[1,2] and rodents.[3,4,5] As suggested in the ICH guidelines for biologics,[6] only a single rodent species was evaluated. The mouse was the species selected as the drug has demonstrated activity in mice, the literature indicates that long-term immunosuppressed mice have an increased incidence of neoplasia (particularly lymphomas),[3,4] and a previous chronic toxicity study in the mouse enabled dose selection. Dose selection for the carcinogenicity study was based on ICH guidelines.[6] The high dose was based on drug-related renal changes (exacerbation of spontaneous, age-related karyomegaly in renal tubular epithelial cells) that were` considered to have a possible impact on 2-year survivability. All doses induced immunosuppression, including suppression of abatacept-specific antibody responses. The low and high doses were at least 2 and 20 times, respectively, the dose that resulted in pharmacologically significant immunosuppression in mice based on models of efficacy and inhibition of bioactivity. The carcinogenicity study was adequately designed, included evaluation of exposure at all dose levels, and was conducted in conformance with applicable ICH guidelines and GLP regulations.

For data analysis, differences in tumor rates between groups were determined using the method of Peto and Pike,[7] which adjusts for both time and cause of death. For these analyses, the 2 control groups were pooled. A positive linear trend was considered statistically significant if P-values were < 0.005 and < 0.025 for common and rare tumors, respectively. The distinction between common (incidence > 1%) and rare (incidence < 1%) tumors was made by averaging concurrent and historical control tumor incidence data for a 5-year period. When the Peto test showed a positive linear trend, additional analyses were performed to find the dose level resulting in no significant trend (eg, by deleting all of the data from the highest dose group and performing the Peto test with the reduced data set). These procedures are consistent with recent guidance on the statistical evaluation of carcinogenicity studies.[8]

In the carcinogenicity study, abatacept was administered subcutaneously (SC) once weekly at doses of 20, 65, or 200 mg/kg. Toxicokinetic (TK) evaluations after the 53rd weekly dose showed that systemic exposures to abatacept were dose related with corresponding exposure multiples of 0.8, 1.,9 and 3.0 times, respectively, that in humans administered 10 mg/kg monthly (Table 1A**)**. At Weeks 84 and 88, 25% survivability was reached in the male and female low-dose groups, respectively, and, after consultation with the FDA, all remaining animals of that sex were sacrificed.

Table 1A Multiples of Abatacept Exposures in Mice at Doses Administered in the Carcinogenicity Study Compared to Humans

Species	Study	Dose (mg/kg)	AUC (TAU) (μg•h/mL)	AUC (30 days) (μg•h/mL)	Multiple of Human Exposure (x)
Human[a]	Multiple dose once monthly, IV	10	50,102	50,102	--
Mouse	Once weekly, subcutaneous	20	8,812	37,889[b]	0.8
		65	22,600	97,178[b]	1.9
		200	34,925	150,178[b]	3.0

[a] Source of human AUC data - Study IM101100; exposure at steady state

[b] AUC, interval = 168 h (7 days), multiplied by 4.3 to normalize for 1 month of exposure; exposures determined after the 53rd dose

Abatacept was associated with a non-dose-dependent increase in the incidence (17-35%) of lymphomas at all doses and a dose-dependent increase in the incidence (12-17%) of mammary tumors in females at the intermediate- and high-doses. The incidences of lymphomas and mammary tumors in control and drug-treated mice are shown in Tables 1B (lymphomas) and 1D (mammary tumors). For additional perspective, historical control tumor incidences for 18- to 24-month mouse carcinogenicity studies conducted at Bristol-Myers Squibb (BMS) are shown in Tables 1C (lymphomas) and 1E (mammary tumors). In order to provide data over a time period comparable to that for BMS data, Charles River Laboratories data from 1995 and 2000 and published literature are also included in Tables 1C and 1E.

