BRIEFING DOCUMENT

Application Type	BLA
Submission Number	125118/0
Reviewer Name	Keith M Hull, MD, PhD
Team Leader	Jeffrey Siegel, MD
Division Director	Marc Walton, MD, PhD
Established Name	Abatacept
(Proposed) Trade Name	Orencia
Applicant	Bristol-Myer-Squibb
Formulation	human, recombinant fusion protein: extracellular domain of CTLA-4 and Fc domain of human IgG1
Dosing Regimen	Tiered-dose based on subject's weight: <60 kg; abatacept 500 mg/kg ≥60 kg to ≤100 kg abatacept 750 mg >100 kg received abatacept 1000 mg
Indication	treatment of signs and symptoms, major clinical response, inhibition of structural damage
Intended Population	moderately to severely active rheumatoid arthritis

TABLE OF CONTENTS

1. BACKGROUND

1.1 Product Information

Abatacept (CTLA-4Ig) is a disulfide-linked homodimer fusion protein of approximately 92 kDa. Each homodimer is a fusion protein composed of the extracellular domain of human CTLA-4 fused to modified sequence from the human IgG1 Fc region. The human IgG1 sequence is derived from the hinge-CH2-CH3 domain.

Abatacept will be supplied as a sterile, white, preservative-free, lyophilized powder for parenteral administration. Each single-use vial of abatacept will provide 250 mg abatacept, 500 mg maltose, 17.2 mg sodium phosphate monobasic, and 14.6 mg sodium chloride for administration.

Abatacept's proposed trade name is Orencia. In the scientific literature this product has been referred to as abatacept, CTLA-4Ig, and BMS-188667. The sponsor proposes that abatacept be administered as an intravenous infusion at a fixed-dose approximating 10 mg/kg for the indication of reducing the signs and symptoms of RA, inducing a major clinical response, inhibiting the progression of structural damage, and improving physical function in adults with moderately to severely active RA, who have had an inadequate response to one or more disease-modifying anti-rheumatic drugs (DMARDs), including TNF-blocking agents. The sponsor also proposes that abatacept may be used in combination with other non-biologic DMARDs.

1.2 Mechanism of Action

CTLA4-Ig acts as an immunosuppressant agent to inhibit the activation of T cells. T-cells require at least 2 distinct signals for full activation, differentiation, and survival. The antigen-specific signal is initiated when the antigen-specific T-cell receptor binds to the antigen- MHC complex found on antigen-presenting cells (e.g., macrophages or dendritic cells). The other signal is antigen-independent and is mediated by T-cell co-stimulatory molecules, of which the CD28-CD80/86 system is the best characterized. CD28 on the surface of the T-cell binds to either CD80 or CD86 on the antigen presenting cell and generates a co-stimulatory signal in the T-cell.

CTLA-4 is a cell surface receptor that normally down-regulates T-cell activation. CTLA-4 is expressed by T-cells following T-cell activation and also binds to CD80 and CD86 on the antigen present cells but with higher avidity than CD28. Consequently, CTLA-4 is able to "out-compete" CD28 for binding to CD80 or CD86 and thereby inhibits further T-cell activation.

Abatacept derives its immunosuppressant activity from its capacity to bind to CD80/86 via the CTLA-4 domain and block CD28-CD80/86 interactions resulting in a decrease in T cell activation. In addition, binding of CTLA4-Ig can result in direct signaling through CD80/86 leading to the emergence of immune suppressive antigen-presenting cells.

Together these activities of CTLA4-Ig may act to suppress the autoimmune disease, rheumatoid arthritis.

1.3 Guidance document for clinical development programs for RA

In the document entitled "Guidance for Industry: Clinical Development Programs for Drugs, Devices, and Biological Products for the Treatment of Rheumatoid Arthritis (RA), 1999" the FDA offers guidance on the conduct of clinical trials in RA. The document describes six efficacy claims: Reduction in the signs and symptoms of RA; Major clinical response; Complete clinical response; Remission; and Improvement in physical function/disability. To support the claim of reduction in signs and symptoms, a clinical trial should be at least six months' duration unless the product belongs to an already well-characterized pharmacologic class (e.g. NSAIDs). Acceptable outcome measures include validated composite endpoints of signs and symptoms as well as well-accepted sets of signs and symptoms measures. Evidence should be provided about symptoms over time during the trial and not just at the final study visit.

The RA guidance document also discusses the importance of assessing the use of new products in combination with concurrent active therapies including corticosteroids and NSAIDs. In particular, because methotrexate is used to treat many patients with RA, the potential for immunosuppression from combination therapy should be assessed.

1.4 Fast Track Designation

Fast Track designation was granted when BMS agreed to extend study IM101029 to a total of 2 years in order to obtain data on improvement in physical function in subjects who had an inadequate response to TNF-blocking agents.

2. PHARMACOKINETICS/PRE-CLINICAL STUDIES

2.1 Pharmacokinetics

Following a single intravenous dose of 10 mg/kg of abatacept in healthy adult subjects, the mean terminal half-life was 16.7 days, ranging from 12 to 23 days. The systemic clearance of abatacept was approximately 0.23 mL/h/kg. The distribution volume (Vss) ranged from 0.06 to 0.13 L/kg. The maximum serum concentration (Cmax) of abatacept following this dose was approximately 290 μg/mL.

After multiple intravenous infusions (days 1, 15, 30, and monthly thereafter), the pharmacokinetics of abatacept in RA patients showed proportional increases of Cmax and AUC over the dose range of 2 mg/kg to 10 mg/kg. At 10 mg/kg, the mean terminal half-life was 13.1 days, ranging from 8 to 25 days. The mean distribution volume (Vss) was 0.07 L/kg and ranged from 0.02 to 0.13 L/kg. The systemic clearance was approximately 0.22 mL/h/kg. Mean steady-state trough concentrations were approximately 25 μg/mL, and mean Cmax concentrations were approximately 290 μg/mL. No systemic accumulation of abatacept occurred upon continued repeated treatment with 10 mg/kg at monthly intervals in RA patients. The pharmacokinetics of abatacept in RA patients and healthy subjects appeared to be comparable.

Population pharmacokinetic analyses revealed that there was a trend toward higher clearance of abatacept with increasing body weight. However, clinical response was not affected by body weight. No trends were noted for age or renal function. After correction for body weight, gender was not found to influence the pharmacokinetics of abatacept. MTX, nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, and TNF blocking agents were not found to influence abatacept clearance.

The pharmacokinetics of abatacept has not been studied in children and adolescents. No formal studies were conducted to examine the effects of either renal or hepatic impairment on the pharmacokinetics of abatacept.

2.2 Animal Pharmacology/Toxicology

The non-clinical toxicology review concludes that the results of the non-clinical toxicology studies submitted by the sponsor adequately support the approval of abatacept for use in patients with RA. The effects observed in the non-clinical studies reflect the intended pharmacological effect of the product. The main concern identified during non-clinical testing was an increase in the incidence of malignant lymphomas and mammary gland tumors (in females) in the mouse carcinogenicity study. The increased incidence of lymphomas and mammary tumors observed in mice treated with abatacept was associated with the decreased control of murine leukemia virus and mouse mammary tumor virus, respectively, in the presence of long-term immunomodulation. No mutagenic potential of abatacept and no chromosomal aberrations in human lymphocytes with abatacept were

observed in a battery of in vitro genotoxicity studies. These findings support the conclusion by the sponsor that the increased malignancies in this study were secondary to long-term induced immunosuppression and the control of these specific oncoviruses.

3 CLINICAL DEVELOPMENT OVERVIEW

3.1 Proposed Indication

The sponsor proposes that 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, including TNF blocking agents. Furthermore, the sponsor proposes that abatacept may be used in combination with methotrexate or other non-biologic DMARD therapy and implies that abatacept can be used as monotherapy.

3.2 Methods

There were a total of 6 well-designed and conducted, double-blind, randomized, placebo-controlled studies (Table 1) used to assess the efficacy of abatacept in subjects with moderately to severely active RA; however, the primary review of the efficacy claims are focused on 3 of the studies:

- Study IM101100 and IM101102 enrolled subjects with an inadequate response to MTX and were designed to assess claims for improvement in signs and symptoms of RA, induction of major clinical responses, improvement in physical function, and inhibition of progression of structural damage. The claims for improvement in signs and symptoms, induction of major clinical response, and physical function are established by the efficacy findings from the 12-month, double-blind period of these studies. Data from the open-label period of study IM101100 was evaluated for demonstrating improvement in physical function through 3 years of abatacept treatment. Evidence for inhibition of structural damage at 12 months is provided in study IM101102.

- Study IM101029 assessed signs and symptoms of RA at 6 months in subjects with an inadequate response to TNF-blocking agents (etanercept and/or infliximab).

The 3 remaining studies (IM101101, IM101031, and IM103002) support the efficacy findings of the 3 principal studies mentioned above. Briefly, IM101101 evaluated the safety and efficacy of abatacept 2 mg/kg with concomitant etanercept in subjects with an inadequate clinical response to etanercept alone. Study IM101031 was a 12-month study in a patient population representative of RA patients in a clinical practice, including patients with clinically important co-morbidities. The primary endpoint of study IM101031 was to demonstrate and characterize the incidence of adverse event (AE) rates between abatacept and placebo treatment arms. A secondary endpoint evaluated

improvement in physical function using the HAQ score and will be discussed below. Study IM103002 was a dose range-finding study that also assessed abatacept monotherapy compared with placebo in subjects without concomitant background DMARD therapy. Data from study IM103002 are used by the sponsor to support the efficacy of abatacept monotherapy.

Abatacept was administered by intravenous infusion over 30-minutes in all studies except for study IM103002 where abatacept was administered over 1 hour. Abatacept was administered on study Days 1, 15, 29 and every 28 days thereafter. The proposed abatacept dose and that used in all Phase III and open-label periods is a "tiered-dose" regimen where subjects weighing < 60 kg received 500 mg, subjects weighing 60 to 100 kg received 750 mg, and subjects weighing > 100 kg received 1 g. The tiered-dose regimen approximates 10 mg/kg (± 25%).

Table 1. Overview of Completed Controlled, Double-Blind Period Studies for Abatacept

Study Phase	Study Design	Background RA Therapy	Control Subjects (n)	Number of Subjects Treated with Abatacept		Total
				Tiered- dose	Other Doses (mg/kg)	
IM101100* Phase IIb	Randomized, dose-ranging, placebo-controlled, double-blind	Day 1-180: MTX (10-30 mg/week) Day 181-360: Adjustment allowed (+1 non-biologic DMARD)	119	115	105 (2.0)	339
IM101101* Phase IIb	Randomized, placebo-controlled, double-blind	Day 1-180: etancercept (25 mg/BIW) Day 181-360: Adjustment allowed (-etan, +1 non-biologic DMARD)	36	0	85 (2.0)	121
IM101102* Phase III	Randomized, placebo-controlled, double-blind	Day 1-169: MTX (10-30 mg/week) Day 170-365: Adjustment allowed (+1 non-biologic DMARD)	219	433	0	652
IM101029* Phase III	Randomized, placebo-controlled, double-blind	Day 1-169: any non-biologic DMARD and/or anakinra	133	258	0	391
IM101031* Phase III	Randomized, placebo-controlled, double-blind	Day 1-85: Stable doses: ± Non-biologic DMARD ± Biologic DMARD Day 86-360: Adjustment allowed: ± Non-biologic DMARD ± Biologic DMARD	482	959	0	1441
IM103002 Phase IIa	Randomized, placebo-controlled, double-blind	None	32	32	58 (0.5 or 2)	122
Totals			1021	1797	248	3066
*** these studies have uncontrolled open-label periods that are currently ongoing.**						

3.3 General Discussion of Endpoints

Rheumatoid arthritis is a systemic, chronic, inflammatory autoimmune disease that primarily involves the synovial joints. The inflammation of the synovium results in joint pain and swelling, and in the majority of subjects, bone erosions within the joint resulting in further joint dysfunction and malformation. Together these processes lead to a decreased physical functioning in the patient and a decrease in the health related quality of life.

Consequently, endpoints for a clinical trial should be chosen that assess these clinical issues of RA. Given the chronicity of RA, the signs and symptoms should be evaluated for a minimum of 6 months and preferably longer to demonstrate durability of the drug effect. Additionally, given the importance of joint destruction in patients with RA a trials lasting a year or longer should include assessment of structural damage. Lastly, it is important that a sponsor demonstrate improved functional ability/quality of life that should be based on trials of at least 6-12 months.

Three endpoints addressing these clinical outcomes have been validated and used in previous approvals of other drugs indicated for patients with moderate to severe RA and are recommended in the agency's RA guidance document

.

- The proportion of subjects achieving a $\geq$ 20% improvement in the American College of Rheumatology (ACR) criteria at 6 months to assess the improvement of signs and symptoms of RA (ACR 20).
- Improvement in the disability index of the Health Assessment Questionnaire (HAQ-DI or HAQ) at 12 months compared to baseline to assess improvement in physical function
- Inhibition of the progression of structural damage by assessing the amount of change in radiographic damage using radiographs of subjects' hands, wrists and feet from baseline and 1 year.

The ACR criteria used for assessing disease improvement include several subjective measurements that are susceptible to investigator bias and therefore blinding of assessors to treatment assignment was instituted in the design of the abatacept RA trials. Similarly, radiograph readers were blinded to treatment group and chronological order of the radiographs. Overall, these endpoints provide a reasonable assessment of meaningful clinical efficacy.

3.4 General Study Design

The abatacept RA trials studies used 1 or more of the 3 primary endpoints discussed. A sequential testing procedure was employed for testing the co-primary hypotheses when more than 1 endpoint was used. A co-primary endpoint was tested only if there was statistical significance for all preceding co-primary endpoints. For each of the tests, the nominal type I error rate was set at 5%, therefore this sequential testing procedure preserves the overall type I error rate at 5%. A brief discussion follows to better describe and define the 3 primary endpoints and secondary endpoints. Specific differences are described in the respective discussion of the study design of the individual trials.

- Improvement of Signs and Symptoms
  The proportion of subjects achieving an ACR 20 at 6 months was used as the primary endpoint for improvement in signs and symptoms. The ACR core data set consists of 7 components:
  - Swollen joint count (66 joints)
  - Tender joint count (68 joints)
  - Subject global assessment of pain (VAS 100mm)
  - Subject global assessment of disease activity (VAS 100mm)
  - Physician global assessment of disease activity (AS 100mm)
  - Subject assessment of physical function using HAQ
  - CRP

  The ACR 20 definition of response specifies a 20% improvement over baseline in swollen and tender joints and in 3/5 of the remaining core data set measures. For the primary endpoint, assessment of the ACR 20 occurred at 6 months (Day 169) in all studies.

- Improvement in Physical Function
  The change from baseline in the HAQ at 6 months and/or 1 year was used as the primary endpoint for the assessment of improvement in physical function. The HAQ is a standardized disability questionnaire developed for use in RA with a scoring range between 0 and 3. A high HAQ score has been shown to be a strong predictor of morbidity and mortality in RA, and low HAQ scores are predictive of better outcomes. A decrease in the HAQ score of >0.22u at 1 year from baseline has been validated as being clinically meaningful to the patient. Therefore, achievement of a numerical significance between treatment arms alone does not necessarily correspond to a clinically meaningful improvement. Consequently, the abatacept RA trials used the proportion of subjects achieving an improvement of HAQ >0.3u, a more conservative figure than the validated improvement of 0.22u.

- Inhibition of Structural Damage
  The inhibition of radiographic progression was assessed using radiographs of subjects' hands, wrists and feet and quantifying the differences between baseline and 1 year (or study termination). Structural damage was quantified using the Genant-modified Sharp score. The total Genant-modified Sharp score ranges from 0 (no radiographic damage) to 292 (worst possible radiographic damage) and is the sum of the erosion score (range 0-140) and the joint space narrowing score (range 0-152). All radiographs were sent to a central reading facility where independent, experienced, radiograph readers who were blinded to treatment and the order of time points scored them in a blinded manner.

  The radiographic data set for the primary radiographic analyses included all observed data at baseline and Day 365. Missing annual radiographic data was imputed with linear extrapolation for discontinued subjects based on the baseline value and the on-treatment assessments at the time of discontinuation, provided both assessments were available.

Subjects with only 1 radiographic film either at baseline, early termination, or Day 365 did not have their scores imputed at other time points. These subjects were excluded form the primary analysis. Sensitivity analyses were performed to assess the robustness of the results with respect to missing data.

To assess the degree of improvement of signs and symptoms, secondary endpoints included the proportion of subjects achieving an ACR 50 and ACR 70 at 6 months as well as ACR 20, ACR 50, and ACR 70 at 12 months. The individual components of the ACR criteria were also analyzed at 6 and 12 months to evaluate whether the effect of abatacept was due to a select number of the ACR criteria or if it affected a broad range of the criteria. Assessment of a major clinical response, defined as maintenance of an ACR 70 response over a continuous 6-month period, was used to determine the proportions of subjects that had a major and sustained response to abatacept.

Secondary endpoints also included the DAS28 score which in contrast to the ACR criteria measures the level of disease activity rather than the proportion of subjects achieving a specified level of improvement. The DAS28 is a continuous measure and is a composite of 4 variables: 28 tender joint count, 28 swollen joint count, ESR and subject assessment of disease activity measure on a VAS of 100 mm. Scores for disease activity are defined as high (>5.1); low (≤3.2); clinically significant improvement (change ≥1.2), and remission (<2.6). It is important to note that the DAS28 usage of remission does not meet the Agency's definition of remission since subjects can have active swollen and tender joints and still meet the DAS28 criteria of remission. In addition, while the definition of remission described in the RA guidance document specifies no radiographic progression, the DAS-based definition of remission does not include an assessment of radiographic progression.

In addition to the HAQ, the effect of abatacept on health related quality of life was assessed based on the SF-36. To assess radiographic progression the total Genant-modified Sharp scores and the individual component of joint-space narrowing scores were assessed as secondary endpoints

All of the RA trials were of similar design. However, only 3 of the 6 RA trials were primarily used to support the efficacy claim of abatacept. Consequently, studies IM101100, IM101102 and IM101029 will be discussed in detail, while only the critical aspects of the study design of trials IM101101, IM101031, and IM103002 will be discussed.

4. CLINICAL TRIALS: STUDY DESIGN AND EFFICACY ANALYSIS

4.1 Study IM101100

4.1.1 Study Design of IM101100

Study IM101100 was a 12-month, randomized (1:1:1), double blind, placebo-controlled, parallel-group, Phase-2 study evaluating 2 different doses of abatacept (2 mg/kg or 10 mg/kg) + methotrexate (MTX) versus placebo + MTX in subjects with active rheumatoid arthritis (RA) despite treatment with MTX. The study was conducted at 66 sites worldwide, of which 32 sites were in the US, 19 sites in Europe, 7 sites in Canada, 4 sites in Australia, 2 sites in Argentina, and 2 sites in South Africa.

All subjects were required to meet the following criteria at screening. Subjects on stable MTX monotherapy were randomized immediately, while subjects on combination DMARD therapy were randomized after washout if they met additional criteria at that time.

- Diagnosis of RA (1987 ACR criteria) >1 year
- RA functional classes I, II, or III
- Treated with MTX (10-30 mg weekly) ≥ 6 months and at stable doses for ≥28 days prior to study treatment.
- Discontinuation of all DMARDs except MTX ≥28 days prior to study treatment
    - Discontinuation of leflunomide or infliximab ≥60 days prior to enrollment and ≥90 days prior to treatment
    - Stable doses of oral corticosteroids (≤10 mg prednisone daily or equivalent) and NSAIDs ≥28 days prior to study treatment
- Active disease despite current DMARD therapy
    - MTX Monotherapy
        - ≥10 swollen joints (66 joint count)
        - ≥12 tender joints (68 joint count)
        - CRP ≥ 1 mg/dL
- After washout and stabilization and at randomization (Day 1)
    - ≥10 swollen joints
    - ≥12 tender joints
    - CRP ≥ 1 mg/dL

The 12-month study period was divided into 2 periods: Days 1-180 and Days 181-360 with the primary endpoint for signs and symptoms of RA occurring at Day 180. During Days 1-180 subjects were maintained on stable doses of MTX (10-30 mg/week) and stable doses of concomitant corticosteroids (≤10 mg prednisone daily or equivalent) and NSAIDs. During Days 181-360 after the primary signs and symptoms endpoint was assessed, investigators could, at their discretion, add one DMARD (hydroxychloroquine, sulfasalazine, gold, or azathioprine),

and add or adjust the dose of corticosteroids (≤10 mg prednisone daily or equivalent) and/or NSAIDs.

Subjects who met the inclusion/exclusion criteria were randomized 1:1:1 to receive one of the following treatments on study Days 1, 15, 30, and every 30 days thereafter for a total of 13 doses:

- Abatacept 10 mg/kg
- Abatacept 2 mg/kg
- Placebo

All subjects must have been treated with MTX (10-30 mg/week) for ≥6 months and have maintained a stable dose ≥28 days prior to study Day 1, and this dose of MTX was maintained during the study. All subjects received concomitant folate supplementation. Subjects had assessments for safety and disease activity on Days 1, 15, 30, 60, 90, 120, 150, 180, 210, 240, 270, 300, 330, and 360. At Day 360, subjects were allowed to crossover to receive open-label tiered-dose abatacept.

The primary endpoint for study IM101100 was the proportion of subjects achieving an ACR20 at Day 180. Important secondary endpoints included inhibition of radiographic progression and improvement in physical function.

Radiographs of the hands, wrists and feet were performed on all subjects at Days 1, 180, and 360. All radiographs were sent to a central reading facility and evaluated by a single experienced radiologist using the Genant-modified Sharp grading score. The pre-specified analysis was as follows:

1. Hands: the scores were summed separately (14 x 3.5 maximum per joint x 2 = 98 for erosion and 13 x 4 maximum per joint x 2 = 104 for joint space narrowing). To provide equal weight to erosions and joint space narrowing, each sum were normalized to a scale of 0 – 100. Both scores were added to obtain a total score (scale of 0 – 200).

2. In the event that a joint was missing or non-evaluable in the hands, the maximum score was adjusted downward according to the number of missing joints and the subject's score was normalized to this new maximum score.

3. Feet: the scores were summed separately (6 x 3.5 maximum per joint x 2 = 42 for erosion and 6 x 4 maximum per joint x 2 = 48 for joint space narrowing). Both scores were added to obtain a total score (scale of 0 - 90).

4. In the event that a joint was missing or non-evaluable in the feet, the maximum score was adjusted downward according to the number of missing joints and the subject's score was adjusted according to this new maximum score.

5. The maximum score achievable (for hands + feet) is 290. The change in score was to be calculated as: Change = Final total score minus initial total score.

6. Only joints that were evaluable at both the baseline and follow-up visits were included in the calculation of total scores and change in scores. If a joint was non-evaluable at one visit but could be read at the other, the scores from this joint were dropped from both visits in the calculations described above.