Table 1B: Incidences of Lymphomas in Mice from Carcinogenicity Study

Group No.	1		2		3		4		5	
Dose (mg/kg/week)	Saline		Vehicle		20		65		200	
Sex	M	F	M	F	M	F	M	F	M	F
No. of Mice	60	60	60	60	60	60	60	60	60	60
No. with Lymphoma	1	4	1	7	18[a]	27[a]	22[a]	35[a]	17[a]	34[a]
Percentage with Lymphoma	1.7	6.7	1.7	11.7	30	45	36.7	58.3	28.3	56.7

[a] P values for the Peto and Pike (mortality adjusted) trend test were < 0.0001 for lymphomas in males and females compared to pooled control groups

Table 1C: Incidences of Lymphomas in Male (M) and Female (F) CD-1 Mice from Prior Studies at Bristol-Myers Squibb and Published Reports

References	Bristol-Myers Squibb Study Numbers[a]				Charles River Laboratories[b]		Tox. Path.[c]
Study No. or Year	90004	93601	96040	96651	1995	2000	1988
No. of Mice	100 M 100 F	100 M 100 F	120 M 120 F	120 M 120 F	423 M 425 F	2565 M 2822 F	891 M 890 F
Lymphoma	4% M 11%F	2% M 12% F	4.2% M 28% F	10% M 15% F	2-24% M 1-28% F	1-21% M 2-28% F	8.1% M 22% F

[a] Data derived from BMS studies

[b] Data derived from the animal vendor consists of several studies; incidence ranges are provided [9,10]

[c] Data derived from published literature[11]

Table 1D: Incidences of Mammary Gland Adenomas and Adenocarcinomas in Females from the Carcinogenicity Study

Group No.	1	2	3	4	5
Dose (mg/kg/week)	Saline	Vehicle	20	65	200
Sex	F	F	F	F	F
No. of Females	60	60	60	60	60
No. Mammary Glands Examined	60	57	55	58	58
No. Females with Adenomas	1 (1.7%)	0	2 (3.6%)	3 (5.2%)	2 (3.4%)
No. Females with Adenocarcinomas	1 (1.7%)	4 (7%)	1 (1.8%)	6[a] (10.3%)	8[b] (13.8%)
No. Females with Adenomas plus Adenocarcinomas	2 (3.3%)	4 (7%)	3 (5.5%)	7[c] (12%)	10[b] (17.2%)

[a] P value for the Peto and Pike (mortality adjusted) trend test was 0.006 compared to pooled controls.

[b] P value for the Peto and Pike (mortality adjusted) trend test was 0.0001 compared to pooled controls.

[c] P value for the Peto and Pike (mortality adjusted) trend test was 0.0017 compared to pooled controls.

Table 1E: Incidences of Mammary Gland Adenomas and Adenocarcinomas in Male and Female CD-1 Mice from Prior Studies at Bristol-Myers Squibb and Published Reports

References	Bristol-Myers Squibb Study Numbers[a]				Charles River Laboratories[b]		Tox. Path.[c]
Study No./Year	90004	93601	96040	99651	1995	2000	1988
No. of mammary glands examined	100	100	120	118	549	2573	890
Adenoma	1%	0%	0%	0%	0-2%	0-2.6%	1%
Adenocarcinoma	1%	3%	0.8%	2.5%	0-12%	0-8.3%	6.3%

[a] Data derived from BMS studies

[b] Data derived from the animal vendor consists of several studies; incidence ranges are provided[9,10]

[c] Data derived from published literature[11]

In mice, murine leukemia virus (MLV) and mouse mammary-tumor virus (MMTV) have been identified as a causative agent for lymphomas and mammary tumors, respectively.[11,12,13,14] Lymphoma, a common spontaneous neoplasm in CD-1 mice, is

usually caused by MLV.[71,12] Endogenous copies of the MLV genome are a permanent, heritable part of the genome of carrier mice, and activation of the virus results in neoplastic transformation.[15,16] Ecotropic DNA, believed to be a requisite for the development of an active viral infection and subsequent leukemia/lymphoma formation,[17,18] was detected in the genome of CD-1 mice used in this study by molecular analysis. Ecotropic-specific DNA comes from a retrovirus. Similarly, the presence of MMTV has been reported to significantly increase the incidence of mammary tumors in certain strains of female mice, and only females develop MMTV-induced mammary tumors[19] as was observed in the carcinogenicity study of abatacept. Ultrastructural and immunohistochemical evaluations confirmed the presence of this oncovirus in the mammary tumors from both the control and abatacept-treated mice.

Both MLV and MMTV are retroviruses that are integrated into the mouse genome. Although the DNA of these viruses is present in the germline of most mice, they are infrequently transcribed and translated into productive virions. If the viral DNA is functional, virus can be produced. MMTV can also be transferred through the mother's milk after birth. Despite an antiviral immune response that controls the acute infection, a persistent viral infection is established with infected cells sequestered in lymphoid and/or mammary tissue. In healthy animals, this infection is held in check by the immune system. In the case of MLV, immunocompetent mice have been shown to develop virus-neutralizing antibodies that block cell-to-cell spread of the virus and a cytotoxic T-lymphocyte response that eliminates virus-infected cells.[20] However, susceptible or immunosuppressed mice can subsequently develop an increase in the number of virus-infected cells. The greater the viral load, the greater the potential viral integration, and thus the greater the likelihood that an insertion will be placed next to a proto-oncogene, ultimately leading to neoplasia.

Lymphomas are a very common finding in carcinogenicity studies conducted with immunosuppressants, but an increase in mammary tumors has not been previously reported. Nonetheless, the immune response, particularly the humoral immune response, has been demonstrated by several laboratories to play an important role in delaying, if not preventing, the onset of mammary tumor development in MMTV-infected mice.[21,22] MMTV-specific antibodies have been found in mice infected as adults or as neonates, but not in uninfected mice. The antibodies that are generated are often directed against the

gp52 env protein and can be neutralizing and/or cytotoxic.[21] Generally, these neutralizing antibodies do not prevent virus persistence, transmission, or mammary tumor formation; however, they have been shown to delay the onset of tumor formation.[22] The exception to this finding is the I/LnJ strain of mice, which, when infected with MMTV, induce a very strong IgG2a neutralizing antibody response that is sustained throughout life.[23] This humoral response effectively controls the infection, but does not completely eliminate it. Because I/LnJ mice maintain a strong humoral response throughout life, they are protected from the oncogenic effects of the virus and do not develop mammary tumors. When this neutralizing antibody response was eliminated in I/LnJ mice by knocking out interferon (IFN)-γ, about 50% of infected mice developed tumors within 150 days, demonstrating the importance of this response in protecting mice from mammary tumor development.[24] Based on the low incidence of mammary tumors in untreated control CD-1 mice in the abatacept carcinogenicity study, it is plausible that a neutralizing antibody response may occur in the CD-1 mouse. The ability of abatacept to suppress humoral immune responses to a variety of T cell-dependent antigens is well established. Thus, one can hypothesize that, in the carcinogenicity study, abatacept suppressed the neutralizing anti-MMTV antibody response, permitting a greater viral load and allowing an accelerated onset of tumor development compared with control mice from this study that were also infected with MMTV.

Investigations to assess this hypothesis have demonstrated that in the outbred strain of mice used in the carcinogenicity study (CD-1 mice), 60% of the mice have the ability to develop IgG2a antibodies directed against MMTV following infection with MMTV. Furthermore, in I/LnJ mice, which are known to induce a strong neutralizing anti-MMTV antibody response, abatacept treatment was able to reduce this neutralizing antibody response. These data further support the hypothesis that, in the mouse carcinogenicity study, abatacept treatment interfered with the ability of the mice to adequately control the MMTV virus compared to controls, leading to an increased incidence of mammary tumors.

Animal carcinogenicity data are not available on the oncogenic potential of marketed protein therapeutic immunomodulators, such as the TNF-α-receptor fusion protein (etanercept),[29] anti-TNF-α monoclonal antibodies (infliximab[30] and adalimumab[31]),

interleukin-1 receptor antagonist (anakinra),[25] anti-IL-2 receptor antibodies (basiliximab[26] and daclizumab[27]) anti-T-cell receptor monoclonal antibody (OKT3),[28] or LFA3 receptor fusion protein (alefacept).[29] Since these drugs are not active in rodents and/or are immunogenic, long-term rodent studies were not considered feasible.