All statistical tests used the intent-to-treat population and were performed using a 2-tailed, 5% level of significance. For the primary endpoint, the proportion of subjects achieving an ACR20, a sequential procedure using the Chi-square test was used whereby if the comparison of the ACR20 response between the abatacept 10 mg/kg group and placebo group was significant, then the comparison between the abatacept 2 mg/kg group and placebo group was subsequently performed. This sequential method preserved the overall alpha level at 5%. For ACR analyses, subjects who discontinued the study due to lack of efficacy were considered ACR non-responders at all subsequent time-points. Last observation carried forward imputation was used for the last ACR response or individual ACR component for all subjects who discontinued the study for reasons other than lack of efficacy. Sensitivity analyses were conducted to evaluate the robustness of any significant responses, the details of which are described in the analysis of the primary endpoint section of this document. Important secondary endpoints included the proportion of subjects achieving a clinically significant improvement in mHAQ score ≥0.3u from baseline between treatment groups at Day 360 and Day 720. Subjects completing the double-blind period of the study could enroll in the open-label period and physical function was assessed using mHAQ score at quarterly visits. The protocol specified analysis of mHAQ response was based on as-observed data. Any subject for whom data were missing at a given visit had the mHAQ response imputed for the missed visit according to the following rules: Data from the previous scheduled visit and from the next scheduled visit at which efficacy was assessed were examined. If positive responses (i.e., improvement in mHAQ score ≥0.3u from baseline) were observed at both visits, a positive response was imputed for the current visit. If the current visit was the subject's last efficacy visit, then imputation depended on the observed responses at the previous 2 consecutive scheduled visits. If both the responses were positive, the imputed value was positive, otherwise the imputed response was declared missing. Sensitivity analyses were performed using non-responder and last observation carried forward imputation methods.

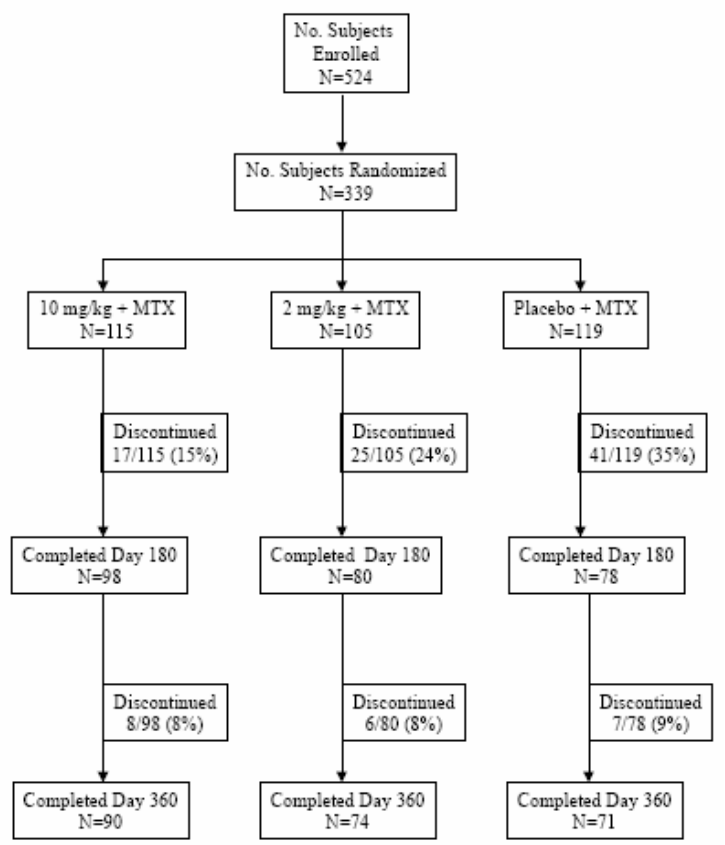
Power calculations assumed a placebo group ACR 20 response rate of 25%, therefore a sample of 107 subjects per treatment group was determined to yield a 94% power to detect a difference of 25% at the 5% level (2-tailed), adjusted for a possible 15% discontinuation rate. If the primary comparison between the abatacept 10 mg/kg group and the placebo group were significant then the power for the subsequent comparison between the abatacept 2 mg/kg group and the placebo group would be at least 88%.

\

4.1.2 Study Conduct of IM101100

A total of 524 subjects were enrolled with 339 subjects being randomized, of which 115 subjects were randomized to abatacept 10 mg/kg + MTX group, 105 subjects to the abatacept 2 mg/kg + MTX group, and 119 subjects to placebo + MTX group (Figure 1). The most frequent reason for not being randomized was subjects not meeting inclusion/exclusion criteria.

Figure 1. Subject Disposition for Study IM101100



Subject disposition for the period of Days 1-180 showed that a higher proportion of subjects in the abatacept 10 mg/kg + MTX group (85%) and abatacept 2 mg/kg + MTX group (76%) completed 180 days of treatment compared to the placebo + MTX group (65%). Adverse events and lack of efficacy were the most common reasons for discontinuation in both of the abatacept arms and the placebo arm (Table 2). A higher rate of discontinuation observed in the placebo arm is attributable to a higher rate of withdrawal due to lack of efficacy and to a lesser degree, to a higher rate of withdrawal due to AEs in the placebo arm as compared to the abatacept 10 mg/kg arm.

Table 2. Day 1-180: Reasons for Discontinuation

	Abatacept 10 mg/kg + MTX (n=115)	Abatacept 2 mg/kg + MTX (n=105)	Placebo + MTX (n=119)
Number Discontinued	17 (15%)	25 (24%)	41 (35%)
Death	0	0	0
Adverse Events	3 (3%)	7 (7%)	9 (8%)
Loss of Efficacy	12 (10%)	16 (15%)	28 (24%)
Withdraw of Consent	2 (2%)	2 (2%)	4 (3%)
Completed 180 days	98 (85%)	80 (76%)	78 (65%)

Subject disposition for the period of Days 180-360 showed that approximately 9% of subjects in each group discontinued by Day 360, with adverse events and lack of efficacy the most common reasons for study discontinuation. A total of 78% of the abatacept 10 mg/kg + MTX group, 71% of the abatacept 2 mg/kg + MTX group, and 60% of the placebo + MTX group completed the study.

Seventy-seven percent of subjects in the abatacept 10 mg/kg group, 70% of subjects in the abatacept 2 mg/kg group, and 59% of subjects in the placebo group had radiographs at both Day 1 and Day 360 of which the pre-specified analysis for inhibition of radiographic progression was assessed.

4.1.3 Study Demographics of IM101100

The baseline characteristics were generally similar across all 3 arms of the study and are shown in Table 3. The majority of subjects were white and female, with a mean age of 55 years, and a mean weight of 79 kg.

Table 3. Baseline Demographic Characteristics

	Abatacept 10 mg/kg + MTX (n=115)	Abatacept 2 mg/kg + MTX (n=105)	Placebo + MTX (n=119)
Age (years, mean ± SD)	56 ± 13	54 ± 11	55 ± 12
Weight (kg, mean ± SD)	78 ± 19	79 ± 21	80 ±18
Gender (female)	86 (75%)	66 (63%)	79 (66%)
Race			
White	100 (87%)	91 (87%)	104 (87%)
Black	6 (5%)	0	3 (3%)
Other	9 (8%)	14 (13%)	12 (10%)

The baseline disease characteristics of the study subjects are shown in Table 4.
Despite an average dose of MTX of 16 mg/week, subjects still demonstrated active RA as demonstrated by the number of swollen joints (~21) and tender joints (~30), the elevation of CRP (~3 mg/dL), and the duration of morning stiffness of ~100 minutes. The subjects exhibited

considerable joint damage with a mean total erosion score of ~44. The mean duration of RA was approximately 10 years. Treatment arms were balanced with respect to baseline demographics.

Table 4. Baseline Disease Characteristics

	Abatacept 10 mg/kg + MTX (n=115)	**Abatacept 2 mg/kg + MTX (n=105)**	**Placebo + MTX (n=119)**
Duration of RA (years, mean ± SD)			
Mean ± SD	10 ± 10	10 ± 8	9 ± 8
Swollen joints (mean ± SD)	21 ± 98	20 ± 9	22 ± 9
Tender joints (mean ± SD)	31 ± 12	28 ± 12	29 ± 13
Subject Pain Assessment (VAS 00mm)	62 ± 21	64 ± 22	65 ± 22
Physical Function (HAQ)	1.0	1.0	1.0
Subject Global Assessment (VAS 100mm)	60 ± 21	59 ± 23	63 ± 22
Physician Global Assessment (VAS 100mm)	62 ± 15	61 ± 17	63 ± 16
CRP	2.9	3.2	3.2
RF (+)	86%	86%	76%
Morning Stiffness (minutes, Mean ± SD)	98 ± 63	104 ± 64	106 ± 64
DAS-28 (mean ± SD)	6.8 ± 1	6.8 ± 1	6.8 ± 1
MTX dose (mg/wk, mean ± SD)	15 ± 4	16 ± 5	16 ± 4
Genant-Modified Sharp Scores (n subjects)	115	103	117
Total (0-292)	51	44	44
Erosion Score (0-140)	22	20	19
Joint Space Narrowing (0-152)	29	24	25

The use of anti-rheumatic medications prior to enrollment was generally comparable in each treatment group as shown in Table 5.

Table 5. Medication Use Prior to Enrollment

	Abatacept 10 mg/kg + MTX (n=115)	Abatacept 2 mg/kg + MTX (n=105)	Placebo + MTX (n=119)
MTX	113 (98%)	103 (98%)	118 (99%)
Other DMARDs	19 (17%)	19 (18%)	25 (21%)
Sulfasalazine	9 (8%)	2 (2%)	10 (8%)
Hydroxychloroquine	9 (7%)	6 (6%)	14 (12%)
Cyclosporine	2 (2%)	4 (4%)	4 (3%)
Chloroquine	1 (1%)	0	0
Leflunomide	0	2 (2%)	2 (2%)
Gold	0	0	1 (1%)
Biologics			
Etanercept	1 (1%)	4 (4%)	1 (1%)
Infliximab	2 (2%)	2 (2%)	2 (2%)
Corticosteroids	68 (59%)	71 (68%)	79 (66%)

The proportion of subject receiving concomitant anti-rheumatic drugs on study Day 1 were comparable among the 3 arms with a mean dose of MTX of approximately 16 mg/week and a mean corticosteroid dose of 7 mg/day of prednisone (Table 6).

Table 6. Anti-Rheumatic Medications on study Day 1

	Abatacept 10 mg/kg + MTX (n=115)	Abatacept 2 mg/kg + MTX (n=105)	Placebo + MTX (n=119)
MTX	114 (99%)	103 (98%)	118 (99%)
Corticosteroids	68 (59%)	69 (66%)	75 (63%)

There were 4 subjects that did not receive MTX therapy on Day 1 that were recorded in the database; 1 subject is listed in the protocol violations table, and the 3 remaining subjects, 1 from each arm, had their MTX start date incorrectly entered into the database. This represents a very small number of subjects and the numbers are equally distributed among study arms and should not affect the overall interpretability of the study.

During study Days 181-360 concomitant anti-rheumatic medication use was comparable between treatment arms (Table 7) with only a minority of subjects having an additional DMARD added to their therapy.

Table 7. Concomitant Anti-Rheumatic Medications During Study Days 181-360

	Abatacept 10 mg/kg + MTX (n=98)	Abatacept 2 mg/kg + MTX (n=80)	Placebo + MTX (n=78)
MTX	98 (100%)	79 (99%)	78 (100%)
Corticosteroids	72 (74%)	54 (68%)	53 (68%)
Other DMARDs	2 (2%)	0	2 (3%)
Azothioprine	1 (1%)	0	0
Hydroxychloroquine	0	0	1 (1%)
Leflunomide	0	0	1 (1%)
Quinine	1 (1%)	0	0

4.1.4 Primary Endpoint Analysis of Study IM101100

At Day 180, 61% of subjects in the abatacept 10 mg/kg + MTX arm achieved an ACR 20 compared to 35% of subjects in the placebo + MTX arm ($p<0.001$; Table 8). There was no significant difference between the abatacept 2 mg/kg + MTX group and the placebo + MTX group, although the response rate was higher in the abatacept 2 mg/kg + MTX group than in the placebo + MTX group.

Table 8. ACR 20 Responders at Day 180*

	Abatacept 10 mg/kg + MTX (n=115)	Abatacept 2 mg/kg + MTX (n=105)	Placebo + MTX (n=119)
ACR 20			
Number of responders	70 (61%)	44 (42%)	42 (35%)
p-value	<0.001	0.31	
* Missing data were imputed using non-responder imputation for the primary analysis			

Sensitivity analyses of the primary endpoint included modified worst-case and worst-case scenarios. The modified worst-case scenario sensitivity analysis treats placebo subjects who discontinued the study due to LOE as ACR non-responders for all visits subsequent to discontinuation, and subjects randomized to placebo who did not complete 6 months (Day 180) of treatment but discontinued for reasons other than LOE were classified based on the last available data observed at or prior to their discontinuation.

The results of the modified worst-case scenario sensitivity analysis was similar to the primary analysis with 58% of subjects in the abatacept 10 mg/kg + MTX arm, 39% of subjects in the abatacept 2 mg/kg + MTX arm, and 32% of subjects in the placebo + MTX arm achieving an ACR 20. A worst observation carried forward analysis was also conducted and demonstrated a similar magnitude of treatment differences between abatacept-treated subjects and placebo-treated subjects. These sensitivity analyses, in conjunction with the primary analysis, support the efficacy of abatacept in inducing ACR 20 responses.

4.1.5 Secondary Analyses of Study IM101100

4.1.5.1 Improvement of Signs and Symptoms

Table 9 shows the improvement of signs and symptoms over time as measured by the ACR 20. These data demonstrate that a significant clinical response to abatacept 10 mg/kg + MTX was apparent by Day 60 and that the proportion of subjects achieving a clinical response appeared to reach a plateau also by Day 120, a level that was maintained through Day 360 (Table 10).

Table 9. Number of Subjects Achieving an ACR 20 Response by Study Visit Day

	Abatacept 10 mg/kg + MTX (n=115)	**Abatacept 2 mg/kg + MTX (n=105)**	**Placebo + MTX (n=119)**
Study Visit			
Day 15	30 (26%)	9 (9%)	24 (20%)
Day 30	48 (42%)	22 (21%)	36 (30%)
Day 60	65 (57%)*	35 (33%)	41 (35%)
Day 90	62 (54%)**	40 (38%)	42 (35%)
Day 120	71 (62%)*	47 (45%)	45 (38%)
Day 150	67 (58%)*	46 (44%)	42 (35%)
Day 180	70 (61%)*	44 (42%)	42 (35%)
Day 240	72 (63%)*	43 (41%)	42 (35%)
Day 300	73 (64%)*	41 (39%)	41 (35%)
Day 360	72 (63%)*	44 (42%)	43 (36%)
*p<0.001; **p=0.004			

Additionally, a higher proportion of subjects receiving abatacept 10 mg/kg + MTX achieved an ACR 50 and ACR 70 compared to placebo-treated subjects at Day 180 with the effect being maintained through Day 360 (Table 10). Subjects receiving abatacept 2 mg/kg + MTX demonstrated improvement in ACR 50 and ACR 70 scores compared with placebo-treated subjects at Day 180. Subjects receiving abatacept 10 mg/kg + MTX attained a higher rate of ACR 50 and ACR 70 responses compared to subjects receiving placebo + MTX as early as day 60 (data not shown).

Table 10. Number of Subjects Achieving an ACR 20, ACR 50 and ACR 70 at Day 180 and Day 360

	Abatacept 10 mg/kg + MTX (n=115)	Abatacept 2 mg/kg + MTX (n=105)	Placebo + MTX (n=119)
Day 180			
ACR 20	70 (61%)*	44 (42%)	42 (35%)
ACR 50	42 (37%)*	24 (23%)**	14 (12%)
ACR 70	19 (17%)*	11 (11%)****	2 (2%)
Day 360			
ACR 20	72 (63%)*	44 (42%)	43 (36%)
ACR 50	48 (42%)*	24 (23%)	24 (20%)
ACR 70	24 (21%)****	13 (12%)	9 (8%)
* p<0.001; **p=0.03; ***p=0.005; ****p=0.003			

Larger proportions of subjects receiving either abatacept 10 mg/kg + MTX or 2 mg/kg + MTX achieved a major clinical response, defined as maintenance of an ACR 70 response over a continuous 6-month period, compared to subjects receiving placebo + MTX (8% and 6% versus 1%, respectively; Table 11).

Table 11. Number of Subjects Achieving a Major Clinical Response

	Abatacept 10 mg/kg + MTX (n=115)	Abatacept 2 mg/kg + MTX (n=105)	Placebo + MTX (n=119)
Number of responders (%)			
Major Clinical Response	9 (8%)	6 (6%)	1 (1%)
p-value	0.008	0.04	-

Each individual component of the ACR 20 showed greater improvement at Days 180 and 360 among abatacept-treated subjects compared to placebo-treated subjects demonstrating that the beneficial effects of abatacept were broadly distributed and not due to a single component of the composite score (Table 12).

Table 12. % Improvement from Baseline for Individual Components of ACR Criteria at Day 180 and Day 360

	Abatacept 10 mg/kg + MTX (n=115)	**Abatacept 10 mg/kg + MTX (n=105)**	**Placebo + MTX (n=119)**
Swollen Joints (66 total)			
Baseline Mean	21	20	22
Day 180 Mean % Improvement	55%	45%	34%
Day 360 Mean % Improvement	60%	46%	36%
Tender Joints (68 total)			
Baseline Mean	31	28	29
Day 180 Mean % Improvement	60%	43%	32%
Day 360 Mean % Improvement	66%	44%	30%
Subject Pain Assessment (VAS 100mm)			
Baseline Mean	63	64	65
Day 180 Mean % Improvement	46%	22%	8%
Day 360 Mean % Improvement	45%	26%	13%
Physical Function (HAQ)			
Baseline Mean	1.0	1.1	1.1
Day 180 Mean % Improvement	41%	22%	14%
Day 360 Mean % Improvement	42%	23%	10%
Subject Global Assessment (VAS 100mm)			
Baseline Mean	61	59	63
Day 180 Mean % Improvement	41%	9%	18%
Day 360 Mean % Improvement	41%	16%	2%
Physician Global Assessment (VAS 100mm)			
Baseline Mean	62	61	63
Day 180 Mean % Improvement	52%	39%	25%
Day 360 Mean % Improvement	54%	38%	24%
CRP (mg/dL)			
Baseline Mean	2.9	3.2	3.2
Day 180 Mean % Improvement	32%	16%	-23%
Day 360 Mean % Improvement	28%	11%	-31%

4.1.5.2 Improvement in Physical Function

At Day 180 subjects treated with abatacept 10 mg/kg + MTX had a statistically significant improvement in physical function compared to placebo + MTX as assessed by HAQ scores (41% improvement versus 14% improvement, respectively). This improvement was maintained through Day 360 (42% versus 10%, respectively). Subjects treated with abatacept 2 mg/kg + MTX had a greater percentage improvement in their HAQ scores compared to subjects treated with placebo + MTX at both Days 180 and 360 but the difference was not statistically different.

The data were also analyzed to determine the proportion of subjects attaining a level of improvement in HAQ that has been previously shown to be clinically meaningful. The level of improvement in HAQ (≥0.3u) that was chosen exceeds the minimally clinically important change (0.22u) and is a conservative analysis.

At Day 180, 47% of subjects treated with abatacept 10 mg/kg + MTX and 38% of subjects treated with abatacept 2 mg/kg + MTX achieved an improvement in HAQ score ≥0.3 u compared to 28% of placebo-treated subjects (p=0.002). This effect was maintained through Day 360 at which time 38% of subjects treated with abatacept 10 mg/kg + MTX and 30% of subjects treated with abatacept 2 mg/kg + MTX achieved an improvement in HAQ score ≥0.3 u compared to 20% of placebo-treated subjects (p=0.002). Thus, subjects treated with abatacept 10 mg/kg + MTX had a statistically significantly greater clinical improvement in their physical function than placebo-treated subjects. Although not statistically significant, subjects treated with abatacept 2 mg/kg + MTX had more improvement in physical function than placebo-treated subjects.

4.1.5.2.1 Durability of Improvement in Physical Function

A total of 235 subjects of the initial 339 randomized subjects completed the double-blind period of the study and 219 of these subjects were enrolled in the open-labeled period. All subjects electing to participate in the open-label period after Day 360 were treated with tiered-dose abatacept approximating 10 mg/kg.

Of the subset of subjects who later entered the long-term extension trial, 55% of subjects treated with abatacept 10 mg/kg + MTX had a clinically significant improvement in physical function compared to 35% of subjects treated with placebo + MTX at Day 360 (p=0.002; Figure 2 and Table 13).

Figure 2. Proportion of Subjects with Clinically Meaningful mHAQ Responses for Subjects Entering Open-Label Therapy; As-Observed Data

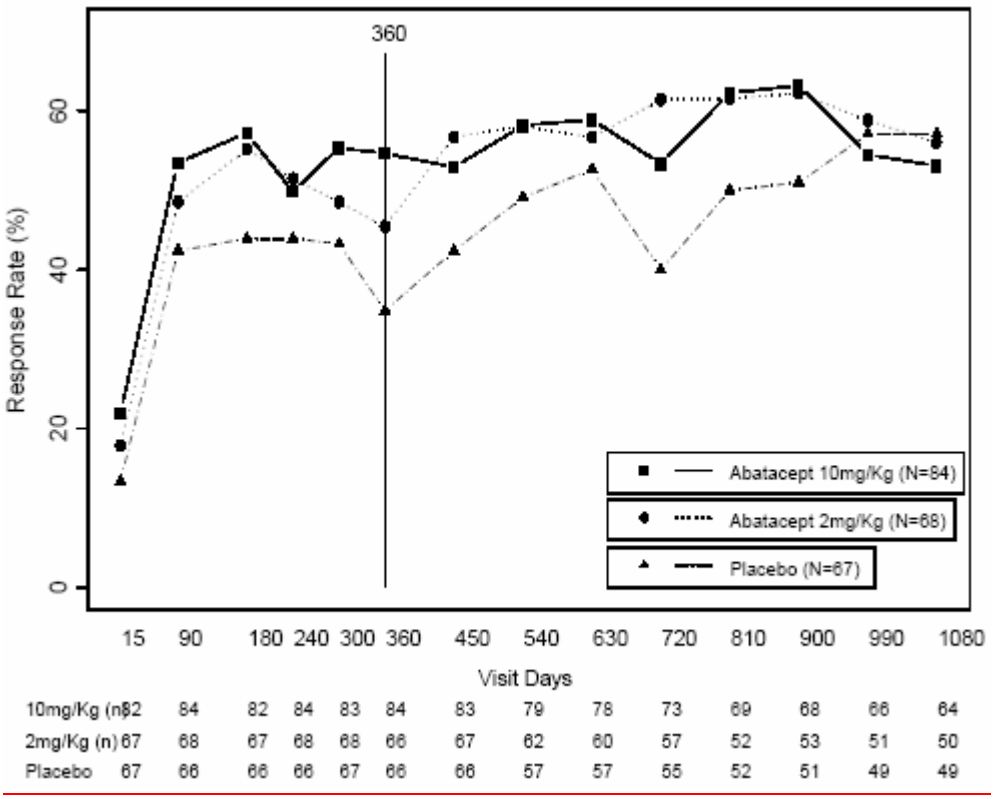


Table 13. Proportion of Subjects with Clinically Significant mHAQ (≥0.3u) Responses for Subjects Who Entered the Open-Label Period; As-Observed Data

	Abatacept 10 mg/kg + MTX		Abatacept 2 mg/kg + MTX		Placebo + MTX	
Study Day	**n**	**n (%)**	**n**	**n (%)**	**n**	**n (%)**
Day 30	84	25 (30%)	68	22 (32%)	66	14 (21%)
Day 90	84	45 (54%)	68	33 (49%)	66	28 (42%)
Day 180	82	47 (57%)	67	37 (55%)	66	29 (44%)
Day 360	84	46 (55%)	66	30 (46%)	66	23 (35%)
Day 720*	73	39 (53%)*	57	35 (61%)*	55	22 (40%)*
* Subjects in the Abatacept 2 mg/kg + MTX and Placebo + MTX groups received abatacept 10 mg/kg starting from Day 360						

Among subjects originally randomized to receive abatacept 10 mg/kg, a similar percentage had clinically meaningful improvement of physical function at Day 720 as at Day 360 (53% and 55%, respectively; Figure 2 and Table 13). Additionally, the percentage of subjects achieving clinically significant improvement in physical function among subjects originally randomized to receive abatacept 2 mg/kg during the double-blind period of the trial increased to approximately the same level as subjects originally randomized to abatacept 10 mg/kg + MTX at Day 360

(Figure 2 and Table 13). Data was missing at Day 720 for 2 subjects in the abatacept 10 mg/kg arm. Sensitivity analyses using non-responder imputation and last observation carried forward demonstrated similar results.

Thus, a greater proportion of subjects treated with abatacept 10 mg/kg + MTX had clinically significant improvement in physical function than placebo-treated subjects at 1 year and this benefit was maintained at 2 years. Similarly, subjects treated with abatacept 2 mg/kg + MTX had more improvement in physical function than placebo-treated subjects.

4.1.5.3 Inhibition of Structural Damage

As shown in Table 13, there was a trend toward inhibition of structural damage that favored abatacept; however, the overall effect was modest and not statistically significant. It should be noted that the analysis of radiographic progression in this study was not performed to the same standard as that performed in the large Phase 3 study IM101102, for which the claim of inhibition of radiographic progression will be based. The current study is complicated by having a large amount of missing data, lack of radiographs at the date of study discontinuation for imputation of missing data, and only a single reader of the radiographs.

Table 14. Genant-Modified Sharp Radiographic Scores from Baseline to Day 360

	Abatacept 10 mg/kg + MTX (n=115)	**Abatacept 2 mg/kg + MTX (n=105)**	**Placebo + MTX (n=119)**
Subjects with paired radiographs	89 (77%)	73 (70%)	70 (59%)
Erosion Score			
Baseline mean ± SD	24u ± 17	21u ± 15	20u ± 15
Mean change from baseline (± SD)	0.5u ± 1.8	0.5u ± 1	0.85u ± 1.7
Joint Space Narrowing			
Baseline mean ± SD	33u ± 28	25u ± 21	26u ± 24
Mean change from baseline (± SD)	0.8u ± 3	0.5u ± 1.2	0.6u ± 1.3
Total Score			
Baseline mean ± SD	58u ± 44	46u ± 36	45u ± 38
Mean change from baseline (± SD)	1.3u ± 4.3	1u ± 2	1.5u ± 2.5

4.2 Study IM101102

4.2.1 Study Design of IM101102

Study IM101102 was a 12-month, randomized (2:1), double blind, placebo-controlled, parallel-arm, Phase-3 study evaluating abatacept + methotrexate (MTX) versus placebo + MTX in subjects with active rheumatoid arthritis (RA) despite previous treatment with MTX. The study was conducted at 116 sites worldwide, of which 36 sites were in Europe, 31 sites in the US, 24 sites in Central and South America, 13 sites in Canada, 5 sites in South Africa, 4 sites in Australia, and 3 sites in Taiwan.

All subjects were required to meet the following key inclusion/exclusion criteria:

- Diagnosis of RA (1987 ACR criteria) >1 year
- RA functional classes I, II, or III
- Treated with MTX ≥ 3 months with at least 15 mg MTX weekly and stable doses of MTX for ≥28 days prior to study treatment. Weekly doses of MTX as low as 10 mg were permitted for subjects who could not tolerate higher doses
- Discontinuation of all DMARDs except MTX ≥28 days prior to study treatment
- Active disease despite current DMARD therapy
    - MTX Monotherapy
        - ≥10 swollen joints
        - ≥12 tender joints
        - CRP ≥ 1 mg/dL
    - Combination DMARD Therapy
        - ≥6 swollen joints
        - ≥8 tender joints
        - no restriction on CRP
- After washout and stabilization and at randomization (Day 1)
    - ≥10 swollen joints
    - ≥12 tender joints
    - CRP ≥ 1 mg/dL
- No serious infections in the previous 3 months

The 12-month study period was divided into 2 periods: Days 1-169 and Days 170-365 with the primary endpoint for signs and symptoms of RA occurring at Day 169. During Days 1-169 subjects were maintained on stable doses of MTX and were allowed to be on stable doses of concomitant corticosteroids (≤10 mg prednisone daily or equivalent) and NSAIDs. During Days 170-365 investigators, at their discretion, could adjust the MTX dose, add one DMARD (hydroxychloroquine, sulfasalazine, gold, or azathioprine), adjust doses of corticosteroids (≤10 mg prednisone daily or equivalent) or ≤2 intra-articular injections and adjust doses of NSAIDs. During both periods, subjects experiencing breakthrough pain could receive acetaminophen,

tramadol, or combination products including narcotic analgesics, except for 12 hours prior to joint evaluation.

Study medication was administered on Days 1, 15, 29, and every 28 days thereafter for a total of 14 doses. Abatacept was administered as an IV infusion of a tiered-dose based on subject's weight at study screening:

- <60 kg: abatacept 500 mg IV
- 60 kg to 100 kg: abatacept 750 mg IV
- ≥100 kg: abatacept 1000 mg IV

All subjects received background MTX (≥15 mg weekly) during the study at the dose level and regimen administered at the time of randomization. All subjects received concomitant folate supplementation.

Radiographs of hands, wrists and feet were performed using the Genant-modified Sharp algorithm on all subjects at Days 1 and 365, or at early termination if applicable. The total Genant-modified Sharp score ranges from 0 (no radiographic damage) to 292 (worst possible radiographic damage) and is the sum of the erosion score (range 0-140) and the joint space narrowing score (range 0-152). All radiographs were sent to a central reading facility where independent, experienced, radiograph readers who were blinded to treatment and the order of timepoints scored them in a blinded manner.

There were 3 co-primary endpoints prospectively defined for the study in the following hierarchical order:

1. Improvement from baseline in signs and symptoms as assessed by the proportion of subjects achieving an ACR20 at Day 169
2. Improvement in physical function as measured by the proportion of subjects achieving an improvement in HAQ-DI of ≥0.3u over baseline at Day 365
3. Inhibition of radiographic progression as assessed by the change from baseline in erosion score using the Genant-modified Sharp method at Day 365

Subjects were allocated using a dynamic process and were randomly assigned to 1 of 2 treatment groups in a 2:1 ratio (abatacept:placebo, respectively). Randomization was stratified by site. A modified intent-to treat analysis was used whereby all subjects who were randomized and received at least 1 dose of blinded study medication. A sequential testing procedure was employed for testing the co-primary hypotheses according to the hierarchy specified above. A co-primary endpoint was tested only if there was statistical significance for all preceding co-primary endpoints. For each of the tests, the nominal type I error rate was set at 5%, therefore this sequential testing procedure preserves the overall type I error rate at 5%. Comparisons of the ACR 20 and HAQ response rates between the two treatment arms were conducted using a Chi-square test with continuity correction and used non-responder imputation. A rank-based nonparametric ANCOVA model was used to compare the changes from baseline in erosion scores using the Genant-modified Sharp method. This model utilized the rank score for change from baseline as the dependent variable with treatment group as a main effect and the rank score for baseline as an additional covariate. The radiographic data set for the primary radiographic

analyses included all observed data at baseline and Day 365. Missing annual radiographic data was imputed with linear extrapolation for discontinued subjects based on the baseline value and the on-treatment assessments at the time of discontinuation, provided both assessments were available. Subjects missing a radiographic film at baseline were excluded from the analysis. This review uses the data from the sponsor's stated first secondary analysis as a sensitivity analysis as it more closely approximated an ITT analysis. Sensitivity analyses were also performed to assess the impact of missing radiographic data by the agency's biostatistics reviewer, which confirmed the primary analysis.

4.2.2 Study Conduct of IM101102

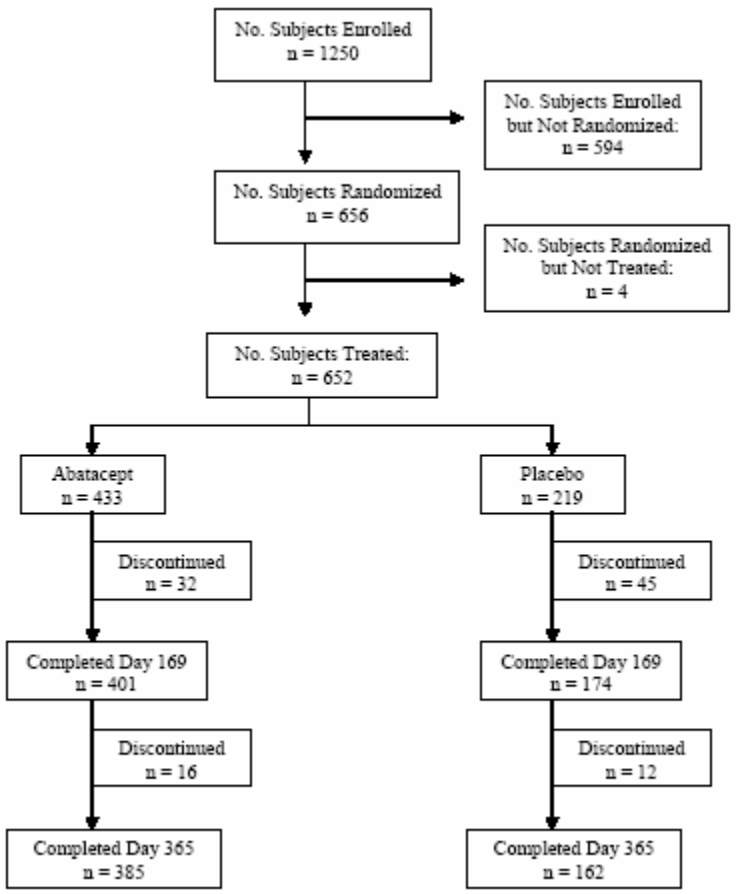
A total of 1250 subjects were enrolled with 656 subjects being randomized. The most frequent reasons for not being randomized were subjects no longer meeting study criteria, "other", and the subject withdrew informed consent. Of the 656 subjects randomized 4 subjects were not treated and of the remaining 652 subjects, 433 were randomized to abatacept + MTX and 219 to placebo + MTX (Figure 3).

subjects but was found to have poor clinical and documentation practices and the site was subsequently closed. BMS excluded this site's data from all analyses of efficacy but included the data in all analyses of safety.

During the double-blind period, 18 subjects (10 in the abatacept + MTX arm; 8 in the placebo + MTX arm) had protocol violations that could potentially be clinically important. FDA review of these protocol violations indicate that they did not affect the conclusions of the study and were included in all analyses.

During the course of the study two subjects (<1%) in the abatacept + MTX arm and four subjects (2%) in the placebo + MTX arm mistakenly received a DMARD prior to Day 169. However, since this is such a small number of subjects compared to the whole, it is unlikely that this had any effect on the final analyses. Subject disposition is schematically illustrated in Figure 3.

Figure 3. Subject Dispostion for Study IM101102



Subject disposition for the period of Days 1-169 showed a greater proportion of subjects in the abatacept + MTX group (93%) completed 169 days of treatment compared to the placebo + MTX group (80%). Overall the higher rate of discontinuation in the placebo arm was attributable to a higher rate of withdrawal due to lack of efficacy and other reasons. Withdrawal due to AEs was more frequent in the abatacept arm (3%) than with placebo (1%; Table 15)

Table 15. Day 1-169: reasons for discontinuation

	Abatacept + MTX (n=433)	**Placebo + MTX (n=219)**
Number Discontinued	32 (7%)	45 (21%)
Death	0	0
Adverse Events	11 (3%)	3 (1%)
Loss of Efficacy	11 (3%)	33 (15%)
Lost to Follow-up	1 (<1%)	1 (<1%)
Withdraw of Consent	7 (2%)	4 (2%)
Other	2 (<1%)	4 (2%)
Completed 169 days	401 (93%)	174 (80%)

Subject disposition for the period of Days 170-365 showed a greater proportion of subjects in the abatacept + MTX group (89%) completed 365 days of treatment compared to the placebo + MTX group (74%). AEs (2%) was the most common reason for discontinuation in the abatacept arm and LOE (3%) was the most common reason for the discontinuation in the placebo + MTX arm, Table 16.

Table 16. Day 170-365: reasons for discontinuation

	Abatacept + MTX (n=433)	**Placebo + MTX (n=219)**
Number Discontinued >169	16 (4%)	12 (6%)
Death	1 (<1%)	1 (<1%)
Adverse Events	7 (2%)	1 (<1%)
Loss of Efficacy	2 (<1%)	7 (3%)
Lost to Follow-up	0	0
Withdraw of Consent	3 (<1%)	1 (<1%)
Other	3 (<1%)	2 (1%)
Completed 365 days	385 (89%)	162 (74%)

Table 17 shows that 586/638 (92%) subjects included in the primary radiographic analysis had adequate radiographs at 2 timepoints: 572 subjects at baseline and Day 365 and 14 subjects at baseline and on the day of discontinuation prior to Day 365. There were 24 subjects with only baseline radiographs who were only included in the secondary analysis, and 17 subjects without baseline radiographs who were not included in any of the analyses, as prespecified in the statistical analysis plan.

Table 17. Subject disposition for evaluable radiographs

Number (%) Subjects with 2 evaluable radiographs	**Abatacept**	**Placebo**	**Total**
Randomized-Treated Subjects	391/433 (90%)	195/219 (89%)	586/650 (90%)
Efficacy Population Analyzed for Primary Endpoint	391/424 (92%)	195/214 (91%)	586/638 (92%)

4.2.3 Study Demographics of Study IM101102

The baseline characteristics of the study subjects are shown in Table 18. There were no baseline imbalances between study arms with the majority of subjects being white and female, mean age of 51 years, and mean weight of 71 kg.

Table 18. Baseline demographic characteristics

	Abatacept + MTX (n=433)	**Placebo + MTX (n=219)**
Age (years, mean ± SD)	52 ± 13	50 ± 12
Weight (kg, mean ± SD)	72 ± 18	70 ±16
Gender (female)	337 (78%)	179 (82%)
Race		
White	379 (88%)	193 (88%)
Black	10 (2%)	4 (2%)
American Indian	3 (<1%)	1 (<1%)
Asian	18 (4%)	10 (5%)
Other	23 (5%)	11 (5%)
Geographical Region		
North America	93 (22%)	46 (21%)
South America	173 (40%)	93 (43%)
Europe	143 (33%)	67 (31%)
ROW	24 (6%)	13 (6%)

The baseline disease characteristics of the study subjects are shown in Table 19.
Despite an average dose of MTX 16 mg/week, subjects still demonstrated active RA as demonstrated by the number of swollen joints (~21) and tender joints (~31), elevation of CRP (~3 mg/dL), duration of morning stiffness (~90 minutes), and total erosion score of 32. The mean duration of RA was approximately 9 years. There were no imbalances between arms.

Table 19. Baseline disease characteristics

	Abatacept + MTX (n=433)	**Placebo + MTX (n=219)**
Duration of RA (years, mean ± SD)		
Median	6	7
Mean ± SD	9 ± 7	9 ± 7
≤2 years	99 (23%)	45 (21%)
>2-≤5 years	93 (22%)	46 (21%)
>5-≤10 years	106 (25%)	54 (25%)
> 10 years	135 (31%)	74 (34%)
Swollen joints (mean ± SD)	21 ± 9	22 ± 9
Tender joints (mean ± SD)	31 ± 13	32 ± 14
Subject Pain Assessment (VAS 00mm)	63 ± 21	66 ± 21
Physical Function (HAQ)	1.7	1.7
Subject Global Assessment (VAS 100mm)	63 ± 21	63 ± 22
Physician Global Assessment (VAS 100mm)	68 ± 16	67 ± 17
CRP	3.3	2.8
RF (+)	354 (82%)	172 (79%)
Morning Stiffness (minutes, Mean ± SD)	98 ± 61	90 ± 61
DAS-28 (mean ± SD)	6.8 ± 1	6.8 ± 1
MTX dose (mg/wk, mean ± SD)	16 ± 4	16 ± 4
Genant-Modified Sharp Scores (n subjects)	396	198
Total (0-292)	32	33
Erosion Score (0-140)	17	17
Joint Space Narrowing (0-152)	16	17

The use of DMARDs prior to enrollment and randomization were generally comparable in both treatment groups and are shown in Table 20. Similar numbers of subjects were taking corticosteroids and NSAIDs at baseline.

Table 20. Medication use at enrollment/randomization

	Abatacept + MTX (n=433)	**Placebo + MTX (n=219)**
MTX	433 (100%)	219 (100%)
Other DMARDs	53 (12%)	19 (9%)
Biologics	1 (<1%)	0
Corticosteroids	312 (72%)	150 (69%)
NSAIDs	370 (86%)	181 (83%)
Other	1 (<1%)	0

25 of 174 subjects (14%) in the placebo + MTX arm had 1 DMARD added for control of disease activity during Days 170-365 compared to 15 of 401 subjects (4%) in the abatacept + MTX arm. At Day 169 and 365 the mean dose of MTX was comparable between study arms (~16 mg/week). The incidence of increases or decreases in MTX dose was comparable between groups (Table 21). Doses of corticosteroids remained stable at approximately 5 mg day and were evenly balanced between arms.

Table 21. Number of subjects changing MTX dose

	Abatacept + MTX (n=424)	**Placebo + MTX (n=214)**
Day 169	403	180
MTX increase	1 (<1%)	0
MTX decrease	17 (4%)	10 (6%)
Day 365	386	162
MTX increase	9 (2%)	5 (3%)
MTX decrease	33 (9%)	15 (9%)

4.2.4 Primary Analysis of Study IM101102

4.2.4.1 Co-Primary Endpoint 1

At Day 169, 68% of subjects in the abatacept + MTX arm achieved an ACR 20 compared to 40% of subjects in the placebo + MTX arm ($p<0.001$; Table 22). Missing data were imputed using non-responder imputation for the primary analysis.

Table 22. ACR 20 Responders at Day 169

	Abatacept + MTX (n=424)	**Placebo + MTX (n=214)**
ACR 20		
Number of responders	288 (68%)	85 (40%)
p-value	<0.001	

Sensitivity analyses of the primary endpoint included modified worst-case and worst-case scenarios. The modified worst-case scenario sensitivity analysis treats placebo subjects who discontinued the study due to LOE as ACR non-responders for all visits subsequent to discontinuation, and subjects randomized to placebo who did not complete 6 months (Day 169) of treatment but discontinued for reasons other than LOE were classified based on the last available data observed at or prior to their discontinuation. In the worst-case sensitivity analysis, subjects treated with placebo who discontinued for any reason prior to Day 169 were considered ACR responders at Day 169.

The results of the modified worst-case scenario sensitivity analysis was the same as the primary analysis with 68% of subjects in the abatacept + MTX arm achieving an ACR 20 compared to 40% of subjects in the placebo + MTX arm. The results of the worst-case scenario sensitivity analysis demonstrated that a higher proportion of subjects in the abatacept + MTX arm achieved an ACR 20 compared to the placebo + MTX arm (68% versus 57%, respectively). The results on the sensitivity analyses indicate that the positive results on the ACR 20 cannot be attributed to bias related to missing data.

4.2.4.2 Co-Primary Endpoint 2

At Day 365, 64% of subjects in the abatacept + MTX arm achieved a HAQ response that was clinically meaningful (defined as an improvement ≥0.3 units in the HAQ disability index) compared to 39% of subjects in the placebo + MTX arm ($p<0.001$; Table 23). Missing data were imputed using non-responder imputation.

Table 23. Proportion of subjects with clinically meaningful HAQ response at Day 365

	Abatacept + MTX (n=424)	**Placebo + MTX (n=214)**
HAQ		
Number of responders achieving ≥0.3 units	270 (64%)	84 (39%)
p-value	<0.001	

Sensitivity analysis using the modified worst-case scenario demonstrated that a greater proportion of subjects in the abatacept + MTX arm (64%) achieved a HAQ ≥ 0.3u compared with subjects in the placebo + MTX (42%) arm, which was consistent with the primary analysis.

Using the proportion of subjects achieving a change in HAQ score ≥0.3u is more conservative than just analyzing the numeric difference of HAQ score since a numerically significant difference may not represent a clinically significant difference. Moreover, the magnitude of the change (≥0.3u) analyzed here is more conservative than the validated score change of ≥0.22u, which has been shown to represent a clinically meaningful improvement in physical function.

The data suggest that abatacept therapy improves physical function over a 1-year timeframe in patients with RA in subjects who have failed DMARDs and/or a TNF blocker. However, obtaining a claim of improvement in physical function will require evidence that these benefits are sustained to two years.

4.2.4.3 Co-Primary Endpoint 3

At week 54, subjects receiving abatacept + MTX demonstrated a mean change in erosion score from baseline of 0.63u compared to 1.14u for subjects treated with placebo + MTX ($p<0.03$; Table 24). This represents an approximately 45% reduction in erosions for subjects treated with abatacept + MTX.