Commonly used small molecule immunosuppressants, such as azathioprine, cyclophosphamide, cyclosporine, leflunomide, tacrolimus, sirolimus, mycophenolate mofetil, and methotrexate, have been evaluated in rodent carcinogenicity studies. Azathioprine and cyclophosphamide are genotoxic. With azathioprine, increases in lymphomas (mice) and ear-duct carcinomas (rats) were observed, but the conclusions were not definitive.[30,31] In an unpublished mouse oral carcinogenicity study with azathioprine, the incidence of lymphocytic lymphoma was 35% at the high dose (100 mg/kg).[32] In humans, azathioprine is believed to be associated with an increased incidence of non-Hodgkin's lymphoma, skin cancer, and hepatobiliary carcinoma, as well as mesenchymal and other rare tumors.[33] Similarly, cyclophosphamide was shown to be carcinogenic in rodents and man. The relative contribution of genotoxicity versus immunosuppression to the development of these malignancies has not been determined.

Cyclosporine, which is non-genotoxic, has been examined in several rodent carcinogenicity studies.[34,35] These studies demonstrated that cyclosporine increased lymphocytic lymphomas, and possibly hepatocellular carcinomas and osteomas in mice.[36,37] In addition, islet cell adenomas significantly exceeded controls at the low dose in rats.[36] With sirolimus, an increase in lymphomas was reported in female mice and an increase in testicular interstitial cell tumors was observed in rats at less than human exposures. Leflunomide was positive for lymphomas and bronchioalveolar tumors in mice.[38] No evidence of carcinogenicity was observed in rats, but it is likely that less than immunosuppressive doses were evaluated, as exposures were only 1/40 of the human exposure.

Rodent carcinogenicity studies have also been conducted with tacrolimus,[39] mycophenolate mofetil,[40] and methotrexate.[41] The findings in these studies were either inconclusive or not suggestive of tumorigenicity. However, the exposure levels were often below those in humans, presumably due to dose-limiting, target-organ toxicity of

these compounds in rodents. Except for methotrexate, these immunosuppressive drugs are not considered genotoxic.

Overall, rodent carcinogenicity studies with small molecule immunosuppressants suggest that the incidence of neoplasia is increased if immunosuppressive doses are administered. The predominant tumor in mice is lymphoma, which is likely virally mediated. Other tumor types have also been noted in mice and rats, but with no obvious pattern. The inherent toxicity of these agents with long-term treatment limited exposures that could be assessed in carcinogenicity studies. High doses in rodent studies are often below those associated with clinical use of these agents.

Significantly, no evidence of lymphomas, other solid tumors, or preneoplastic morphologic changes, such as lymphoid hyperplasias, were observed in the 6-month or 1-year monkey toxicity studies conducted with BMS-224818 or abatacept, respectively. Furthermore, in a renal transplant study in which 16 rhesus monkeys received 10 to 20 mg/kg of BMS-224818 intermittently for up to 71 days, either alone or in combination with other immunosuppressants, there was no evidence of lymphoma or preneoplastic morphologic changes. Six of these animals did not survive beyond Day 50 due to transplant failure; the remaining 10 animals lived 100 days or longer.[42]

The absence of neoplastic or preneoplastic changes in monkeys treated with abatacept is in contrast with some other immunomodulatory drugs. In a study in which macaques received cardiac or heart-lung allografts, lymphomas were observed in 12 of 55 monkeys treated with either cyclosporine alone (25 mg/kg/day for 14 days and every other day thereafter or 17 mg/kg/day) or cyclosporine in combination with other immunosuppressants. Eighty percent of the lymphomas developed between 60 and 140 days after commencement of cyclosporine therapy, and viral particles were observed within neoplastic cells in 7 of the 8 cases examined.[43] In another study in which cyclosporine was administered at 10 mg/kg for at least 160 days to rhesus monkeys to prevent renal allograft rejection, lymphomas were not observed and no evidence of viral infection was found.[44] The findings from these 2 studies suggest a relationship between the degree of immunosuppression, the viral status in non-human primates, and the risk of neoplasia.