Table 24. Radiographic Erosion Score at Day 365

	Abatacept + MTX (n=391)	**Placebo + MTX (n=195)**
Baseline mean ± SD	22u ± 18	22u ± 19
Mean change from baseline (± SD)	0.59u ± 1.77	1.24u ± 2.81
Median change from baseline (range)	0 (0-1.02)	0.27 (0-1.30)
p-value	p<0.03	

Table 25 shows the results of a sensitivity analysis for the erosion score. The analysis differed from the primary analysis in that subjects with only baseline radiographic data were included and their Day 365 scores were imputed as follows. All subjects were identified across treatment groups who had non-missing radiographic data at both baseline and Day 365. These subjects were grouped according to the quartiles of their baseline values. These subgroups were denoted as G_1, G_2, G_3 and G_4. If the baseline value of a subject with missing annual assessment fell into a specific quartile associated with G_i, then their annual assessment was imputed with the median of annual assessments from all subjects in G_i. This imputation was performed for Genant-modified Sharp erosion score and joint space narrowing score at Day 365. Subjects without baseline data were excluded. Similar results were obtained for the joint space narrowing and total scores. The results on the sensitivity analyses suggest that the positive results on the erosion score, joint space narrowing, and total score cannot be attributed to bias related to missing data. The agency's biostatistics reviewer additionally carried out a sensitivity analysis using the full intent-to-treat population imputing median values for any subject who lacked a paired set of radiographs. This full intent-to-treat analysis showed a similar result to the prespecified primary analysis, with mean erosion scores of 1.07 and 0.66 in the placebo and abatacept arms, respectively; JSN scores of 1.19 and 0.59 and and total scores were 2.16 and 1.14.

Table 25. Sensitivity Analysis of Erosion Scores Using All Subjects with ≥1 Radiograph*

		Abatacept (n=424)	**Placebo (n=214)**
Erosion Score	n	406	204
	Baseline Mean (SD)	22u ± 18	22u ± 19
	Mean Change from baseline (SD)	0.59u ± 1.77	1.24u ± 2.81
	Median Change from baseline (range)	0 (0-1.02)	0.27 (0-1.30)
*Subjects without baseline radiographs were not included			

4.2.5 Secondary Analyses of Study IM101102

4.2.5.1 Improvement of Signs and Symptoms

Table 26 shows the improvement of signs and symptoms over time as measured by the ACR 20. These data demonstrate that a clinical response to abatacept was apparent by Day 15 and that the proportion of subjects achieving a clinical response continues to rise as late as by Day 225. , Responses were maintained through Day 365.

Table 26. Number of subjects achieving an ACR 20 response by study visit day

	Abatacept + MTX (n=424)	Placebo + MTX (n=214)
Study Visit		
Day 15	97 (23%)*	30 (14%)
Day 29	155 (37%)**	51 (24%)
Day 57	237 (56%)***	75 (35%)
Day 85	262 (62%)***	80 (37%)
Day 113	283 (67%)***	86 (37%)
Day 141	291 (69%)***	93 (44%)
Day 169	288 (68%)***	85 (40%)
Day 225	318 (75%)***	91 (43%)
Day 281	312 (74%)***	94 (44%)
Day 365	310 (73%)***	85 (40%)
* p=0.01; **p=0.002; ***p<0.001		

Additionally, a higher proportion of subjects receiving abatacept + MTX achieved an ACR 50 and ACR 70 compared to placebo-treated subjects at Day 169 with the effect being maintained through Day 365 (Table 27). Subjects receiving abatacept + MTX first achieved a statistically significant difference in ACR 50 at Day 57 and ACR 70 at Day 85 compared to subjects receiving placebo + MTX (data not shown).

Table 27. Number of subjects achieving an ACR 50 and ACR 70 at Day 169 and Day 365

	Abatacept + MTX (n=424)	Placebo + MTX (n=214)
Day 169		
ACR 20	288 (68%)*	85 (40%)
ACR 50	169 (40%)*	36 (17%)
ACR 70	84 (20%)*	14 (7%)
Day 365		
ACR 20	310 (73%)*	85 (40%)
ACR 50	205 (48%)*	39 (18)
ACR 70	122 (29%)*	13 (6%)
* p<0.001		

Larger proportions of subjects receiving abatacept + MTX achieved a major clinical response, defined as maintenance of an ACR 70 response over a continuous 6-month period, compared to subjects receiving placebo + MTX (14% versus 2%, respectively; Table 28). Additionally a greater percentage of subjects (6%) in the abatacept + MTX achieved an extended major clinical response, defined by the sponsor as maintenance of an ACR 70 response over a 9-month period, compared to subjects in the placebo + MTX arm (<1%; Table 13).

Table 28. Number of subjects achieving a major clinical response and extended major clinical response

	Abatacept + MTX (n=424)	**Placebo + MTX (n=214)**
Number of responders (%)		
Major Clinical Response	60 (14%)	4 (2%)
p-value	<0.001	
Extended Major Clinical Response	26 (6%)	1 (<1%)
p-value	0.002	

Each individual component of the ACR 20 showed greater improvement at Days 169 and 365 among abatacept-treated subjects compared to placebo-treated subjects demonstrating that the beneficial effects of abatacept were broadly distributed and not due to a subset of over-weighted component of the composite score (Table 29).

Table 29. Improvement from baseline for individual components of ACR criteria at Day169 and Day 365

	Abatacept + MTX (n=424)	**Placebo + MTX (n=214)**
Swollen Joints (66 total)		
Baseline Median	19	20
Day 169 Median	5	11
Day 365 Median	4	10
Tender Joints (68 total)		
Baseline Median	28	31
Day 169 Median	7	14
Day 365 Median	6	14
Subject Pain Assessment (VAS 100mm)		
Baseline Median	67	70
Day 169 Median	27	50
Day 365 Median	23	48
Physical Function (HAQ Index)		
Baseline Median	1.75	1.75
Day 169 Median	1.13	1.38
Day 365 Median	1	1.38
Subject Global Assessment (VAS 100mm)		
Baseline Median	66	64
Day 169 Median	29	48
Day 365 Median	23	45
Physician Global Assessment (VAS 100mm)		
Baseline Median	69	68
Day 169 Median	21	40
Day 365 Median	17	38
CRP (mg/dL)		
Baseline Median	2.2	2.1
Day 169 Median	0.9	1.8
Day 365 Median	0.8	1.7

While the ACR criteria measure the proportion of subjects achieving a prespecified level of improvement, the DAS28 is a measure of the level of disease activity. The DAS28 is a continuous measure which is a composite of 4 variables: 28 tender joint count, 28 swollen joint count, ESR and subject assessment of disease activity measure on a VAS of 100 mm. Scores for disease activity are defined as high (>5.1); low (≤3.2); clinically significant improvement (change ≥1.2), and remission (<2.6). It is important to note that the DAS28 usage of remission does not meet the agency's definition of remission in part because subjects can have active swollen and tender joints and still meet the DAS28 criteria of remission. According to the DAS28 criteria, a greater proportion of subjects receiving abatacept + MTX, compared to subjects receiving placebo + MTX, achieved clinical improvement (82% versus 51%, respectively), had low disease activity (22% versus 4%, respectively), and were in remission (10% versus 0.6%, respectively; Table 30). These results were maintained through Day 365.

Table 30. Mean change from baseline in DAS28 at Day 169 and 365 (LOCF Analysis)

	Abatacept + MTX (n=366)	**Placebo + MTX (n=179)**
Baseline Mean	6.8	6.8
Day 169		
Post-Baseline Mean	4.3*	5.5
Subjects with improvement (DAS28 change ≥1.2)	301 (82%)	91 (51%)
Subjects with EULAR-defined low Disease activity (DAS ≤3.2)	82 (22%)	7 (4%)
Subjects in EULAR-defined remission (DAS <2.6)	35 (10%)	1 (<1%)
Day 365		
Post-Baseline Mean	4*	5.4
Subjects with improvement (DAS28 change ≥1.2)	328 (88%)	108 (59%)
Subjects with EULAR-defined low Disease activity (DAS ≤3.2)	103 (28%)	7 (4%)
Subjects in EULAR-defined remission (DAS <2.6)	65 (17%)	4 (2%)
*p<0.001		

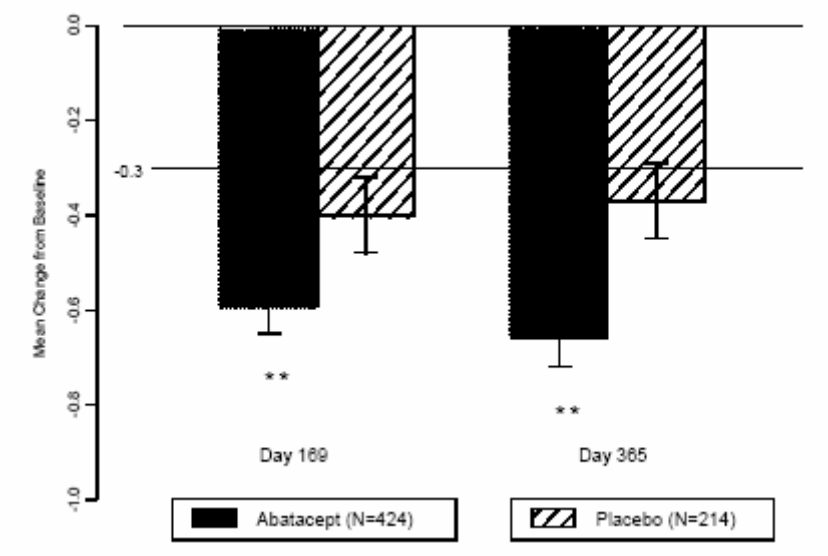
4.2.5.2 Improvement in Physical Function

Greater mean reductions from baseline were observed for the HAQ index at Days 169 and 365 for the abatacept + MTX group compared with the placebo + MTX group (Figure 4). In addition to the Day 365 data discussed above, a higher proportion of subjects in the abatacept arm (61%) achieved a clinically significant improvement (pre-specified as a change >0.3u) as compared to subjects receiving placebo + MTX (45%) at Day 169 (Table 31).

Table 31: Mean change in HAQ score from baseline through Day 169 and Day 365 (LOCF Analysis)**

	Abatacept + MTX (n=366)	**Placebo + MTX (n=179)**
Day 169		
Baseline Mean	1.69	1.69
Adjusted Mean Change from Baseline	-0.59	-0.4
p-value	<0.001	
Day 365		
Baseline Mean	1.69	1.69
Adjusted Mean Change from Baseline	-0.66	-0.37
p-value	<0.001	
*p<0.001; ** minimum 0-maximum 3		

Figure 4. HAQ index: change from baseline



**p<0.001

4.2.5.3 Inhibition of Radiographic Progression

Similar to the effect of abatacept on erosion score, subjects in the abatacept + MTX had significantly less progression of structural damage compared with subject receiving placebo + MTX as measured by joint space narrowing and total score (Table 32) of the Genant-modified Sharp score.

Table 32. Genant-Modified Sharp Radiographic Scores at Day 365

	Abatacept + MTX (n=391)	**Placebo + MTX (n=195)**
Erosion Score		
Baseline mean ± SD	22u ± 18	22u ± 19
Mean change from baseline (± SD)	0.63u ± 1.77	1.14u ± 2.81
Median change from baseline (range)	0 (0-1.02)	0.27 (0-1.27)
p-value	0.029	
Joint Space Narrowing		
Baseline mean ± SD	23u ± 20	23u ± 20
Mean change from baseline (± SD)	0.58u ± 1.54	1.18u ± 2.58
Median change from baseline (range)	0 (0-0.49)	0.27 (0-0.97)
p-value	0.009	
Total Score		
Baseline mean ± SD	44u ± 37	45u ± 38
Mean change from baseline (± SD)	1.21u ± 2.94	2.32u ± 5.04
Median change from baseline (range)	0 .25 (0-1.78)	0.53 (0-2.54)
p-value	0.012	

The proportion of subjects with no new erosions was evaluated using the definition of no new erosions as any change ≤0 from baseline. Based on this definition, 54% of subjects treated with abatacept + MTX had no new erosions compared with 47% of subjects treated with placebo + MTX (data not shown).

4.2.6 Subgroup Analysis of Study IM101102

4.2.6.1 Improvement of Signs and Symptoms

Responses of the ACR 20 at Day 169 were analyzed in relation to baseline demographics. Eighty-four percent of subjects were younger than 65 years of age. The 65 subjects at least 65 years old who received abatacept demonstrated an overall beneficial effect similar to younger subjects as assessed by ACR20 (Table 33). Greater clinical responses were seen in males and females receiving abatacept+ MTX as compared to placebo + MTX (Table 18).
Analysis by race, geographical location, and body weight demonstrated that a higher proportion of subjects receiving abatacept + MTX achieved an ACR 20 compared to the respective subjects receiving placebo + MTX (Table 18).

Table 33. Subgroup analysis of ACR 20 responses by baseline demographics.

	n	Abatacept + MTX	n	Placebo + MTX
Age (years)				
<65	359	248 (69%)	188	77 (41%)
≥65	65	40 (62%)	26	8 (31%)
Sex				
Female	331	217 (66%)	176	71 (40%)
Male	93	71 (76%)	38	14 (37%)
Race				
White	370	249 (67%)	189	71 (38%)
Black	10	6 (60%)	4	2 (50%)
Asian	18	12 (67%)	10	4 (40%)
Other	26	21 (81%)	11	8 (73%)
Geographical Region				
North America	84	47 (56%)	41	9 (22%)
South America	173	131 (76%)	93	44 (47%)
Europe	143	99 (69%)	67	25 (37%)
ROW	24	11 (46%)	13	7 (54%)
Body Weight (kg)				
<60	107	69 (65%)	57	17 (30%)
60-100	288	203 (71%)	145	65 (45%)
>100	29	16 (55%)	12	3 (25%)

A variety of baseline disease-activity characteristics could influence the likelihood of clinical responses including disease duration, number of swollen and tender joints, CRP, baseline Genant-modified Sharp score, and level of disability as measured by the HAQ disability index. Analysis of disease duration demonstrated a clinical benefit as assessed by ACR 20 in subjects receiving abatacept regardless of disease duration (Table 34). Similarly, subjects receiving abatacept demonstrated a higher proportion of subjects achieving an ACR 20 than subjects treated with placebo regardless of the number of swollen and tender joints, CRP, baseline Genant-modified Sharp score, or level of physical function (Table 34).

Improvement in physical function (assessed by HAQ-DI) was analyzed in subject subsets. Similar improvements in HAQ-DI were observed in subjects subsetted by sex, age, race, weight, disease duration, baseline disease activity and baseline level of radiographic damage (data not shown).

Table 34. Subgroup analysis of ACR 20 responses by baseline disease characteristics

	n	Abatacept + MTX	n	Placebo + MTX
Disease Duration (years)				
≤2	95	67 (71%)	41	19 (46%)
>2 to ≤5	91	64 (70%)	46	20 (44%)
>5 to ≤10	105	72 (69%)	54	22 (41%)
>10	133	85 (64%)	73	24 (33%)
# Swollen Joints				
Upper Quartile	91	61 (67%)	52	72 (42%)
Other Quartiles	333	227 (68%)	162	63 (39%)
# Tender Joints				
Upper Quartile	92	59 (64%)	56	22 (46%)
Other Quartiles	332	229 (69%)	59	(37%)
CRP				
Upper Quartile	112	82 (73%)	46	19 (41%)
Other Quartiles	312	206 (66%)	168	66 (39%)
Genant-modified Sharp Score				
Upper Quartile	104	64 (62%)	48	13 (22%)
Other Quartiles	302	210 (70%)	156	68 (44%)
HAQ				
Upper Quartile	93	65 (70%)	38	19 (52%)
Other Quartiles	329	221 (67%)	176	66 (38%)

4.2.6.3 Inhibition of Radiographic Progression

Responses for inhibition of radiographic progression at Day 365 as assessed by Genant-modified Sharp score were analyzed in relation of baseline demographics. Subjects receiving abatacept + MTX demonstrated inhibition of progession in total Genant-modified Sharp scores compared to subjects receiving placebo + MTX regardless of age, sex, race, geographical region, and weight (Table 35). Two possible exceptions appeared to be with Asian subjects and subjects weighing >100 kg. Both groups had small numbers of subjects, ranging between10-30 subjects/group, and in both groups where the subjects were treated with abatacept + MTX there was skewing of the mean by several outlying values. On a whole both Asian subjects and subjects weighing >100 kg benefited from abatacept in terms of achieving an ACR 20 (Table 34) and improvement in physical function (Table 35).

Table 35. Subgroup analysis of total Genant-modified Sharp score by baseline demographics

Mean Change from Baseline (SD)	n	Abatacept + MTX	n	Placebo + MTX
Age (years)				
≤65	330	1.31 (3.0)	174	2.47 (5.25)
>65	61	0.69 (2.51)	21	1.08 (2.57)
Sex				
Female	311	1.31 (3.14)	161	2.49 (5.32)
Male	80	0.84 (1.94)	34	1.51 (3.43)
Race				
White	341	1.19 (3.0)	170	2.4 (5.3)
Black	6	0.83 (1.06)	4	4.02 (4.89)
Asian	18	2 (3.54)	10	1.09 (1.34)
Other	26	0.96 (1.73)	11	1.69 (2.68)
Geographical Region				
North America	72	1.28 (2.25)	40	2.42 (6.73)
South America	166	1.1 (3.45)	85	205 (3.91)
Europe	129	1.09 (2.39)	58	2.6 (5.06)
ROW	24	2.41 (3.37)	12	2.53 (6.16)
Body Weight (kg)				
<60	104	1.43 (3.0)	51	1.91 (3.16)
60-100	259	1.1 (2.92)	132	2.7 (5.74)
>100	28	1.4 (2.94)	12	-0.14 (1.24)

Subjects receiving abatacept + MTX also demonstrated less radiographic progression as assessed by the total Genant-modified Sharp score compared to subjects receiving placebo + MTX regardless of disease duration, swollen and tender joints, CRP, Genant-modified Sharp score, and baseline HAQ (Table 36).

Table 36. Subgroup analysis of total Genant-modified Sharp score by baseline disease activity

Mean Change from Baseline (SD)	n	Abatacept + MTX	n	Placebo + MTX
Disease Duration (years)				
≤2	91	1.13 (2.88)	35	4.03 (8.2)
>2 to ≤5	83	2.05 (4.36)	42	2.99 (5.72)
>5 to ≤10	99	0.91 (2.77)	51	1.49 (2.96)
>10	118	0.93 (2.11)	67	1.64 (3.22)
# Swollen Joints				
Upper Quartile	85	1.38 (4.14)	48	3.37 (5.76)
Other Quartiles	306	1.16 (2.51)	147	1.98 (4.76)
# Tender Joints				
Upper Quartile	83	1.63 (4.31)	54	2.63 (4.23)
Other Quartiles	308	1.1 (2.41)	141	1.13 (2.59)
CRP				
Upper Quartile	105	1.88 (3.44)	41	3.2 (7.42)
Other Quartiles	286	0.96 (2.69)	154	2.09 (4.2)
Genant-modified Sharp Score				
Upper Quartile	97	1.34 (2.08)	46	2.83 (4.85)
Other Quartiles	294	1.17 (2.93)	149	2.17 (5.11)
HAQ				
Upper Quartile	89	2.12 (4.52)	34	2.34 (4.94)
Other Quartiles	300	0.93	161	2.32 (5.08)

4.3 Study IM101029

4.3.1 Study Design of IM101029

Study IM101029 was a randomized, double-blind, placebo-controlled study with parallel dosing for 6 months. Subjects with active RA who met the inclusion/exclusion criteria for this study were randomized 2:1 to receive abatacept or placebo on a background of DMARDs. Subjects must have been treated with TNF blocker therapy for at least 3 months and designated as TNF blocker therapy failure due to inadequate efficacy. Subject randomization was stratified into 2 groups according to whether the subject was currently receiving TNF blocker therapy (current users) or had discontinued this therapy previously (prior users). 393 subjects were enrolled at 101 sites worldwide, of which 69 sites were in the US, 24 sites in Europe, and 8 sites in Canada.

All subjects were required to meet the following key inclusion/exclusion criteria:

- Diagnosis of RA (1987 ACR criteria) >1 year
- RA functional classes I, II, or III
- Subjects who were currently receiving or previously received a TNF blocker therapy at an approved labeled dose for ≥3 months designated as TNF blocker therapy failures for lack of efficacy (see details below). Subjects who discontinued a TNF blocker therapy due to intolerance or safety were not considered as TNF blocker therapy failures unless they were primarily efficacy failures.
- Drug stabilization requirements:
    - Prior to Day 1, subjects must have discontinued etanercept ≥ 28 days or infliximab ≥ 60 days
    - Subjects must be on anakinra or DMARD(s) for ≥3 months with stable doses ≥ 28 days
    - Oral corticosteroid treatment must have been ≤ 10mg prednisone (or equivalent) daily for ≥ 28 days
    - NSAIDs must have been at approved doses and at stable doses for ≥28 days
- Subjects must have met washout/drug stabilization requirements for TNF blocker therapy (see below)

Subjects continued to receive background DMARDs or anakinra during this study at the dosage and regimen administered at the time of randomization. TNF blocker therapy failures in subjects with RA were defined as follows:

- ***Current*** TNF blocker therapy failures were defined as those subjects currently receiving etanercept or infliximab at an approved labeled dose who after 3 months of therapy were determined by a treating physician to still have active disease as defined by persistent disease activity of a minimum of 10 swollen and 12 tender joints. Investigators were required to provide documentation stating that the subject was failing TNF blocker

therapy for inadequate efficacy and that the subject had a minimum of 10 swollen and 12 tender joints.

- ***Prior*** TNF blocker therapy failures were defined as those subjects previously receiving etanercept or infliximab at an approved labeled dose who after 3 months of therapy that were determined by a treating physician to still have active disease as defined by persistent disease activity of a minimum of 10 swollen and 12 tender joints. For subjects designated as prior TNF blocker therapy failures, the 10 swollen and 12 tender joint count was offered only as a benchmark of minimally acceptable disease severity in support of TNF blocker therapy failure. This acknowledges that joint counts are not routinely recorded in clinical practice. Joint counts for these subjects were not required to be documented at the time of enrollment for study eligibility provided that the TNF blocker failure designation by the treating physician incorporated this benchmark and that the subject had at least 10 swollen and 12 tender joints. Investigators were required to indicate on the CRF that documentation was available to support that the subject had failed TNF blocker therapy for inadequate efficacy and the date that TNF blocker therapy was discontinued. Acceptable documents included: medical records, letter provided by a referring physician, or other "reason for referral" documents (e.g., insurance authorization form).

Prior to randomization on study Day 1, prior TNF blocker therapy subjects were required to have the following disease activity:

- ≥10 swollen joints (66 joint count)
- ≥12 tender joints (68 joint count)
- CRP >1.3 mg/dL

At the screening visit, current TNF blocker therapy subjects were required to have the following disease activity:

- ≥6 swollen joints (66 joint count)
- ≥8 tender joints (68 joint count)
- no restriction on CRP

All subjects receiving etanercept at screening visit were required to undergo a 28-day washout period, while all subjects receiving infliximab were required to undergo a 60-day washout period. Following the washout period and prior to randomization on study Day 1, current TNF blocker therapy subjects were required to have the following disease activity:

- ≥10 swollen joints (66 joint count)
- ≥12 tender joints (68 joint count)
- CRP >1.3 mg/dL

\

Study medication was administered on Days 1, 15, 29, and every 28 days thereafter for a total of 7 doses. Abatacept was administered as an IV infusion of a tiered-dose based on subject's weight at study screening:

- <60 kg: abatacept 500 mg IV
- 60 kg to 100 kg: abatacept 750 mg IV
- ≥100 kg: abatacept 1000 mg IV

Doses of abatacept could be modified or discontinued if there was evidence of an AE, and could only be restarted if there was complete resolution of the AE. Subjects who missed >1 consecutively scheduled dose of study medication was to be discontinued from the study. Concomitant medications included the stable dosages of DMARDs, corticosteroids, and NSAIDs. Use of corticosteroids included ≤2 intra-articular injections but the injected joint was counted as "active" in all subsequent assessments. Subjects had assessments for safety and disease activity on Days 1, 15, 29, 57, 85, 113, 141, and 169. Independent blinded joint assessors determined joint counts and scores.