B-cell lymphoma was noted during a 1-year toxicity study in 1 high-dose monkey treated with alefacept (LFA-3 receptor fusion protein) after 28 weeks of dosing, and additional monkeys in this study developed B-cell hyperplasia of the spleen and lymph nodes.[45] Evaluation of the lymphoid tissue of these and other monkeys treated with alefacept showed evidence of B-cell hyperplasia, presumably mediated by gammaherpesvirus (LCV), which was detected in lymphocytes by molecular analysis.[45,46] Latent LCV infection is generally asymptomatic, but has been associated with B-cell lymphomas in immunosuppressed Old World primates.[47] No evidence of lymphoma was noted with the anti-TNF-α inhibitor, adalimumab, following 39 weeks of treatment in monkeys (evaluation for B-cell hyperplasia was not reported).[48] In the 1-year monkey study with abatacept, molecular analysis of lymphocytes obtained prior to study start demonstrated that 38/40 monkeys were DNA positive for LCV; yet, neither hyperplastic, preneoplastic, or neoplastic changes were seen in lymphoid tissues of any of the monkeys dosed with abatacept for 1 year. Due to the subtle nature of B-cell hyperplasia that can be induced by LCV in immunosuppressed primates, special attention was given by the study pathologists to the review of the lymphoid tissue for this microscopic lesion in this study, as well as the 6-month study with LEA29Y, to ensure that this lesion was not present.

Immunosuppression, whether due to natural disease states or drugs, is known to increase the incidence of tumors in humans. Examples include severe primary or acquired immunodeficiency syndromes and treatment with chemotherapeutic anticancer agents, which are associated with increased incidences of non-Hodgkin's lymphoma, leukemia, and other rare tumors in humans.[49] In these cases, it is likely that neoplastic cells arise from somatic mutations or oncogenic viral infection as a result of impaired immune surveillance. Strong circumstantial evidence links EBV, herpes, and papilloma viruses with tumors associated with immunosuppression in humans.[50,51,52] Herpes viruses have also been implicated in the pathogenesis of lymphoproliferative tumors and carcinoma of the skin and cervix, particularly in transplant recipients.[50]

Whereas MLV and MMTV retroviruses are endogenous to mice with no analogous counterparts in humans, there are other human cancers with a viral component, notably papilloma virus, HTLV-1, Hepatitis B and C, and EBV. Clearly, lymphomas are considered to be a class effect for marketed small molecule immunosuppressant compounds. Although an increased incidence of lymphomas has been observed with the

recently marketed TNF-α inhibitors, insufficient data are available to determine if the increased incidence is related to the treatment or if patients with the highest risk of developing lymphoma preferentially receive TNF-α inhibitors.[53] Although still controversial, most experts in the field do not believe that a clear link has been established between human breast cancer and MMTV or a human homologue of the virus (HMTV) because:

1) human tissue lacks the appropriate cell-surface receptor for entry of MMTVs/HMTVs,
2) unlike other virally induced human malignancies, immunodeficiency does not predispose to an increased incidence, or prevalence, of human breast cancers, and
3) reports of PCR amplification of MMTV/HMTV sequences from breast cancers have been robustly disputed by 4 independent laboratories.[54]

Virus-induced malignancies are a potential concern in humans treated with immunomodulating drugs, as demonstrated by the mouse carcinogenicity findings with abatacept. The overall incidence of malignancies in abatacept-treated subjects was similar to that of the placebo group. The incidence of lymphoma were similar to that expected in an RA population. Breast cancer was rare and less frequent than expected based on the incidence rate for the US general population.[55] However, given the low event rates for malignancies, the number of subjects studied in the abatacept development program, and known latency period for some malignancies, definitive assessment of the potential risk of malignancy cannot be made at this time.

2 LIST OF ABBREVIATIONS

Term	Definition
AUC	Area under the concentration vs. time curve
AUC(INF)	Area under the concentration vs. time from time 0 to infinity
AUC(TAU)	Area under the concentration vs. time during a specified interval
BMS	Bristol-Myers Squibb
DCN	Document Control Number
DNA	Deoxyribonucleic acid
EBV	Epstein Barr Virus
F	Female
FDA	Food and Drug Administration
GLP	Good Laboratory Practice (USA)
H	Hour
HMTV	Human mammary tumor virus
ICH	International Conference on Harmonization
IFN	Interferon
Ig	Immunoglobulin
IL	Interleukin
kg	Kilogram
LCV	Lymphocryptovirus
M	Male
MLV	Murine leukemia virus
MMTV	Mouse mammary tumor virus
µg	Microgram
mg	Milligram
NOAEL	No-observable-adverse-effect level
NOEL	No-observable-effect level
No.	Number
SC	Subcutaneous
TK	Toxicokinetic
TNF	Tumor necrosis factor

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Table S.5.4.1.5:
Baseline Clinical Rheumatoid Arthritis Characteristics

		Abatacept N = 433	Placebo N = 219
Duration of RA (yrs)	N	433	219
	Mean	8.5	8.9
	SD	7.3	7.1
	Median	6.0	7.0
	Min	0.0	1.0
	Max	44.0	35.0
Duration of RA Disease	<= 2 Years	99 (22.9%)	45 (20.5%)
	> 2 to <= 5 Years	93 (21.5%)	46 (21.0%)
	> 5 to <= 10 Years	106 (24.5%)	54 (24.7%)
	> 10 Years	135 (31.2%)	74 (33.8%)
Tender Joints	N	433	219
	Mean	31.0	32.3
	SD	13.2	13.6
	Median	28.0	31.0
	Min	3.0	6.0
	Max	66.0	68.0
Swollen Joints	N	433	219
	Mean	21.4	22.1
	SD	8.8	8.8
	Median	19.0	20.0
	Min	9.0	9.0
	Max	56.0	48.0

Population: All randomized and treated subjects.
Upper limit of 180 mins was imposed for Morning Stiffness; Range 0-180 mins.
RUN DATE: 30-JUL-2004 11:46

Table S.5.4.1.5:
Baseline Clinical Rheumatoid Arthritis Characteristics

		Abatacept N = 433	Placebo N = 219
Subject Pain Assessment (VAS 100 mm)	N	433	219
	Mean	63.3	65.9
	SD	21.1	20.6
	Median	67.0	70.0
	Min	4.0	3.0
	Max	99.0	99.0
Physical Function (HAQ Disability Index)	N	431	219
	Mean	1.7	1.7
	SD	0.7	0.6
	Median	1.8	1.8
	Min	0.0	0.0
	Max	3.0	3.0
Subject Global Assessment (VAS 100 mm)	N	433	219
	Mean	62.7	62.8
	SD	21.2	21.6
	Median	64.4	64.0
	Min	5.0	3.0
	Max	99.0	97.0

Population: All randomized and treated subjects.
Upper limit of 180 mins was imposed for Morning Stiffness; Range 0-180 mins.
RUN DATE: 30-JUL-2004 11:46

Table S.5.4.1.5:
Baseline Clinical Rheumatoid Arthritis Characteristics

		Abatacept N = 433	Placebo N = 219
Physician Global Assessment (VAS 100 mm)	N	433	219
	Mean	68.0	67.4
	SD	16.0	17.0
	Median	69.0	68.0
	Min	5.0	12.0
	Max	99.0	99.0
CRP (mg/dL)	N	433	219
	Mean	3.3	2.8
	SD	3.1	2.5
	Median	2.2	2.0
	Min	0.1	0.1
	Max	21.1	12.5
Rheumatoid Factor (IU/mL)	Negative	52 (12.0%)	31 (14.2%)
	Positive	354 (81.8%)	172 (78.5%)
Morning Stiffness (in minutes)	N	432	219
	Mean	97.8	89.6
	SD	60.9	61.2
	Median	90.0	60.0
	Min	0.0	0.0
	Max	180.0	180.0

Population: All randomized and treated subjects.
Upper limit of 180 mins was imposed for Morning Stiffness; Range 0-180 mins.
RUN DATE: 30-JUL-2004 11:46