There were 2 co-primary endpoints prospectively defined for the study in the following hierarchical order:

1. Improvement from baseline in signs and symptoms as assessed by the proportion of subjects achieving an ACR20 at Day 169
2. Improvement in physical function as measured by the proportion of subjects with a ≥0.3u improvement in the HAQ at Day 169

Subjects were randomized in a 2:1 ratio to the abatacept group or placebo group. Additionally, subjects were stratified based on their TNF blocker failure designation (i.e., prior or current) and were monitored so that no more than 67% of the randomized subjects would be from either TNF blocker failure group. An interactive voice recognition system (IVRS) was used for study randomization. The IVRS was programmed to record TNF blocker user status at the time of enrollment (using the definitions described above for current or prior TNF blocker use) and then to stratify subjects across treatments by this variable. The TNF blocker user status was also determined based on the date of discontinuation of the TNF blocker medication on the CRFs. Discrepancies regarding TNF blocker user status were noted between the IVRS and CRFs. Consequently, for the primary endpoints, the designation of baseline TNF blocker user status for use as covariates in the Cochran-Mantel Haenszel tests was based on the stratified randomization schedule of the IVRS, thus keeping consistent with the intent-to treat (ITT) principle. A sensitivity analysis of the primary efficacy endpoints was subsequently performed to assess the impact of the true assignments of the TNF blocker user status.

Power calculations for the ACR 20 response rate used an estimate for the placebo group at Day 169 of 25% with a sample size of 256 subjects in the abatacept group and 128 subjects in the placebo group yielding a 96% power to detect a difference of 20% at the 5% level of significance (2-tailed). Improvement in physical function was calculated to yield a power of 87% to detect a treatment difference of 18%. A modified ITT analysis was used whereby all subjects who were randomized and received at least 1 dose of double-blinded study medication were included in all efficacy analyses.

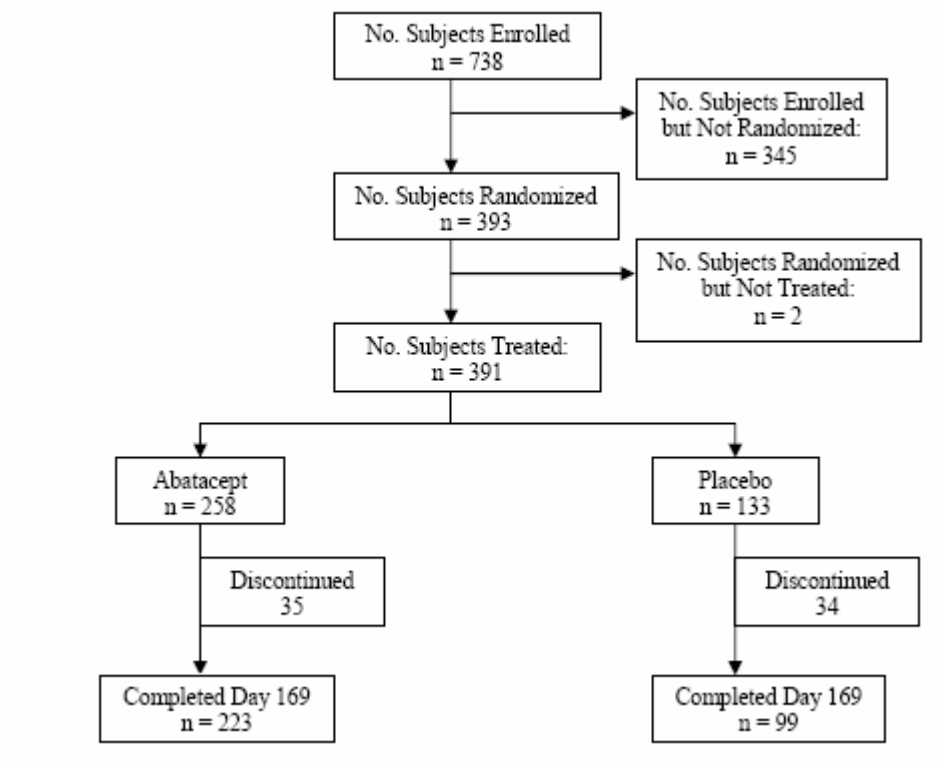
Missing data for the primary analyses (ACR and HAQ) were handled as follows. All subjects who discontinued the study were considered treatment failures (i.e., non-responders). Subjects receiving treatment who were missing data for either the ACR response status or HAQ score were considered a non-responder; however, if a subject was a responder at the visit immediately preceding the missed visit and immediately after the missed visit then a positive response was imputed for the current visit. If the current visit occurred on study Day 169 then imputation depended on the observed responses at the previous 2 consecutive scheduled visits.

A sequential testing procedure was employed for testing the co-primary hypotheses according to the hierarchy specified above. A co-primary endpoint was tested only if there was statistical significance for the preceding co-primary endpoints. First, a 2-sided Cochran-Mantel-Haenszel Chi square test, which was stratified based on the baseline TNF blocker use, was used to compare the abatacept group with the placebo group at the 0.05 level of significance. For each of the tests, the nominal type I error rate was set at 5%, therefore this sequential testing procedure preserves the overall type I error rate at 5%.

4.3.2 Study Conduct of IM101029

A total of 738 subjects were enrolled with 393 subjects being randomized. The most frequent reason for not being randomized was subjects not meeting study criteria (primarily due to subjects having a lower CRP than required for study entry). Of the 393 subjects randomized 2 subjects were not treated and of the remaining 391 subjects, 258 were randomized to abatacept and 133 to placebo (Figure 5).

Figure 5. Study Disposition for IM101029



subjects but was found to have poor clinical and documentation practices and the site was subsequently closed. BMS excluded this site's data from all analyses of efficacy but included the data in all analyses of safety.

FDA review of the 20 subjects with protocol violations (15 subjects in the abatacept arm; 5 subjects in the placebo arm) that could potentially be clinically important did not affect the conclusions of the study and data for these subjects were included in the analyses.

Subject disposition for the period of Days 1-169 showed a greater proportion of subjects in the abatacept group (86%) completed 169 days of treatment compared to the placebo group (74%). Lack of efficacy (5%) and AEs (4%) were the most common reasons for discontinuation in the abatacept arm and LOE (20%) and AEs (4%) were the most common reasons for discontinuation in the placebo arm (Table 37). The higher rate of discontinuation in the placebo group was attributable to a higher rate of discontinuation due to lack of efficacy.

Table 37. Day 1-169: Reasons for Discontinuation

	Abatacept (n=256)	**Placebo (n=133)**
Number Discontinued	35 (14%)	34 (26%)
Death	0	0
Adverse Events	9 (4%)	5 (4%)
Loss of Efficacy	14 (5%)	27 (20%)
Lost to Follow-up	5 (2%)	0
Withdraw of Consent	5 (2%)	2 (2%)
Other	2 (1%)	4 (2%)
Completed 169 days	223 (86%)	99 (74%)

4.3.3 Study Demographics of IM101029

The baseline characteristics of the study subjects are shown in Table 38. The baseline demographic characteristics of each stratified group were similar to the population as a whole. There were no baseline imbalances between study arms with the majority of subjects being white and female, with a mean age of 53 years, and a mean weight of 78 kg.

Table 38. Baseline Demographic Characteristics

	Abatacept + MTX (n=256)	**Placebo + MTX (n=133)**
Age (years, mean ± SD)	53 ± 12	53 ± 11
Weight (kg, mean ± SD)	78 ± 19	78 ± 21
Gender (female)	199 (77%)	106 (80%)
Race		
White	248 (96%)	1124 (93%)
Black	9 (4%)	5 (4%)
American Indian	1 (<1%)	1 (<1%)
Asian	0	2 (2%)
Other	0	1 (<1%)
Geographical Region		
North America	189 (73%)	99 (74%)
South America	0	0
Europe	69 (27%)	34 (26%)

The baseline disease characteristics of the study subjects are shown in Table 39. Baseline demographic characteristics of each stratified group were similar to the population as a whole. Subjects demonstrated active RA as evidenced by the number of swollen joints (~22) and tender joints (~31), elevated level of CRP (~4 mg/dL), and prolonged morning stiffness (~120 minutes). The mean duration of RA was approximately 12 years. There were no imbalances between study arms.

Table 39. Baseline Disease Characteristics

	Abatacept + MTX (n=256)	**Placebo + MTX (n=133)**
Duration of RA (years, mean ± SD)		
Median	11	10
Mean ± SD	12 ± 9	11 ± 9
≤2 years	32 (12%)	16 (12%)
>2-≤5 years	31 (12%)	26 (20%)
>5-≤10 years	59 (23%)	25 (19%)
> 10 years	136 (53%)	66 (50%)
Swollen joints (mean ± SD)	22 ± 10	22 ± 10
Tender joints (mean ± SD)	31 ± 13	33 ± 13
Subject Pain Assessment (VAS 00mm)	71 ± 20	70 ± 19
Physical Function (HAQ)	1.8	1.8
Subject Global Assessment (VAS 100mm)	69 ± 20	70 ± 20
Physician Global Assessment (VAS 100mm)	69 ± 18	67 ± 17
CRP	4.6	4
RF (+)	189 (73%)	97 (73%)
Morning Stiffness (minutes, Mean ± SD)	121 ± 62	115 ± 61
DAS-28 (mean ± SD)	6.9 ± 1	6.9 ± 1
MTX dose (mg/wk, mean ± SD)	15 ± 5	14 ± 6
Current or Prior TNF blocker use		
Current	98 (38%)	55 (41%)
Prior	160 (62%)	78 (59%)

The proportion of subjects who were current or prior TNF blocker users was similar between study arms. Approximately 65% of subjects had failed infliximab therapy while 35% had failed etanercept with similar proportions between groups. The majority of subjects had received a TNF blocker >8 months prior to discontinuation with only 4% of all subjects receiving a TNF blocker drug <3 months (Table 40).

Table 40. Duration of TNF blocker Use Prior to Randomization

	Abatacept (n=256)		**Placebo (n=133)**	
	Etanercept (n=32)	Infliximab (n=66)	Etanercept (n=23)	Infliximab (n=32)
Current TNF blocker users				
<3 months	3 (9%)	3 (5%)	1 (4%)	3 (9%)
3-8 months	10 (31%)	14 (21%)	9 (39%)	3 (9%)
>8 months	19 (59%)	49 (74%)	13 (57%)	26 (81%)
	Etanercept (n=51)	Infliximab (n=109)	Etanercept (n=30)	Infliximab (n=48)
Prior TNF blocker users				
<3 months	1 (2%)	6 (6%)	0	0
3-8 months	20 (39%)	36 (33%)	8 (27%)	22 (46%)
>8 months	30 (59%)	67 (62%)	22 (73%)	26 (54%)
Time since discontinuation (median days)	213	182	163	197

The use of DMARDs prior to enrollment and randomization were generally comparable in both treatment groups and are shown in Table 41. Similar numbers of subjects were taking corticosteroids and NSAIDs at baseline.

Table 41. Previous RA Medication History

	Abatacept (n=256)	**Placebo (n=133)**
DMARDs*		
MTX	195 (76%)	109 (82%)
Hydroxychloroquine/Chloroquine	23 (9%)	13 (10%)
Leflunomide	23 (9%)	11 (8%)
Sulfasalazine	18 (7%)	13 (10%)
Azathioprine	7 (3%)	3 (2%)
Biologics		
Anakinra	7 (3%)	3 (2%)
Corticosteroids	181 (70%)	86 (65%)
NSAIDs	181 (70%)	95 (71%)
* some subjects were on >1 DMARD		

During the double-blind period of the study, concomitant anti-rheumatic medication use was comparable between the 2 arms. The study protocol did not allow for dose adjustment or additions of DMARDs during the double-blind period of the study; however, 2 subjects in the abatacept group did have a protocol violation with 1 subject adding a DMARD and 1 subject receiving etanercept on the day after their last dose of study medication. These 2 subjects represent an extremely small percentage of the whole group and are not expected to alter the results or interpretation of the study.

4.3.4 Primary Analysis of Study IM101029

4.3.4.1 Co-Primary Endpoint 1

At Day 169, 50% of subjects in the abatacept arm achieved an ACR 20 compared to 20% of subjects in the placebo arm ($p<0.001$; Table 42). Missing data were imputed using non-responder imputation for the primary analysis.

Table 42. ACR 20 Responders at Day 169

	Abatacept (n=256)	**Placebo (n=133)**
ACR 20		
Number of responders	129 (50%)	26 (20%)
p-value	<0.001	

A greater proportion of abatacept-treated subjects achieved an ACR 20 response compared to placebo-treated subjects regardless of whether subjects were enrolled as current TNF blocker therapy failures (45% vs. 15%, respectively) or prior TNF blocker therapy failures (54% vs. 23%). The clinical benefit of abatacept was also consistent in subjects who failed etanercept or infliximab therapies. Sensitivity analyses including modified worst-case and worst-case scenarios supported the results of the primary analysis.

4.3.4.2 Co-Primary Endpoint 2

At Day 169, 47% of subjects in the abatacept arm achieved a HAQ response that was clinically meaningful (defined as an improvement ≥0.3 units in the HAQ disability index) compared to 23% of subjects in the placebo arm ($p<0.001$; Table 43).

Table 43. Proportion of Subjects with Clinically Meaningful HAQ Response at Day 169

	Abatacept (n=256)	**Placebo (n=133)**
HAQ		
Number of responders achieving ≥0.3 u improvement	121 (47%)	31 (23%)
p-value	<0.001	

A greater proportion of abatacept-treated subjects achieved a HAQ-DI response compared to placebo-treated subjects regardless of whether subjects were enrolled as current TNF blocker therapy failures (43% vs. 22%, respectively) or prior TNF blocker therapy failures (50% vs. 24%). The clinical benefit of abatacept was also consistent in subjects who failed etanercept or infliximab therapies.

Sensitivity analysis using the modified worst-case scenario demonstrated that a greater proportion of subjects in the abatacept arm (47%) achieved a HAQ ≥ 0.3u compared with subjects in the placebo (24%) arm, which was consistent with the primary analysis.

Concluding clinical efficacy based on using the proportion of subjects achieving a change in HAQ score ≥0.3u is more conservative than analyzing the numeric difference between mean changes in HAQ scores since a statistically significant difference in scores may not represent a clinically significant difference. Moreover, the magnitude of the change (≥0.3u) analyzed here is more conservative than the validated score change of ≥0.22u, which has been shown to represent a clinically meaningful improvement in physical function.

Overall, the data suggest that abatacept therapy improves physical function over a 6-month timeframe in patients with RA in subjects who have failed DMARDs and/or a TNF blocker.

4.3.5 Secondary Analyses

4.3.5.1 Improvement of Signs and Symptoms

A greater proportion of subjects receiving abatacept achieved an ACR 50 and ACR 70 compared to placebo-treated subjects at Day 169 (Table 44). Subjects receiving abatacept first achieved a statistically significant difference in ACR 50 at Day 85 and ACR 70 at Day 57 compared to subjects receiving placebo (data not shown).

Table 44. Number of subjects achieving an ACR 50 and ACR 70 at Day 169

	Abatacept (n=256)	Placebo (n=133)
Day 169		
ACR 20	129 (50%)*	26 (20%)
ACR 50	52 (20%)*	5 (4%)
ACR 70	26 (10%)**	2 (2%)
* p<0.001; **p=0.003		

Each individual component of the ACR 20 showed greater improvement at Days 169 among abatacept-treated subjects compared to placebo-treated subjects demonstrating that the beneficial effects of abatacept were broadly distributed and not due to a subset of over-weighted component of the composite

Unlike the ACR criteria, which measure improvement from baseline, the DAS28 score is a measure of disease activity. The DAS28 is a continuous measure which is a composite of 4 variables: 28 tender joint count, 28 swollen joint count, ESR and subject assessment of disease activity measure on a VAS of 100 mm. Scores for disease activity are defined as high (>5.1); low (≤3.2); clinically significant improvement (change ≥1.2), and remission (<2.6). It is important to note that the DAS28 usage of remission does not meet the Agency's definition of remission since subjects can have active swollen and tender joints and still meet the DAS28 criteria of remission and because the DAS remission criteria do not take into account radiographic progression. According to the DAS28 criteria, at study Day 169 a greater proportion of subjects receiving abatacept, compared to subjects receiving placebo, achieved clinical improvement (71% versus 32%, respectively), had low disease activity (17% versus 4%, respectively), and were in remission (10% versus 1%, respectively; Table 45).

Table 45. Mean Change from Baseline in DAS 28 at Day 169 (LOCF Analysis)

	Abatacept (n=182)	Placebo (n=98)
Baseline Mean	6.9	6.9
Day 169		
Post-Baseline Mean	4.9*	6.2
Subjects with improvement (DAS28 change ≥1.2)	129 (71%)	31 (32%)
Subjects with EULAR-defined low disease activity (DAS ≤3.2)	30 (17%)	4 (4%)
Subjects in EULAR-defined remission (DAS <2.6)	19 (10%)	1 (1%)
*p<0.001		

4.4 Study IM101101

4.4.1 Study Design of IM101101

Study IM101101 was a 12-month, randomized (2:1), double blind, placebo-controlled, parallel-group, Phase-2 study evaluating the safety and efficacy of abatacept 2 mg/kg in combination with etanercept 25mg BIW to subjects with active rheumatoid arthritis. The study randomized 121 subjects at 40 sites in the US.

All subjects were required to meet the following key inclusion/exclusion criteria:

- Diagnosis of RA (1987 ACR criteria) >1 year
- RA functional classes I, II, or III
- Treated with etanercept 25mg BIW for at least 3 months and at a stable dose for 28 days prior to study treatment
- Active disease despite current etanercept therapy
    - Etanercept Monotherapy
        - ≥8 swollen joints
        - ≥10 tender joints
        - No restriction on CRP
    - Etanercept + oral DMARD Therapy
        - ≥6 swollen joints
        - ≥8 tender joints
        - no restriction on CRP

The 12-month study period was divided into 2 periods: Days 1-180 and Days 181-360 with the primary endpoint for signs and symptoms of RA occurring at Day 180. During Days 1-180 subjects received abatacept 2 mg/kg via intravenous infusion or placebo on a background of etanercept 25 mg SC BIW. Subjects who achieved at least a 50% reduction in their swollen and tender joint counts at Day 180 were to discontinue etanercept and continue on their original treatment assignment of abatacept or placebo for an additional 6 months. Subjects who did not reach this level of response were to continue on etanercept and their originally assigned therapy of abatacept or placebo for the remainder of the study. Subjects could continue in a long-term extension trial after completing the 12-month study period.

The primary endpoint for study IM101101 was the proportion of subjects achieving a modified ACR20 response at Day 180. The ACR criteria were modified to exclude CRP from the composite ACR response due to low baseline CRP levels observed in subjects with active RA receiving etanercept. Therefore, subjects had to achieve a ≥20% improvement over baseline in swollen and tender joints and in 2/5 of the remaining core data set measures. Important secondary endpoints included ACR50 and ACR70.

All statistical tests used the intent-to-treat population and were performed using a 2-tailed, 5% level of significance. The primary endpoint was the proportion of abatacept-treated subjects

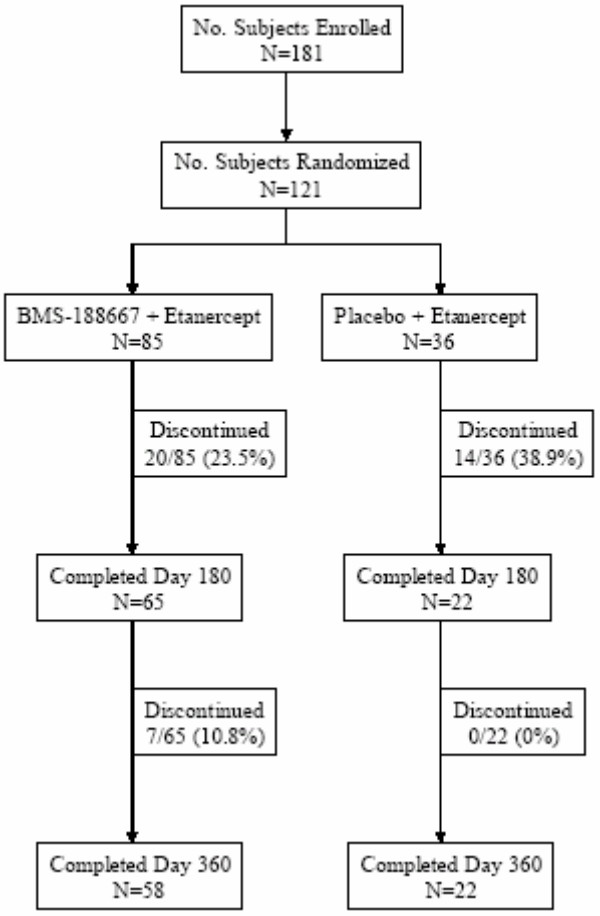
achieving a modified ACR20 response compared to the placebo-treated subjects using the Chi-square test.

4.4.2 Study Conduct of IM101101

A total of 176 subjects were enrolled and 121 subjects were randomized. The most frequent reason for not being randomized was subjects failing to meet inclusion and/or exclusion criteria. Of the 121 subjects randomized, 85 were randomized to abatacept and 36 to placebo (Figure 6).

During Days 1-180, 7 subjects had protocol violations that could potentially be clinically important. These violations would not be expected to affect the conclusions of the study and were included in all analyses.

Figure 6. Subject Disposition for Study IM101101



Subject disposition for the period of Days 1-180 showed that a higher proportion of subjects in the abatacept + etanercept group (77%) completed 180 Days of treatment compared to the placebo + etanercept group (61%). The higher rate of discontinuation in the placebo arm can be attributed to a higher rate of discontinuation due to lack of efficacy in the placebo group compared to the abatacept group (33% vs. 11%). A greater proportion of subjects in the abatacept arm discontinued due to an AE than in the placebo arm (7% vs. 3%, respectively) (Table 46).