Table S.5.4.1.5:
Baseline Clinical Rheumatoid Arthritis Characteristics

		Abatacept N = 433	Placebo N = 219
DAS-28	N	394	198
	Mean	6.8	6.8
	SD	0.9	0.8
	Median	6.8	6.8
	Min	3.7	4.4
	Max	8.7	8.7
MTX (Oral/Parenteral) Dose (mg/wk)	N	433	219
	Mean	16.1	15.7
	SD	3.6	3.5
	Median	15.0	15.0
	Min	7.5	7.5
	Max	30.0	25.0

Population: All randomized and treated subjects.
Upper limit of 180 mins was imposed for Morning Stiffness; Range 0-180 mins.
RUN DATE: 30-JUL-2004 11:46

Table S.5.4.2.3: Baseline Clinical Rheumatoid Arthritis Characteristics (Study IM101100)

Characteristic	Abatacept 10 mg/kg + MTX (N=115)	Abatacept 2 mg/kg + MTX (N=105)	Placebo + MTX (N=119)
Duration of RA (yrs)	n=114	n=105	n=117
Mean ± SD (Range)	9.7±9.8 (0-38)	9.7±8.1 (0-36)	8.9±8.3 (0-41)
Tender Joints	n=115	n=105	n=119
Mean ± SD	30.8 ± 12.2	28.2 ± 12.0	29.2 ± 13.0
Range	11.0-66.0	3.0-62.0	4.0-68.0
Swollen Joints	n=115	n=105	n=119
Mean ± SD	21.3 ± 8.4	20.2 ± 8.9	21.8 ± 8.8
Range	9.0-54.0	4.0-48.0	8.0-64.0
Pain (VAS 100 mm)	n=113	n=104	n=119
Mean ± SD	62.1 ± 21.4	64.3 ± 22.3	65.2 ± 22.1
Range	0.0-99.0	8.0-100.0	3.0-95.0
Physical Function (mHAQ 0-3)	n=115	n=105	n=119
Mean ± SD	1.0 ± 0.5	1.0 ± 0.5	1.0 ± 0.6
Range	0.0-2.5	0.0-2.5	0.0-2.3
Subject Global Assessment (VAS 100 mm)	n=113	n=105	n=119
Mean ± SD	60.1 ± 20.7	59.4 ± 23.7	62.8 ± 21.6
Range	10.0-100.0	8.0-99.0	4.0-94.0
Physician Global Assessment (VAS 100 mm)	n=113	n=105	n=119
Mean ± SD	62.1 ± 14.8	61.0 ± 16.7	63.3 ± 15.5
Range	20.0-98.0	8.0-95.0	18.0-93.0
CRP (mg/dL)	n=112	n=99	n=115
Mean ± SD	2.9 ± 2.8	3.2 ± 2.5	3.2 ± 3.2
Range	0.2-19.9	0.2-10.8	0.2-20.9
Morning Stiffness (in minutes)	n=115	n=103	n=119
Mean ± SD	97.9 ± 63.1	104.1 ± 63.9	106.0 ± 64.2
Range	0.0-180.0	0.0-180.0	0.0-180.0
MTX Dose (mg/wk)[a]	n=113	n=103	n=117
Mean ± SD	15.0 ± 4.4	15.8 ± 4.5	15.9 ± 4.1
Range	7.5-25.0	10.0-30.0	7.5-25.0
Rheumatoid Factor (IU/mL)% Positive	n=9986%	n=9086%	n=9076%

All treated subjects.

N= total number of subjects in each treatment group; n= subset of N.

[a] On Day 1, MTX use was not recorded for IM101100-18-8 (10 mg/kg), IM101100-18-14 (2 mg/kg), IM101100-76-10 (2 mg/kg) and IM101100 (placebo).

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Table S.5.4.3.4:
Baseline Clinical Rheumatoid Arthritis Characteristics

		Abatacept N = 258	Placebo N = 133
Duration of RA (yrs)	N	258	133
	Mean	12.2	11.4
	SD	8.5	8.9
	Median	11.0	10.0
	Min	1.0	0.0
	Max	43.0	44.0
Duration of RA Disease	<= 2 Years	32 (12.4%)	16 (12.0%)
	> 2 to <= 5 Years	31 (12.0%)	26 (19.5%)
	> 5 to <= 10 Years	59 (22.9%)	25 (18.8%)
	> 10 Years	136 (52.7%)	66 (49.6%)
Tender Joints	N	258	133
	Mean	31.2	32.8
	SD	13.0	13.4
	Median	30.0	32.0
	Min	4.0	12.0
	Max	67.0	67.0
Swollen Joints	N	258	133
	Mean	22.3	22.0
	SD	10.2	10.0
	Median	21.0	20.0
	Min	6.0	7.0
	Max	62.0	61.0

Population: All randomized and treated subjects.
Upper limit of 180 mins was imposed for Morning Stiffness; Range 0-180 mins.
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Table 5.4.3.4:
Baseline Clinical Rheumatoid Arthritis Characteristics

		Abatacept N = 258	Placebo N = 133
Subject Pain Assessment (VAS 100 mm)	N	255	133
	Mean	70.8	69.9
	SD	19.8	19.0
	Median	73.0	74.0
	Min	5.0	9.0
	Max	100.0	100.0
Physical Function (HAQ Disability Index)	N	258	133
	Mean	1.8	1.8
	SD	0.6	0.6
	Median	1.9	2.0
	Min	0.0	0.0
	Max	3.0	2.9
Subject Global Assessment (VAS 100 mm)	N	255	133
	Mean	69.2	69.7
	SD	19.7	20.3
	Median	71.0	74.0
	Min	8.0	6.0
	Max	100.0	100.0

Population: All randomized and treated subjects.
Upper limit of 180 mins was imposed for Morning Stiffness; Range 0-180 mins.
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Table 5.4.3.4:
Baseline Clinical Rheumatoid Arthritis Characteristics

		Abatacept N = 258	Placebo N = 133
Physician Global Assessment (VAS 100 mm)	N	258	132
	Mean	68.8	67.3
	SD	17.7	16.8
	Median	70.5	69.5
	Min	13.0	16.0
	Max	100.0	100.0
CRP (mg/dL)	N	258	133
	Mean	4.6	4.0
	SD	4.0	3.6
	Median	3.3	2.9
	Min	0.1	0.3
	Max	24.9	15.1
Rheumatoid Factor (IU/mL)	Negative	52 (20.2%)	30 (22.6%)
	Positive	189 (73.3%)	97 (72.9%)
Morning Stiffness (in minutes)	N	258	133
	Mean	121.1	115.3
	SD	61.5	60.8
	Median	120.0	120.0
	Min	0.0	5.0
	Max	180.0	180.0

Population: All randomized and treated subjects.
Upper limit of 180 mins was imposed for Morning Stiffness; Range 0-180 mins.
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Table 5.4.3.4:
Baseline Clinical Rheumatoid Arthritis Characteristics

		Abatacept N = 258	Placebo N = 133
DAS-28	N	222	109
	Mean	6.9	6.9
	SD	1.0	1.0
	Median	7.0	7.0
	Min	3.9	2.6
	Max	8.9	8.7
MTX (Oral/Parenteral) Dose (mg/wk)	N	194	109
	Mean	15.2	14.4
	SD	5.3	6.1
	Median	15.0	15.0
	Min	0.5	1.0
	Max	35.0	28.0
Current/Prior Anti-TNF Status	Current	98 (38.0%)	55 (41.4%)
	Prior	160 (62.0%)	78 (58.6%)

Population: All randomized and treated subjects.
Upper limit of 180 mins was imposed for Morning Stiffness; Range 0-180 mins.
RUN DATE: 18-AUG-2004 13:56

Table S5.5.2: Modified ACR 20 Responses at Month 6 (Study IM101101)

Parameter	Abatacept 2 mg/kg + Etanercept (N = 85)	Placebo + Etanercept (N = 36)
n (%)	41 (48.2)	11 (30.6)
Estimate of the difference with respect to placebo (95% CI)	17.7 (-1.6, 37.0)	NA
p-value	0.072	NA

ITT Population.

N = total number of subjects randomized in each treatment group; n= number of subjects with an assessment.

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.