Table 46. Day 1-169: Reasons for Discontinuation

	Abatacept 2 mg/kg + Etanercept (n=85)	**Placebo + Etanercept (n=36)**
Number Discontinued	20 (24%)	14 (39%)
Death	0	0
Adverse Events	6 (7%)	1 (3%)
Loss of Efficacy	9 (11%)	12 (33%)
Lost to Follow-Up	1 (1%)	0
Withdraw of Consent	3 (4%)	1 (3%)
Non-Compliance	1 (1%)	0
Completed 180 days	65 (77%)	22 (61%)

From Days 181-360, an additional 7 subjects (11%) in the abatacept + etanercept group discontinued the study with LOE remaining the most common reason for study discontinuation (data not shown). Eighty-six percent of subjects in the abatacept + etanercept group and 89% of placebo + etanercept subjects received all study infusions throughout the course of the trial.

4.4.3 Study Demographics of IM101101

The baseline characteristics were generally similar across both treatment arms of the study and are shown in Table 47. The majority of subjects were white and female, mean age of ~51 years, and mean weight of 80 kg.

Table 47. Baseline Demographic Characteristics

	Abatacept 2 mg/kg + Etanercept (n=85)	**Placebo + Etanercept (n=36)**
Age (years, mean ± SD)	50 ± 11	54 ± 11
Weight (kg, mean ± SD)	81 ± 22	79 ±19
Gender (female)	66 (78%)	26 (72%)
Race		
White	80 (94%)	36 (100%)
Black	2 (2%)	0
Other	3 (4%)	0

The baseline disease characteristics of the study subjects are shown in Table 48.
Subjects had active RA at baseline as demonstrated by the number of swollen joints (~20) and tender joints (~29), elevation of CRP (~2 mg/dL), and prolonged morning stiffness (~100 minutes). The mean duration of RA was approximately 13 years. Treatment arms were imbalanced in several ways. There was a lower subject pain assessment score in the placebo arm, a higher proportion of subjects who were RF (+) in the placebo arm, and a higher baseline total Genant-Modified Sharp score. These differences could affect the validity of the results of the study. The imbalances may be accounted for by the small sample size in the placebo group.

Table 48. Baseline Disease Characteristics

	Abatacept 2 mg/kg + Etanercept (n=85)	**Placebo + Etanercept (n=36)**
Duration of RA (years, mean ± SD)	13 ± 10	13 ± 9
Swollen joints (mean ± SD)	20 ± 9	20 ± 11
Tender joints (mean ± SD)	29 ± 14	29 ± 13
Subject Pain Assessment (VAS 100mm)	66 ± 17	35 ± 23
Physical Function (HAQ)	1.0	0.9
Subject Global Assessment (VAS 100mm)	62 ± 19	62 ± 14
Physician Global Assessment (VAS 100mm)	62 ± 17	62 ± 14
CRP	2.0	2.4
RF (+)	68%	78%
Morning Stiffness (minutes, Mean ± SD)	107 ± 65	103 ± 57
Total Genant-Modified Sharp Score at baseline	38 ± 40	50 ± 44

4.4.4 Analysis of Primary Endpoint Study IM101101

4.4.4.1 Improvement of Signs and Symptoms

At Day 180, 48% of abatacept-treated subjects achieved a modified ACR 20 response compared to 31% of placebo-treated subjects, which did not reach statistical significance (p=0.07; Table 49).

Table 49. Modified ACR 20 Responders at Day 180

	Abatacept 2 mg/kg + Etanercept (n=85)	Placebo + Etanercept (n36)
Modified ACR 20 (%)		
Number of responders	41 (48%)	11 (31%)
p-value	0.072	

Since study IM101101 is not a pivotal trial for the assessment of the clinical efficacy of abatacept, and given the results of the trial, further analyses that were conducted will not be presented or discussed in this review. Overall, study IM101101 did not provide significant evidence of clinical efficacy with the combination therapy of abatacept 2 mg/kg + etanercept 25 mg BIW. However, the results did trend toward a benefit of the drug combination. A larger trial would be needed, perhaps with abatacept dose-ranging, to definitively study the risks and benefits of combination therapy with abatacept and etanercept.

4.5 Study IM101031

4.5.1 Study Design of IM101031

Study IM101031 was a 12-month, multinational, multicenter, randomized, double-blind, placebo-controlled, 2-arm, parallel-dosing Phase-3 study. The primary objective was to summarize the incidence of AEs, Serious adverse events (SAEs), and discontinuations due to AEs during the 12-month period of combined treatment with abatacept and ≥1 DMARDS and/or biologic RA therapies in subjects with active RA with or without co-morbid medical conditions. The study randomized 1441 subjects at 161 study centers worldwide.

All subjects were required to meet the following key inclusion/exclusion criteria:

- Diagnosis of RA (1987 ACR criteria) >1 year
- RA functional classes I, II, III, or IV
- Subject's average global assessment of disease activity (VAS) at screening and Day1 ≥20mm
- Treated with 1 or more non-biologic and/or biologic RA therapy ≥3months and on a stable dose for 28 days prior to Day1.
- Subjects with co-morbid conditions were permitted to participate in the study.

Subjects were randomized to 1 of 2 treatment arms: abatacept tiered-dose (<60 kg: abatacept 500 mg IV; 60 kg to 100 kg: abatacept 750 mg IV; ≥100 kg: abatacept 1000 mg IV) or placebo infusions. All subjects continued background RA therapies throughout the double-blind treatment period. Subjects received study drug on Days 1, 15, 29, then every 28 days thereafter for a total of 14 doses. Adjustments in background RA therapy were not allowed during the initial 3 months of the double-blind period except for decreases in dose due to toxicity. After the first 3 months, background RA therapy was permitted, including the addition of non-biologic and/or biologic therapies

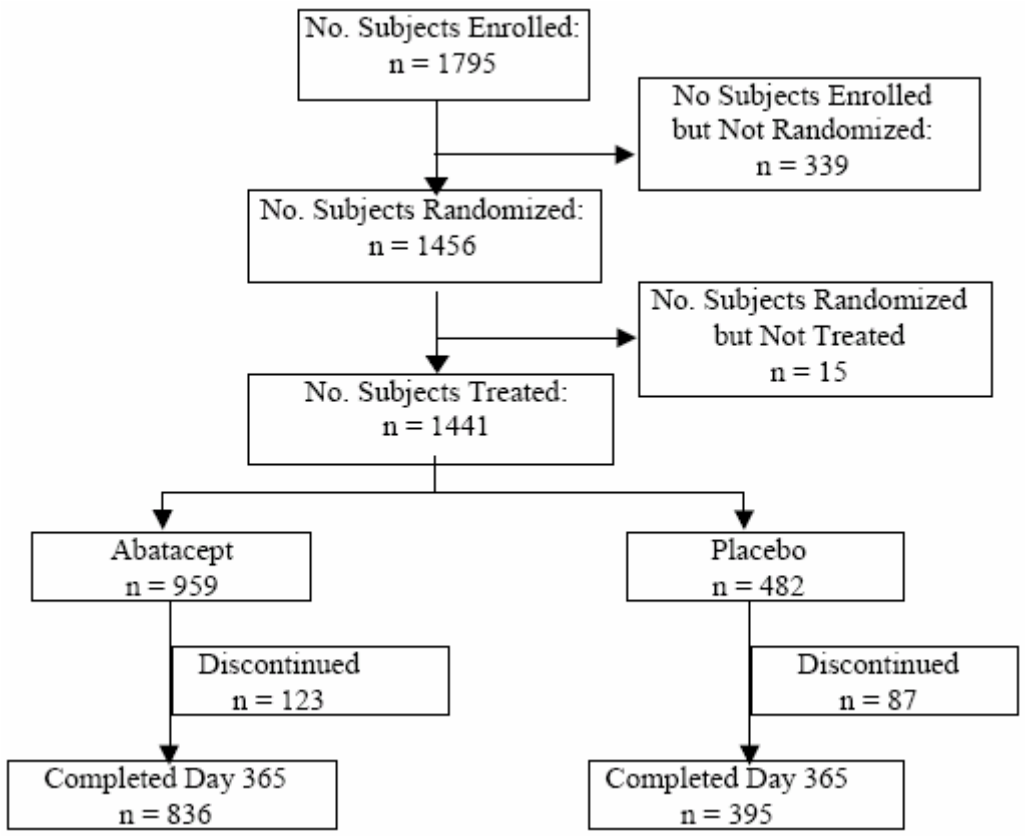
A 3:1 randomization of abatacept to placebo was planned but a 2:1 randomization schedule was inadvertently used. This was discovered after the database was locked and treatment group assignment was unblinded. Despite this error the number of subjects treated with abatacept approximated the intended number with adequate power to detect an AE occurring at a rate of 0.2%.

The primary endpoint of IM101031 was to demonstrate and characterize the safety profile of abatacept in subjects representative of patients in a RA clinical practice. All subjects receiving ≥1 study treatment infusion were included in the analysis. No formal statistical tests were planned to compare AE incidence rates between treatment arms.

4.5.2 Study Conduct of IM101031

A total of 1795 subjects were enrolled and 1441 subjects were randomized. The most frequent reason for not being randomized was subjects' failing to meet study criteria. Of the 1441 subjects randomized, 959 were randomized to abatacept and 482 to placebo (Figure 7).

Figure 7. Subject Disposition for Study IM101031



During the double-blind period of Days 1-365, 17 subjects had protocol violations that could potentially be clinically important. These violations were unlikely to affect the conclusions of the study and were included in all analyses.

subjects but was found to have poor clinical and documentation practices and the site was subsequently closed. BMS excluded this site's data from all analyses of efficacy but included the data in all analyses of safety.

Subject disposition for the study showed that a higher proportion of subjects in the abatacept treatment arm (87%) completed 365 days of treatment compared to the treatment arm (82%). Adverse events (5%) and lack of efficacy (3%) were the most common reasons for discontinuation in the abatacept arm, while lack of efficacy (9%) and AEs (4%) were the most common reason for the discontinuation in the placebo treatment arm (Table 50). The lower proportion of placebo-treated subjects completing 365 days of treatment is attributable to a higher rate of discontinuation due to lack of efficacy (9% vs. 3%).

Table 50. Day 1-365: Reasons for Discontinuation

	Abatacept (n=959)	**Placebo (n=482)**
Number Discontinued	123 (13%)	87 (18%)
Death	5 (0.5%)	3 (0.6%)
Adverse Events	51 (5%)	19 (4%)
Loss of Efficacy	26 (3%)	44 (9%)
Lost to Follow-Up	3 (<1%)	4 (1%)
Withdraw of Consent	24 (3%)	10 (2%)
Other	14 (2%)	7 (2%)
Completed 365 days	836 (87%)	395 (82%)

A total of 856 of 959 subjects (89%) assigned to the abatacept arm were receiving concomitant non-biologic RA therapy and 103/959 (11%) subjects were receiving concomitant biologic RA therapy. Similar proportions of subjects were receiving concomitant non-biologic RA therapy (418/482; 87%) and biologic RA therapy (64/482; 13%) in the placebo arm as compared to the abatacept arm.

Discontinuation rates for abatacept- (12%) and placebo-treated (16%) subjects who were receiving non-biologic RA therapy were similar to those for the overall population, which is expected since >85% of the overall safety study population was receiving background non-biologic RA therapy (Table 51). Discontinuation rates for abatacept (20%) and placebo-treated (31%) subjects receiving concomitant biologic RA therapy was higher overall compared to subjects receiving background non-biologic RA therapies (Table 51). Adverse events (9%) and lack of efficacy (8%) were the most common reasons for discontinuation in the abatacept arm, while lack of efficacy (22%) was the most common reason for the discontinuation in the placebo treatment arm.

Table 51. Reasons for Discontinuation: Concomitant Non-Biologic- vs. Biologic RA Therapy

	Concomitant Non-Biologic RA Therapy		Concomitant Biologic RA Therapy	
	All Abatacept (n=856)	All Placebo (n=418)	All Abatacept (n=103)	All Placebo (n=64)
Number Discontinued	102 (12%)	67 (16%)	21 (20%)	20 (31%)
Death	5 (0.5%)	3 (0.6%)	0	0
Adverse Events	42 (5%)	17 (4%)	9 (9%)	2 (3%)
Loss of Efficacy	18 (2%)	30 (7%)	8 (8%)	14 (22%)
Lost to Follow-Up	3 (<1%)	4 (1%)	0 (<1%)	0 (1%)
Withdraw of Consent	21 (3%)	8 (2%)	3 (3%)	2 (3%)
Other	13 (2%)	5 (1%)	1 (1%)	2 (3%)
Completed 365 days	754 (88%)	351 (84%)	82 (80%)	44 (69%)

A higher rate of discontinuation among abatacept-treated subjects receiving concomitant biologic RA therapy was observed compared to those receiving non-biologic therapies (20% vs. 12%). This difference was attributable to a higher rate of discontinuation due to AEs (9% vs. 5%) and lack of efficacy (8% vs. 2%).

4.5.3 Study Demographics for IM101031

The baseline characteristics were generally similar across both treatment arms of the study and are shown in Table 52. The majority of subjects were white and female, with a mean age of ~52 years, and a mean weight of 72 kg.

Table 52. Baseline Demographic Characteristics

	All Abatacept (n=959)	All Placebo (n=482)
Age (years, mean ± SD)	52 ± 12	52 ± 12
Weight (kg, mean ± SD)	71 ± 19	73 ±20
Gender (female)	789 (82%)	398 (83%)
Race		
White	818 (85%)	407 (84%)
Black	49 (5%)	29 (6%)
Asian	76 (8%)	41 (9%)
Other	16 (2%)	5 (1%)

The baseline disease characteristics of the study subjects are shown in Table 53 and demonstrate that subjects had active RA. The mean duration of RA was approximately 10 years. The study arms were balanced with respect to baseline disease characteristics.

Table 53. Baseline Disease Characteristics

	All Abatacept (n=959)	All Placebo (482)
Duration of RA (years, mean ± SD)	10 ± 10	10 ± 9
Subject Pain Assessment (VAS 100mm)	61 ± 20	61 ± 21
Physical Function (HAQ)	1.5	1.5
Subject Global Assessment (VAS 100mm)	61 ± 20	61 ± 20
Physician Global Assessment (VAS 100mm)	58 ± 17	58 ± 18
CRP	1.8	2.0

The use of non-biologic and biologic RA therapies at randomization was comparable between treatment groups as shown in Table 54. At the time of randomization 97% of abatacept- and placebo-treated subjects were on DMARDs with approximately 75% of subjects receiving MTX. Approximately 10% of subjects in both treatment arms were receiving a biologic RA therapy with the majority of those subjects receiving TNF blockers. Similar proportions of subjects in both treatment arms were on daily oral corticosteroids and NSAIDs.

Table 54. Medication Use at Randomization

Anti-Rheumatic Medications	All Abatacept (n=959)	All Placebo (n=482)
DMARDs	932 (97%)	468 (97%)
MTX	754 (78%)	362 (75%)
Hydroxychloroquine/Chloroquine	195 (20%)	121 (25%)
Leflunomide	111 (12%)	63 (13%)
Sulfasalazine	130 (14%)	64 (13%)
Gold	24 (3%)	10 (2%)
Azathioprine	23 (2%)	18 (4%)
Cyclosporine	0	1 (<1%)
Biologics	92 (10%)	45 (9%)
TNF blocker Therapy	79 (8%)	38 (8%)
Etanercept	57 (6%)	31 (6%)
Infliximab	17 (2%)	3 (<1%)
Adalimumab	5 (<1%)	4 (<1%)
Anakinra	13 (1%)	7 (2%)
Corticosteroids	604 (63%)	298 (62%)
NSAIDs	743 (78%)	384 (80%)

Table 67 shows that the majority of subjects in both treatment arms were only on 1 RA therapeutic drug at randomization and approximately 25% were on 2 RA therapies.

Table 55. Subject's Use of RA Therapies at Randomization

Number of Anti-Rheumatic Medications	All Abatacept (n=959)	All Placebo (n=482)
0	0	0
1	662 (69%)	312 (65%)
2	234 (24%)	141 (29%)
3	55 (6%)	25 (5%)
4+	7 (1%)	4 (1%)

4.5.4 Analysis of Efficacy Endpoints

There were 4 exploratory efficacy measures. Subject's pain assessment, subject's global assessment of disease activity, and physician global assessment of disease activity were measured using VAS, and physical function as assessed by the HAQ index.

At Day 365, the median percent improvements from baseline in subject's pain assessment, subject global assessment of disease activity, and physician's global assessment of disease activity were higher for abatacept-treated subjects (48%, 47%, and 63%, respectively) compared to placebo-treated subjects (26%, 30%, and 43%, respectively, Table 56). Subjects treated with abatacept achieved a greater improvement in physical function as assessed by HAQ score at Day 365 compared to placebo-treated subjects (29% vs. 14%, respectively).

Table 56. Median Percent Improvement from Baseline in Select ACR Components on Day 365

	All Abatacept (n=948)	**All Placebo (n=477)**
Subject's Pain Assessment (VAS 100mm)		
Baseline Median	61	64
Day 365 Median	29	44
Median % Improvement	48%	26%
Subject's Global Assessment (VAS 100mm)		
Baseline Median	60	61
Day 365 Median	30	42
Median % Improvement	47%	30%
Physician's Global Assessment (VAS 100mm)		
Baseline Median	58	59
Day 365 Median	21	31
Median % Improvement	63%	43%
Physical Function (HAQ Index)		
Baseline Median	1.50	1.50
Day 365 Median	1.00	1.38
Median % Improvement	29%	14%

Median percent improvements at Day 365 in each of the 4 efficacy measures were larger for both treatment-arms in subjects receiving concomitant non-biologic RA therapies compared to

biologic RA therapies; however, within each subgroup the median percent improvement at all time points were higher with abatacept than with placebo.

Table 57 shows the mean change from baseline in HAQ scores during the double-blind period by DMARD used.

Table 57. Mean Change from Baseline in HAQ Scores during Double-Blind Period

	Number of Subjects (%; n of subgroup)			
Background RA Therapy	**Abatacept**	**95% CI**	**Placebo**	**95% CI**
Total in Biologic Subgroup	-0.33 (n=103)	-0.44,-0.21	-0.23 (n=64)	-0.38,-0.07
Etanercept	-0.34 (n=66)	-0.49,-0.19	-0.22 (n=42)	-0.30,-0.08
Infliximab	-0.12 (n=34)	-0.40,-0.15	-0.56 (n=9)	-1.58,0.58
Adalimumab	-0.14(n=11)	-0.55,-0.27	-0.20 (n=10)	-0.48,-0.09
Anakinra	-0.40 (n=13)	0.70,-0.09	-0.59 (n=10)	-1.06,-0.13
Total in Non-Biologic Subgroup	-0.47 (n=856)	-0.52,-0.43	-0.26 (n=418)	-0.32,-0.20
MTX	-0.49 (n=691)	-0.54,-0.44	-0.26 (n=336)	-0.33,-0.19
Hydroxychloroquine/ Chloroquine	-0.47 (n=194)	-0.56,-0.38	-0.36 (n=123)	-0.46,-0.25
Sulfasalazine	-0.46 (n=137)	-0.56,-0.36	-0.24 (n=72)	-0.39,-0.10
Leflunomide	-0.39 (n=106)	-0.50,-0.28	-0.21 (n=59)	-0.42,-0.00
1 DMARD	-0.48 (n=598)	-0.53,-0.43	-0.24 (n=257)	-0.32,-0.16
2 DMARDs	-0.46 (n=202)	-0.55,-0.37	-0.29 (n=123)	-0.42,-0.17
3 DMARDs	-0.49 (n=45)	-0.65,-0.33	-0.20 (n=31)	-0.39,-0.01
4 DMARDs	-0.55 (n=10)	-0.89,-0.21	-0.75 (n=6)	-1.68,0.18

4.6 Study IM103002

4.6.1 Study Design of IM103002

Study IM103002 was a 6-month, multicenter, randomized, double-blind, placebo-controlled, parallel dosing, Phase-2 study evaluating 3 different doses of abatacept monotherapy (0.5 mg/kg, 2 mg/kg, and 10 mg/kg) compared with placebo in subjects with active rheumatoid arthritis. The study randomized 122 subjects at 57 study centers in Europe, Canada, and the US.

All subjects were required to meet the following key inclusion/exclusion criteria:

- Diagnosis of RA (1987 ACR criteria) ≤7 years
- RA functional classes I, II, or III
- Failed ≥1 DMARD, including etanercept
- Active disease despite current DMARD therapy
    - MTX Monotherapy
        - ≥10 swollen joints
        - ≥12 tender joints
        - ESR ≥ 28 mm/h
        - Morning stiffness ≥45 minutes

Subjects were randomized to 1 of 4 treatment arms with study drug administered by IV infusion at Day 1, 15, 29 and 57.

The primary endpoint was set at 85 days and subjects followed for safety, immunogenicity, and disease flares through Day 169.

All subjects who received ≥1 dose of study drug was included in the safety and efficacy analyses. Frequency distributions of ACR 20, ACR 50, and ACR 70 at Day 85 were determined for each group with the differences in response rates between active treatment groups and placebo being computed together with 95% confidence intervals. Descriptive statistics were determined for clinical variables at baseline and Day 85. The mean percent improvement (or change) from baseline, and differences in responses for active treatment relative to placebo were computed with 95% confidence intervals. Similar calculations were performed for the "modified" ACR responses and clinical variables for Day 85 and other study days. Subject assessment of function was only measured on Days 1, 85, and 169, so ACR determinations made on other days were considered modified. Safety assessments, including AEs and laboratory measures, were summarized.

4.6.2 Study Conduct of IM103002

A total of 122 subjects were randomized to receive abatacept or placebo. The 122 subjects were randomized as follows:

- Abatacept (90 subjects)
  - 0.5 mg/kg: 26 subjects
  - 2 mg/kg: 32 subjects
  - 10 mg/kg: 32 subjects
  -
- Placebo (32 subjects)

Study drug was administered by intravenous infusion on Days 1, 15, 29, and 57. The number of missed infusions was distributed evenly among the 3 arms.

Table 58 shows the reasons for subject discontinuations during the active treatment phase. More subjects in the placebo group (38%) discontinued compared to subjects in the abatacept group (22%). Loss of efficacy, noted as worsening RA, was the most common reason for discontinuation in both treatment arms but to the greatest degree in the placebo arm (10%).

Table 58. Subject Discontinuations During the Active Treatment Phase

	Placebo	Abatacept		
	(n=32)	0.5 mg/kg (n=26)	2 mg/kg (n=32)	10 mg/kg (n=32)
Total Discontinued	12	8	8	4
Death	0	0	0	0
Adverse Events	0	2	2	0
Loss of Efficacy	10	5	4	3
Lost to Follow-Up	1	0	0	1
Withdrawal of Consent	1	1	0	0
Other	0	0	2	0

As noted in the study design section, concomitant RA therapies (e.g., DMARDS, biologic RA therapies) were prohibited during the active treatment phase of the study; however, subjects were allowed to continue to receive stable doses of NSAIDs and corticosteroids. Overall, approximately 80% of subjects in each group received NSAIDs and approximately 65% of subjects in each group received corticosteroids.

4.6.3 Study Demographics for IM103002

The baseline characteristics were generally similar across all treatment arms of the study and are shown in Table 59. The majority of subjects were white and female, with a mean age of ~48 years, and a mean weight of 71 kg.

Table 59. Baseline Demographics

	Placebo	Abatacept		
	(n=32)	0.5 mg/kg (n=26)	2 mg/kg (n=32)	10 mg/kg (n=32)
Age (years, mean ± SD)	48 ± 12	47 ± 12	46 ± 13	52 ± 12
Weight (kg, mean)	73	71	73	70
Gender (female %)	81%	85%	72%	69%
Race (%)				
White	94%	88%	94%	94%
Black	6%	0	0	3%
Other	0%	12%	6%	3%

The baseline disease characteristics of the study subjects are shown in Table 60.
Subjects had active RA at baseline as demonstrated by the number of swollen joints (~22) and tender joints (~30), elevated level of CRP (~4 mg/dL), and prolonged morning stiffness (~153 minutes). The mean duration of RA was approximately 3.5 years. Treatment arms were balanced.

Table 60. Baseline Disease Characteristics

	Placebo	Abatacept		
	(n=32)	0.5 mg/kg (n=26)	2 mg/kg (n=32)	10 mg/kg (n=32)
Duration of RA (years, mean ± SD)	3.2 ± 2.0	4.2 ± 2.0	3.3 ± 1.7	3.4 ± 2.1
Swollen joints (mean ± SD)	24 ± 10	19 ± 6	27 ± 11	23 ± 13
Tender joints (mean ± SD)	32 ± 15	32 ± 15	32 ± 15	29 ± 15
Morning Stiffness (min)	157	212	145	150
CRP (mg/dL)	5.7	2.6	4.8	3.4

4.6.4 Analysis of Primary Endpoint

4.6.4.1 Improvement of Signs and Symptoms

The primary endpoint was the proportion of subjects achieving an ACR 20 at Day 85. As shown in Table 61, 31% of placebo-treated subjects achieved an ACR 20. Except for the abatacept 0.5 mg/kg group, a greater proportion of subjects achieved an ACR 20 response in each active treatment group. There was a dose-response relationship evident.

Table 61. ACR 20 Response on Day 85

	Placebo	Abatacept		
	(n=32)	0.5 mg/kg (n=26)	2 mg/kg (n=32)	10 mg/kg (n=32)
ACR 20 Responders N (%)	10 (31%)	6 (23%)	14 (44%)	17 (53%)
95% CI	NA	-31, 15	-11, 26	-2, 46

4.6.5 Analysis of Secondary Endpoints

4.6.5.1 Improvement of Signs and Symptoms

The proportions of subjects achieving a modified ACR 50 and ACR 70 response at Day 85 are shown in Table 62. Except for abatacept 0.5 mg/kg, the proportions of subjects achieving an ACR 50 and ACR 70 responses were higher in the active treatment groups than in placebo.

Table 62. ACR 50 and ACR 70 Responders at Day 85

	Placebo	Abatacept		
	(n=32)	0.5 mg/kg (n=26)	2 mg/kg (n=32)	10 mg/kg (n=32)
ACR 50 Responders N (%)	2 (6%)	0	6 (19%)	5 (16%)
95% CI	NA	-15, 2	-3, 28	-6, 25
ACR 70 Responders N (%)	0	0	4 (13%)	2 (6%)
95% CI	NA	0	1, 24	-2, 15

Each of the individual components of the ACR criteria demonstrated improvement in the active treatment groups suggesting the effects were broad and not due to a subset of individual components (data not shown). Including all treatment groups, abatacept treatment was associated with a reduction in mean morning stiffness, which is not an ACR core criterion, from 153 minutes at baseline to 44 minutes at Day 85.

In an exploratory analysis abatacept showed clinical activity in preventing the incidence of "new" active joints as assessed by new swelling or tenderness in 28 representative joints that are a subgroup of the validated subset of the larger 66/68 joints. Abatacept decreased the incidence of "new" active joints in a dose-dependent manner but the improvement was greatest in the tender joint assessment and to a lesser degree in swollen joints where only the 10 mg/kg dose was able to decrease the number of new swollen joints.

At Day 169, the proportion of subjects who achieved an ACR 20, ACR 50, and ACR 70 were similar to, or less than placebo. The decreased efficacy at Day 169 is most probably due to the final dose of abatacept being administered at Day 57. It should also be noted that anti-abatacept antibodies were not detected at Day 169 or later suggesting that abatacept monotherapy would not be limited by anti-abatacept antibody formation.

4.7 Additional Efficacy Analyses

4.7.1 DAS28 and ≤1 Swollen or Tender Joint

Although it would be expected to be uncommon, the DAS28 definition of remission (DAS28 score ≤2.6) can theoretically still be achieved despite a subject having several swollen or tender joints. An alternative criterion for very low disease activity would be achievement of a DAS28 ≤2.6 and no more than one swollen or tender joint. Consequently, the Agency performed additional analyses for studies IM101102 and IM101029 to determine the proportion of subjects who achieved a DAS28-defined remission and had ≤ 1 tender or swollen joint.

At Day 169 in study IM101102, a total of 35 abatacept-treated subjects achieved a DAS28 score ≤2.6 compared to 1 subject receiving placebo (Table 63); however, only 17 of these 35 abatacept-treated subjects had ≤1 tender or swollen joint (compared to the 1 placebo-treated subject). At Day 365, 44 (11%) abatacept-treated subjects achieved a DAS28 score ≤2.6 with ≤1 tender or swollen joint compared to 2 (1%) of placebo-treated subjects (Table 63).

Table 63. Subjects Achieving DAS28 ≤2.6 and ≤1 Swollen or Tender Joints in Study IM101102

	Abatacept	Placebo
N	394	195
Day 169		
Total Subjects with EULAR-defined remission (DAS <2.6)	35 (9%)	1 (<1%)
Total Subjects with EULAR-defined remission (DAS <2.6) AND ≤1 swollen or tender joint	17 (4%)*	1 (<1%)
N	406	202
Day 365		
Total Subjects with EULAR-defined remission (DAS <2.6)	65 (17%)	4 (2%)
Total Subjects with EULAR-defined remission (DAS <2.6) AND ≤1 swollen or tender joint	44 (11%)**	2 (1%)
*p<0.05; **p<0.001		

Similar results were seen in study IM101029 where 10 (5%) abatacept-treated subjects and 0 placebo-treated subjects achieved a DAS28 ≤2.6 with ≤1 swollen or tender joint at month 6 (Table 64).

Table 64. Subjects Achieving DAS28 ≤2.6 and ≤1 Swollen or Tender Joints in Study IM101029

	Abatacept (n=202)	Placebo (n=111)
Baseline Mean	6.9	6.9
Day 169		
Total Subjects with EULAR-defined remission (DAS <2.6)	19 (9%)	1 (1%)
Total Subjects with EULAR-defined remission (DAS <2.6) AND ≤1 swollen or tender joint	10 (5%)*	0
*p<0.05		

In summary, more abatacept-treated subjects achieved a EULAR-defined remission (DAS<2.6) and the more stringent criteria requiring subjects to achieve a DAS28 <2.6 and have ≤1 swollen or tender joint. The clinical utility of these various criteria for categorizing subjects as achieving very low disease activity will be discussed at the Arthritis Advisory Committee meeting.

4.8 Efficacy Conclusions

Analysis of the primary and secondary endpoints provides consistent support for the clinical activity of abatacept. Subgroup and sensitivity analyses further support the clinical benefits of abatacept. Discussion of the evidence for the individual efficacy endpoints appears below.

4.8.1 Reduction of Signs and Symptoms of RA

Studies IM101100, IM101102, and IM101029 provide the principal evidence demonstrating the clinical efficacy of abatacept in subjects with RA on background concomitant non-biologic RA therapy, the vast majority of which was MTX. Each of these studies used the proportion of subjects achieving an ACR 20 response at 6 months as the primary endpoint for evidence of improvement in signs and symptoms. In studies IM101100, IM101102, and IM101029, a statistically significantly greater proportion of abatacept-treated subjects (61%, 68%, and 50%, respectively) achieved an ACR 20 response compared to placebo-treated subjects (35%, 40%, and 20%, respectively). Secondary analyses demonstrated that the improvement in the ACR 20 response was due to improvement in each of the individual ACR response components and that the clinical benefit of abatacept was observed as early Day 15 (i.e., 2-weeks after the first abatacept infusion). Additionally, a greater proportion of abatacept-treated subjects achieved ACR 50 (37% vs. 12%, 40% vs. 17%, and 20% vs. 4%, respectively) and ACR 70 (17% vs. 2%, 20% vs. 7%, and 10% vs. 2%, respectively) responses compared to placebo-treated subjects.

Eight percent of abatacept-treated subjects in Study IM101100 and 14% of abatacept-treated subjects in Study IM101102 achieved a major clinical response, defined as maintenance of an ACR 70 response over a continuous 6-month period, compared to placebo-treated subjects (1% and 2%, respectively).

Study IM103002 evaluated the safety and clinical efficacy of abatacept monotherapy. A greater proportion of subjects receiving abatacept monotherapy (44%, and 53% for the 2 mg/kg and 10 mg/kg arms, respectively) achieved an ACR 20 response at Day 85 compared to placebo-treated subjects (31%). These data support the findings in the larger trials discussed above and also demonstrate efficacy of abatacept monotherapy. The FDA guidance document states that biologic RA therapies should demonstrate efficacy at a 6 month endpoint. A limitation of study IM103002 is that it was 3 months in duration as opposed to 6 months. The results nonetheless suggest efficacy of abatacept monotherapy based on:

- the proportion of subjects achieving an ACR 20 response at the proposed marketing dose of 10 mg/kg (53%) compared to placebo (31%)
- the demonstration of a dose-response
- a greater proportion of abatacept-treated subjects achieving an ACR 50 and ACR 70 compared to placebo
- the lack of formation of anti-abatacept antibodies

Overall, the data presented in the sponsor's submission appear to demonstrate that abatacept therapy can reduce the signs and symptoms of RA in subjects who have failed DMARDs and/or a TNF blocker. Furthermore, the data suggest that abatacept as monotherapy may be clinically

effective as compared to placebo. Study IM101029 was conducted in subjects with persistent RA disease activity despite treatment with a TNF-blocker, and analysis of the trial suggests that abatacept therapy can decrease the signs symptoms of RA in patients who have had an inadequate clinical response to TNF-blocking drugs.

4.8.2 Improvement of Physical Function

The principal evidence demonstrating that abatacept treatment improves physical function in subjects with RA is provided by data from the placebo-controlled periods of Studies IM101100, IM101102, IM101029, and IM101031. For Studies IM101100 and IM101102, a greater proportion of subjects treated with abatacept 10 mg/kg achieved a clinically significant improvement in HAQ score (≥0.3u) from baseline compared to the respective placebo-treated groups at 1 year (38% vs. 20% and 64% vs. 39%, respectively). Similarly, in Study IM101029 a greater proportion of subjects treated with abatacept 10 mg/kg achieved a clinically meaningful improvement in HAQ score (≥0.3u) from baseline compared to placebo-treated subjects (47% vs. 23%). At Day 365 of Study IM101031, subjects treated with abatacept 10 mg/kg demonstrated a greater median improvement in total HAQ score compared to placebo-treated subjects (29% vs. 14%). Open-label data from Study IM101100 demonstrated that for subjects participating in the long-term treatment study the percentage with clinically meaningful improvement in physical function at 1 year was maintained at 2 years in subjects receiving abatacept 10 mg/kg (55% at 1 year; 53% at 2 years).

Overall, the data suggest that abatacept therapy may improve physical function over a 1-year timeframe in patients with RA in subjects who have failed DMARDs and/or a TNF blocker and the effect appears to be maintained at 2 years.

4.8.3 Inhibition of Structural Damage

The principal evidence to support the claim that abatacept inhibits structural damage associated with RA is provided in trial IM101102, which demonstrated a mean increase in erosion score from baseline for abatacept-treated subjects of 0.63u compared to 1.14u for placebo-treated subjects. This represents an approximately 45% reduction in progression of erosions for subjects treated with abatacept.

These data indicate that abatacept slows the rate of progression of structural damage. However, the data also indicate that abatacept prevents less than half the radiographic progression seen in untreated patients, indicating that radiographic progression is slowed but not halted by abatacept.

5. SAFETY ANALYSIS

5.1 Methods and Findings

The safety assessment of abatacept is based primarily on the 2944 subjects enrolled in the 5 core RA studies: IM101100, IM101101, IM101102, IM101029, and IM101031. As outlined in Section 4, these 5 trials were multicenter, randomized, double-blind, placebo-controlled studies. Each of these studies enrolled subjects who were on concomitant background DMARD therapy (non-biologic and biologic therapies) therefore representing the most likely scenario in which abatacept will be used when marketed. Thus, while these studies provide a less clear assessment of the safety of abatacept alone due to concomitant background DMARDs, they provide a more accurate safety assessment of abatacept as it is likely to be used. Study 103002 evaluated abatacept monotherapy (n=90) compared to placebo (n=32) and is reviewed separately providing some limited data on the safety of abatacept administration alone.

During the double-blind, placebo-controlled study periods, 1955 subjects were treated with abatacept representing 1688 person-years of exposure and 989 subjects were treated with placebo representing 795 person-years of exposure. Treatment length during the double-blind period was either 6 months (abatacept n=256 and placebo n=133) or 1 year (abatacept n=1697 and placebo n=856). A total of 2339 subjects who completed the double-blind period enrolled continued into an open-label period.

A total of 2760 subjects were exposed to abatacept in the combined double-blind and open-label periods for all of the Phase II and III RA trials (Table 65). Of these, 2670 subjects were from the 5 core RA studies (IM101100, IM101101, IM10102, IM101029, and IM101031) and 90 subjects from the Phase II study IM103002 (discussed separately). All doses of abatacept were administered in a similar manner to that being proposed for licensure, namely, intravenous infusions at 0, 2 and 4 weeks then every 4 weeks thereafter, with 2638 subjects receiving abatacept at, or approximately at, the dose proposed for licensure (i.e., 10 mg/kg or tiered-dose abatacept that approximates ~10 mg/kg). Approximately 58% of subjects were exposed to 10 mg/kg of abatacept for >12 months.

Table 65. Extent of Exposure to Abatacept in all RA Studies

	Number (%) of Subjects			
Months	Abatacept 0.5 mg/kg (n=26)	Abatacept 2 mg/kg (n=222)	Abatacept 10 mg/kg (n=2638)	All Abatacept (n=2760)
<3	7 (27%)	19 (8%)	460 (17%)	483 (17%)
3-<6	19 (73%)	46 (21%)	310 (12 %)	369 (13%)
6-<12	0	68 (31%)	272 (10%)	286 (10%)
12-<18	0	89 (40%)	1333 (51%)	1340 (49%)
18-<24	0	0	40 (2%)	34 (1%)
24-<36	0	0	157 (6%)	97 (4%)
≥36	0	0	66 (2%)	151 (6%)
Mean (month)	4	9	12	12
Median (month)	4	12	14	14

In the double blind periods of the 5 core RA studies, 1765/1955 subjects received tiered-dose abatacept (~10 mg/kg) for a total exposure of 1527 person-years. Of these, 1751/1955 (90%) subjects were on background non-biologic DMARDs and 204/1955 (10%) subjects were on background biologic RA therapy. In the open-label periods of the 5 core RA studies, 2285 subjects were exposed to the recommended dose of abatacept, resulting in a total exposure of 1094 person-years. Combining data from the double-blind and open-label periods of the 5 core RA studies shows that 2670 subjects were exposed to abatacept for a mean of approximately 13 months, with 2606/2670 subjects (98%) receiving the recommended dose of abatacept for a mean of 12 months representing 2621 person years of exposure.

5.2 Deaths And Serious Adverse Events

5.2.1 Deaths

There were a total of 23 deaths reported during the RA trials evaluating abatacept; 15 subjects died during the double-blind periods (Table 66) and 8 subjects died during the open-label periods (Table 67). Of the 15 deaths that occurred during the double-blind portions of the RA studies: 9 (0.5%) subjects were treated with abatacept and 6 (0.6%) subjects received placebo.

Table 66. Subject Deaths During Double-Blind Periods of RA Studies

Subject Number (age/gender)	Onset Day	Cause of Death
Abatacept (n=1955)		
Subject 1 (67/M)	30	CHF s/p 5-vessel CABG and valve replacement
Subject 2 (58/F)	17	Found Dead at Home. Autopsy: hypertensive heart disease
Subject 3 (56/F)	294	MI undiagnosed in ER Autopsy: ischemic cardiomyopathy
Subject 4 (49/M)	262	Found Dead at Home Autopsy: Grade III CAD, myocardial hypertrophy
Subject 5 (77/F)	101	Found Dead at Home. Cause of death unknown
Subject 6 (49/M)	306	Cardiac Arrest in subject with DM-type I s/p 3rd-degree burns
Subject 7 (61/F)	259	Cardiac Arrest s/p MI and CABG and complicated post-op course
Subject 8 (83/M)	332	Lung CA
Subject 9 (53/M)	346	Bronchopulmonary Aspergillosis
PLACEBO (n=989)		
Subject 10 (60/F)	195	Found Dead at Home Cause of death unknown
Subject 11 (58/F)	376	Myocardial Infarction
Subject 12 (61/F)	321	PCP, HIV
Subject 13 (36/M)	364	CVA
Subject 14 (55/F)	231	Endometrial CA
Subject 15 (77/M)	342	Pneumonia Sepsis

Table 67. Subject Deaths During the Open-Label Periods of RA Studies

Subject Number (age/gender)	Onset Day	Cause of Death
Subject 1 (61/M)	429	Myocardial Infarction Subject with history of 2 angioplasties/stents
Subject 2 (36/M)	365	Aortic Dissection
Subject 3 (78/F)	505	Pancytopenia Sepsis (?)
Subject 4 (70/F)	232	Cholangiocarcinoma
Subject 5 (61/F)	1115	B-cell Lymphoma
Subject 6 (83/M)	538	Lung adenocarcinoma
Subject 7 (65/M)	1051	MTX-induced pulmonary fibrosis & Pulmonary Emboli
Subject 8 (65/M)	649	Cardiopulmonary failure

There was no difference in the rate of deaths between the abatacept and placebo groups during the double-blinded portions of the studies (0.5% versus 0.6%, respectively). Analysis of the individual deaths, including the temporal relationship to abatacept infusion, does not suggest a safety signal from any single type of adverse event. It is interesting to note that 8 of the 17 (47%) deaths occurred in study IM101031 which enrolled subjects similar to those seen in clinical practice and whose enrollment allowed patients with co-morbidities.

5.2.2 Serious Adverse Events

During the double-blind periods a total of 266 of 1955 (14%) abatacept-treated subjects reported a SAE compared with 122 of 989 (12%) of placebo-treated subjects (Table 68). Thus the frequency of SAEs was comparable between the 2 groups. Infections were the only SAE by system organ system class (SOC) that was more frequently reported among subjects treated with abatacept as compared to placebo (3% vs. 2%, respectively). It should be noted that although pneumonia was reported to occur as a SAE in similar frequency between abatacept and placebo groups (0.5%), further analysis demonstrated that pneumonia was reported in greater frequency in abatacept-treated subjects compared to placebo-treated subjects as a whole. The most common SAEs (≥0.5%) by preferred term in the abatacept and placebo groups respectively, were RA (2% in both groups), basal cell carcinoma (0.5% vs. 0.3%) and CHF (0.2% vs. 0.5%). Most other SAEs were reported by 1 or 2 subjects in either treatment group.

Table 68. Most Frequently Reported (>1%) SAE in the Double-Blind Periods

System Organ Class Preferred term	Abatacept (n=1955)	Placebo (n=989)
Total Subjects with Serious Adverse Events	266 (14%)	122 (12%)
Musculoskeletal and Connective Tissue Disorders	59 (3%)	37 (4%)
RA	37 (2%)	19 (2%)
Infections	58 (3%)	19 (2%)
Pneumonia	9 (0.5%)	5 (0.5%)
Sepsis	1 (<0.1%)	3 (0.3%)
Neoplasms (Benign and Malignant)	28 (1%)	11 (1%)
Basal cell carcinoma	9 (0.5%)	3 (0.3%)
Gastrointestinal Disorders	23 (1%)	13 (1%)
Cardiac Disorders	18 (1%)	17 (2%)
CHF	4 (0.2%)	5 (0.5%)
General Disorders & Administration Site Conditions	16 (1%)	9 (1%)
Respiratory, Thoracic and Mediastinal Disorders	16 (1%)	6 (1%)

During the open-label period 6% of subjects reported a SAE with the most common being RA (1%) and basal cell carcinoma (0.3%). RA was the most commonly reported SAE in the open-label periods of the Phase II studies and in the double-blind dataset, where it was reported in similar proportions of abatacept- and placebo treated subjects. The significance of RA reporting as an AE is explained by the fact that during the Phase II studies investigators were instructed to report worsening of RA as an AE, while in Phase III studies investigators were instructed not to report worsening of RA as an AE. The majority of reports of RA were associated with surgical procedures common in the RA population. Serious infections (1%) and neoplasms (benign and malignant; 0.7%) were the most commonly reported SAE during the open-label periods.

These data do not suggest a clinically important difference in overall SAEs between abatacept-treated subjects and placebo-treated subjects. SAEs that were malignancies are examined in further detail in section 7.1.11. SAEs that were infectious in nature are examined in more detail below (section 7.1.2.1).

5.3 Malignancies

Several factors warrant closer analysis of the risk of malignancy with abatacept: immunosuppressant drugs (e.g., azathioprine, MTX, cyclosporine) have been associated with an increased risk of malignancy; patients with RA have an increased risk of lymphoma; and pre-clinical studies in mice demonstrated an increased risk of mammary tumors and lymphoma albeit attributed to abatacept-induced immunosuppression and consequent reactivation of retroviruses.

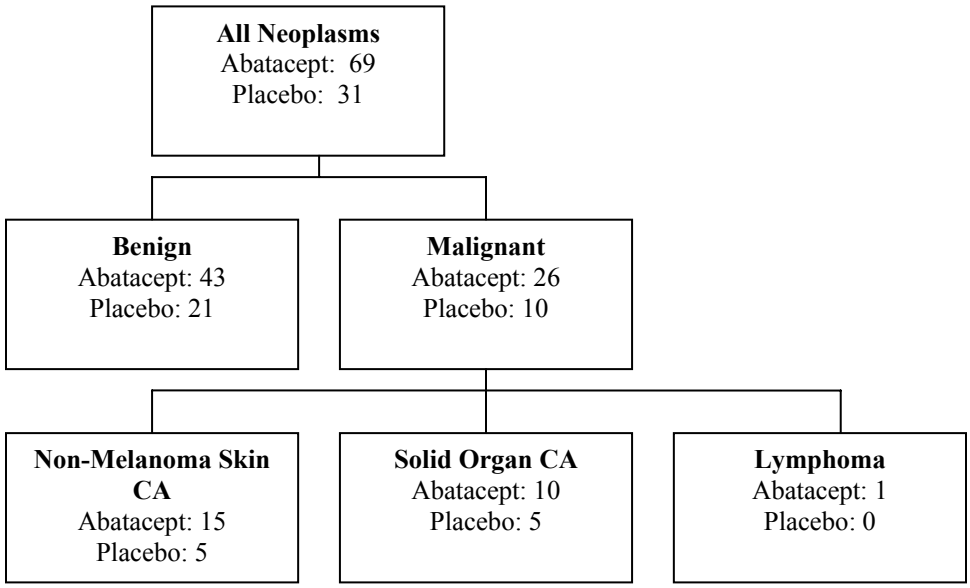
In addition to examining the overall malignancy rates in the abatacept trials, the agency specifically analyzed the rates of lung, breast cancer, and lymphoma in greater detail. Lung cancer was explored because of a higher rate seen in abatacept-treated subjects than in placebo-treated subjects in randomized trials. Breast cancer and lymphomas were explored because of a finding of mammary tumors and lymphoma during preclinical studies of mice treated with abatacept. Subsequent testing of these mice by the sponsor confirmed that the 2 murine retroviruses, MMTV and MLV, respectively, were responsible for these tumors as a result of sustained immunosuppression that occurred at all dose levels of abatacept. Lymphoma rates were explored because of a finding of lymphoma in preclinical study of mice treated with abatacept, the evidence that the rate of lymphoma is increased in RA, and because of concerns that some immunosuppressives may increase the risk of lymphoma (e.g., MTX, azathioprine, and TNF blockers).

In summary, the overall frequency of benign and malignant neoplasms was similar for the abatacept (3%) and placebo (3%) arms during the randomized, double-blind portions of the studies. The overall malignancy (excluding non-melanoma skin cancer) incidence rates during the double-blind periods are similar between the abatacept group (0.59), placebo group (0.63), and the SEER database (0.47) with overlapping 95% confidence intervals. Also, the observed and expected overall malignancies (excluding non-melanoma skin cancer) was similar between the abatacept group (10) and the SEER database (12.66) with overlapping 95% confidence intervals. The incidence rate of malignancies as assessed in 6-month intervals did not demonstrate an increase in the rate of malignancies in either the double-blind or open-label periods of the RA studies with increasing abatacept exposure. Preclinical studies had demonstrated an increased incidence of lymphoma and mammary tumors in a murine model, which was subsequently demonstrated to be secondary to 2 distinct murine retroviruses in the setting of chronic immunosuppresssion. Consequently, lymphoma and breast cancer were identified as possibly occurring at greater frequency than that of a normal population or RA patients not on abatacept; however, the data presented to date have not suggested an increased risk for either lymphoma or breast cancer. Nonetheless, the ability to reach firm conclusions is limited by the modest number of subjects and the relatively short period of drug exposure.

5.3.1 Malignancies During the Double-Blind Periods

During the double-blind, controlled study periods a total of 69 neoplasms occurred in 1955 (3%) subjects treated with abatacept compared to 31 neoplasms that occurred in 989 (3%) placebo-treated subjects (Figure 8). Of the 69 neoplasms that occurred in the abatacept-treated subjects, 43 (62%) were benign. The remaining 26 were malignant and included: 15 non-melanoma skin cancers, 10 solid organ cancers, and 1 case of lymphoma. Of the 31 neoplasms that occurred in the placebo-treated subjects, 21 (68%) were benign. The remaining 10 were malignant and included: 5 non-melanoma skin cancers and 5 solid organ cancers.

Figure 8. Subjects with Malignancies During Double-Blind Portion of RA Studies



Overall there was no difference in the frequency of solid organ malignancies between treatment groups. Of the 9 solid organ cancers observed in abatacept-treated subjects, 4 involved lung cancer: 2 subjects with unknown histology (IM101031-203-10 and IM101100-35-2), 1 subject with non-small cell lung cancer (IM01031-161-5), and 1 subject with squamous cell lung cancer (IM101031-97-25) who also developed a simultaneous renal cell carcinoma. Additionally, there was 1 case each of breast cancer, bladder cancer, ovarian cancer, prostate cancer, thyroid cancer, and lymphoma in subjects treated with abatacept (Table 69). Of note, the lymphoma occurred in a subject with a history of Hashimoto's thyroiditis, a condition associated with a higher risk of lymphoma. The 5 malignancies in the placebo-treated subjects included 2 cases of breast cancer, 2 cases of endometrial cancer, and 1 case of melanoma.

Table 69. Malignancies (excluding non-melanoma skin cancer) in Abatacept-Treated Subjects During the Double-Blind Period

Subject Age/Gender/Race	Abatacept Dose	No. of Infusions	Onset Day	Malignancy
IM101031-203-10 69/F/W	500 mg	3	29	Lung Neoplasm
IM101031-161-5 68/M/W	750 mg	5	100	Non-small cell lung CA
IM1031-97-25 72/F/W	500 mg	13	320	Squamous Cell lung CA Renal Cell CA
IM101100-35-2 83/M/W	10 mg/kg	13	332	Lung Neoplasm
IM101100-61-21 53/M/W	10 mg/kg	8	203	Bladder CA
IM101031-155-3 71/F/W	500 mg	14	349	Breast CA
IM101102-39-9 81/F/W	750 mg	10	241	Lymphoma
IM101100-25-5 63/F/W	2 mg/kg	4	42	Ovarian CA
IM101029-115-7 74/M/W	750 mg	5	97	Prostate CA
IM101029-25-14 52/F/W	750 mg	6	115	Thyroid CA

5.3.2 Malignancies During the Open-Label Period

During the open-label portions of abatacept treatment, there were a total of 45 subjects presenting with 50 neoplasms representing 33 of 2089 or 2% of subjects who were receiving abatacept + MTX and 12 of 196 or 7% of subjects who were receiving abatacept plus an additional biologic RA treatment. Of the 50 neoplasms reported, 25 were benign and 25 were malignant and included: 13 non-melanoma skin cancers, 10 solid organ cancers, and 1 case of lymphoma. The 10 solid organ malignancies consisted of 4 cases of lung cancer, 1 case each of cervical carcinoma, papillary thyroid, rectal, prostate, uterine, and ovarian cancer.

There were 2 malignancies referred to above (a single case each of breast cancer and cervical carcinoma) that are not included in the sponsor's summary statistics since the events occurred outside the pre-specified period of 2 months following discontinuation of study drug but are included in our review of malignancies.

5.3.3 Malignancy Incidence Rates

Malignancy rates with abatacept were scrutinized carefully because cancer is a potential concern with many immunosuppressive agents. Since malignancies are uncommon and randomized clinical trials have limited power to detect differences in incidence rates between treatment

groups (in this case between abatacept and placebo on different background DMARDs), it is particularly important to examine the incidence rate for malignancies in the total safety database, including the long-term, open-label abatacept treatment studies as well as in the randomized controlled studies. However, analysis of the total safety database is hampered by the lack of an internal control. One way to analyze cancer incidence rates in the total safety database is by comparison to expected rates from epidemiologic data. Rates can be compared to those expected in the general population and to expected rates in patients with RA when those data are available. In analyzing cancer incidence rates for TNF blockers, the Agency has derived expected incidence rates from the National Cancer Institute's *S*urveillance, *E*pidemiology, and *E*nd *R*esults (SEER) database, which reflects the general population of people living in the United States. Although the majority of subjects in the abatacept RA trials were not from the US, the primary analysis utilized in this review will compare the sponsor's RA studies with abatacept to the SEER database.

There exists a body of literature demonstrating that patients with RA are at increased risk of certain types of malignancy, especially hematologic malignancies. These increased incidence rates of malignancies are based on RA observational cohorts in North America and Europe with the vast majority of subjects receiving treatment with non-biologic RA therapy. Consequently, these databases may serve as an informative comparison for analyzing malignancy rates in abatacept studies in which the majority of control subjects were on background non-biologic DMARDs. These databases include the British Columbia (BC) RA Registry, the Norfolk Arthritis Registry (NOAR) in the United Kingdom, the National Data Bank for Rheumatic Diseases (NDB) in the US, and PharMetrics Medical and Pharmacy Claims (PharMetrics) in the US.

The BC RA Registry is a population-based longitudinal cohort consisting of RA subjects from the Province of BC that were identified from an administrative database. Data for 27,710 RA subjects were obtained from administrative databases of the Canadian Ministry of Health from January 1990 until December 2002. The registry includes data recorded for physician visits, hospitalizations, and data on all medications prescribed for individuals covered under the provincial medication plan. Additionally, data for medications dispensed to all RA patients covered by any payment mechanism from January 1996 until December 2001 are available. Strengths of this cohort include the involvement of an entire population of RA patients in the context of normal clinical practice that includes all medications prescribed for the RA subjects. Limitations include those inherent to data from administrative databases, e.g., uncertainty involving accuracy of diagnosis, severity of disease, and the limitation that some of the data refers to medications dispensed rather than prescribed or consumed. In an attempt to reduce the limitation regarding accuracy of diagnosis, analysis was conducted based on identifying RA by including only those subjects with 2 visits at least 2 months apart which was validated against self-reporting of a physician's diagnosis of RA, yielding a positive predictive value of 0.92.

The NOAR was designed to ascertain all new cases of early inflammatory polyarthritis (IP) following the first episode attended by physicians in general practices arising within the geographic region of the former Norwich Health Authority. All NOAR cases recruited between 1989 and 1999 were considered for analysis in this report. Strengths of the NOAR database

include that it is a population-based cohort and theoretically aimed to capture all cases of IP as they arose within the general population. Limitations are the ability of the relatively small cohort size (2,153 subjects) to detect rare events and the possibility that some outcomes might have been missed due to hospitalization at a remote hospital not recalled by the subject. An additional limitation includes a proportion of patients who do not meet criteria for RA, thus incidence rates may differ from those in the other cohorts.

The NDB is a longitudinal data bank for the study of the treated natural history of RA, osteoarthritis, fibromyalgia, and other rheumatic diseases consisting of 21,229 subjects. It includes data on medications, adverse events, infections, cancer, co-morbid conditions, disease status, medical costs, work disability, joint replacement, quality of life, and other measures. Self-reported data for key outcomes are validated by medical record review and physician contact. Data on all cases entered into the NDB between 1998 and 2003 were considered for analysis in this report. Limitations of this database include the fact that serious illnesses may lead to hospitalization and death and in a databank that depends on self-reporting to trigger event investigation; it is possible that cases are missed. At the NDB, all non-respondents and/or their physicians are contacted by telephone. Validation studies for events, such stroke or cancer, indicate very few cases, if any, are missed.
Self-reported data require validation for most events. From records for cases that have been validated, it has been determined that overall, reporting is correct in >93% of cases.

The PharMetrics integrated claims database includes information from fully adjudicated pharmacy, provider, and facility claims for members enrolled in nearly 70 health plans across the United States. A total of 132,883 subjects in the PharMetrics database are representative of the national, commercially insured population for a variety of demographic measures, including geographic region, age, gender, and health plan type. Entries to the database are subjected to a series of rigorous data quality checks to ensure minimal error rates. Data on all RA cases in the PharMetrics database between 1995 and 2002 were considered for analysis in this report. Strengths of the PharMetric database include: the database is a large, nationally representative sample of people in managed care plans with RA; the large number of RA patients allows for the examination of rare outcomes; and the database is comprehensive because it links physician, hospital, drug, and other medical care data. The database has several limitations: the data originated from a claims database, which is not designed primarily for research; limited clinical detail, lack of data on over-the-counter medications, potential omissions of services provided, little or no data on compliance, and lack of lifetime medical history. In general, high sensitivity but poor specificity for many diagnoses has been reported when comparing claims databases with clinical records. The quality and consistency of coding in PharMetrics is not verifiable, and there will inevitably be some misclassification of patients, infections, or medication exposure. Since many subjects will have had RA at the time of entry into the insurance plan, it is difficult to assign the true duration of RA in this data source.

Compared to these databases, the subject population of the abatacept RA studies had a larger proportion of females compared with the RA observational studies (79% compared with 60%-73%), and a proportion of subjects ≤65 years of age on the lower end of the observational studies (14% compared to 7%-40%). Analyses were performed comparing the rate of malignancies in the abatacept studies with that in the RA observational studies.

As shown in **Error! Reference source not found.**, the point estimate of the crude malignancy incidence rate in abatacept-treated subjects (1.4/100 person-years) during the double-blind period was similar to that in placebo-treated subjects (1.3/100 person-years). Although there is no respective comparison available in the SEER database, these incidence rates are lower than those seen in the RA observational studies. Similarly, the crude incidence rates for all malignancies, excluding non-melanoma skin cancer, were similar in the abatacept-treated subjects (0.6/100 person-years) and placebo-treated subjects (0.6/100 person-years), and higher but comparable to the incidence rates in the SEER database (0.5/100 person-years), and lower than the incidence rates from the RA observational studies (0.9-2.6/100 person-years). Specific incidence rates for breast cancer and lymphomas for abatacept-treated subjects were comparable to the SEER database and lower than the RA observational cohorts. The incidence rate for lung cancer in subjects receiving abatacept was 0.2/100 person-years compared with the incidence rate of the SEER database of 0.06/ person-years, more than 3-fold higher; however, the 95% confidence intervals for the abatacept incidence rates overlap those of the SEER database, and are comparable to the RA observational cohorts (**Error! Reference source not found.**).

Table 70. Crude Malignancy Incidence Rates in the Double-Blind Periods of RA Trials

	Malignancy Rate/100 person-years (95% CI)						
	RA Blinded Trials		RA Observational Cohorts				SEER
	Abatacept (n=1955)	Placebo (n=989)	BC (n=12337)	NOAR (n=998)	NDB (n=10499)	PharmM (n=52444)	
Overall malignancies	1.43 (0.92-2.13)	1.26 (0.61-2.32)	3.23 (3.08-3.39)	1.11 NA	3.37 (3.19-3.56)	3.58 (3.31-3.85)	NA
Overall malignancies (excluding non-melanoma skin cancer)	0.59 (0.28-1.09)	0.63 (0.20-1.47)	2.321 (2.19-2.44)	0.87 NA	NA	2.60 (2.38-2.83)	0.47
Breast	0.06 (0-0.33)	0.25 (0.03-0.91)	0.35 (0.30-0.40)	0.11 NA	0.36 (0.30-0.42)	0.57 (0.47-0.68)	0.14
Lung	0.24 (0.06-0.61)	0 (0-0.46)	0.37 (0.32-0.42)	0.14 NA	0.15 (0.12-0.19)	0.28 (0.21-0.36)	0.06
Lymphoma	0.06 (0-0.33)	0 (0-0.46)	0.16 (0.13-0.19)	0.10 NA	0.13 (0.09-0.18)	0.256 (0.19-0.33)	0.02

Table 71 illustrates the observed and expected malignancies in abatacept-treated subjects, controlling for differences in age and sex, for overall malignancies, overall malignancies excluding non-melanoma skin cancer, and the specific malignancies of breast, lung, and lymphoma. The number of overall malignancies excluding non-melanoma skin cancer and breast cancer in the abatacept group during the double-blind studies was lower than that expected based on the SEER database. There were a higher number of lung cancers (4) in the abatacept group than expected based on the SEER database (1.8), but the 95% confidence intervals were overlapping. The number of lymphomas (1) was similar to the expected number (0.5). Overall malignancies, overall malignancies excluding non-melanoma skin cancer, and the specific malignancies of breast cancer and lymphoma were all lower in subjects treated with abatacept during the RA trials compared with the RA observational cohorts. There were a comparable number of lung cancers between the abatacept-treated group and the RA observation cohorts. The observed number of overall malignancies, overall malignancies excluding non-melanoma skin cancer, and the specific malignancies of breast, lung, and lymphoma in the placebo group was lower than or comparable to the expected range of the SEER and RA observational cohorts.

Table 71. Observed and Expected Malignancies in Abatacept Subjects in the Double-Blind Periods of RA Trials

	N (95% CI)					
	Trial Observed Events	**RA Observational Cohorts**				**SEER**
	Abatacept (n=1955)	BC (n=12337)	NOAR (n=998)	NDB (n=10499)	PharMetrics (n=52444)	
Overall malignancy	24 (15.4-35.7)	41.6 (35.5-49.3)	NA	43.4 (35.8-54.5)	70 (55.4-89.8)	NA
Overall malignancy (excluding non-melanoma skin cancer)	10 (4.8-18.4)	30.2 (25.1-36.8)	13.1 (6.6-28.9)	NA	50.2 (38.3-66.9)	12.66 (12.6-12.7)
Breast	1 (0-0-5.6)	5.8 (3.8-7.8)	3.75 (1.2-12.6)	4.71 (3.1-7.6)	10.86 (7.2-17.7)	3.42 (3.4-3.5)
Lung	4 (1.1-10.2)	4.4 (2.8-7.1)	2.07 (0.46-9.9)	1.57 (0.8-3.6)	5.6 (2.6-12.8)	1.77 (1.7-1.8)
Lymphoma	1 (0-0.)	1.05 (0.4-2.9)	1.29 (0.27-7.2)	1.37 (0.5-4.2)	4.52 (2.18-10.2)	0.47 (0.46-0.48)

Observed incidence rates by 6-month intervals of exposure for the abatacept- and placebo-treated subjects during the double-blind periods are shown in
Table 72.

Table 72. Incidence Rates of Malignancies in the Double-Blind Periods in 6-Month Intervals

	N (rate/100 person-years)			
	Days 1-180		Days181-360	
	Abatacept (n=1955)	Placebo (n=989)	Abatacept (n=1955)	Placebo (n=989)
Overall malignancy	13 (1.41)	6 (1.34)	11 (0.72)	4 (0.57)
Overall malignancy (excluding non-melanoma skin cancer)	5 (0.54)	1 (0.22)	5 (0.32)	4 (0.57)
Breast	0	0	1 (0.07)	2 (0.29)
Lung	2 (0.22)	0	2 (0.13)	0
Lymphoma	0	0	1 (0.07)	0

These data demonstrate that abatacept- and placebo-treated subjects have similar incidence rates of overall malignancy and overall malignancy excluding skin cancers in the double-blind period, and that the rates are lower during the second 6-month interval for both groups. Observed incidence rates by 6-month intervals of exposure for the abatacept- and placebo-treated subject including the open-label period are shown in Table 73.

Table 73. Incidence Rates of Malignancies Through the Open-Label Periods of the RA Trials

	N (rate/100 person-years)					
	Days 1-180	Days181-160	Days 361-540	Days 541-720	Days 721-900	Days 901-1080
Overall malignancy	7 (0.34)	2 (0.33)	3 (0.54)	2 (0.33)	1 (0.16)	0
Overall malignancy (excluding non-melanoma skin cancer)	3 (0.15)	0	2 (0.36)	1 (0.16)	1 (0.16)	1 (0.16)
Breast	0	0	0	0	0	0
Lung	2 (0.10)	0	0	0	0	0
Lymphoma	0	0	0	0	0	1 (0.16)

Incidence rates of overall malignancies and overall malignancy excluding skin cancers were lower in each consecutive 6-month interval suggesting that there was not an increased incidence of malignancies with cumulative increases of drug exposure.

5.3.4 Lung Cancers

There were a total of 8 lung cancers reported in abatacept-treated subjects and none in placebo-treated subjects; with 4 cases occurring in the double-blind periods and 4 cases during the open-label periods of the clinical studies.

During the double-blind period, 3 of the 4 cases of lung cancer had a medical history significant for smoking, a well-known risk factor for lung cancer. There were 2 males and 2 females affected whose ages ranged from 68 to 83 years of age. Malignancy was present in 1 of the cases prior to treatment with abatacept as determined by a retrospective review of the subject's pre-treatment chest X-ray that revealed a small lesion in the left pulmonary apex, and was originally read as small calcifications in the left pulmonary apex, which were considered abnormal but not of a nature requiring further work-up. Given the results of the baseline chest X-ray it would appear that the subject had pre-existent lung cancer prior to study enrollment. Additionally, this same subject was found to have a left renal mass that was believed to be a simultaneously occurring primary renal cell carcinoma. It is difficult to ascertain what role, if any, abatacept may have played in the simultaneous occurrence of the renal cell carcinoma.

During the open-label period, all 4 cases of lung cancer had a medical history significant for smoking. There was 1 male and 3 females affected whose ages ranged from 61 to 71 years of age. A retrospective review of the pre-treatment chest X-ray of 1 subject revealed an apical dorsal consolidation of the left superior lobe of the lung measuring 5.2 x 2.6 cm, suggesting that the lung cancer was pre-existent prior to study enrollment .

As discussed above, the incidence rate for lung cancer in abatacept-treated subjects was more than 3-fold higher than that expected based on the SEER database but was still within the 95% confidence interval. Overall, the reported tobacco use was similar in the abatacept (females: 20%; males: 43%) and placebo (females: 16%; males: 44%) arms. The observed number of lung cancers among known tobacco users treated with abatacept was 7/633 (1%), and an incidence ratio of 0.75/100 person-years (Table 74).

Table 74. Incidence Rates of Lung Cancer in Abatacept-Treated Subjects

	Lung Cancer Cases	Abatacept Exposure (person-years)	IR/100 person-years	95% CI
All Abatacept	8	3826	0.21	(0.09, 0.41)
Abatacept Smokers	7	933	0.75	(0.3, 1.55)
Females	4	576	0.69	(0.19, 1.78)
Males	3	358	0.84	(0.17, 2.45)
Abatacept non-smokers	1	2839	0.03	(0.00, 0.19)

Bain et al. recently published an incident rate of lung cancer in the US population of smokers as 0.253 events/100 person-years for females and 0.232 events/100 person-years for males.[1] Flanders et al. reported a mortality rate of 0.139/100 person-years for female-and 0.297 for male-smokers in the US population[3]. The use of mortality rates for lung cancer in smokers instead of incidence rates can serve as a surrogate since annual mortality rates can approximate the incidence rates of lung cancer diagnosis due to the poor prognosis of subjects with lung cancer after diagnosis. Thus, the rate of lung cancer in smokers treated with abatacept (0.75 events/100

1 Bain C, Feskanich D, Speizer FE, Thun M, Hertzmark E, Rosner BA, Colditz GA. Lung cancer rates in men and women with comparable histories of smoking. J Natl Cancer Inst. 96(11):826-34, 2004.

person-years) was higher that the rate of lung cancer reported for smokers in the general US population.

Since several studies have reported a higher incidence of lung cancer in RA patients compared to the general population,[2,3,4] it would be useful to compare the incidence rate of lung cancers in smokers treated with abatacept to a population of RA subjects who smoked. Unfortunately the reference RA databases discussed above are not stratified by tobacco use and the comparison cannot be performed. However, using the whole patient population (i.e., smokers and non-smokers) of the above RA cohorts and combining the observed versus expected lung malignancies for both the double-blind and open-label periods allows us to further compare the entire abatacept population to a comparable RA cohort (Table 75). These analyses demonstrate the expected number of lung cancers in the abatacept group would range from 3.6 to 10 (data not shown).

Table 75. Observed and Expected Malignancies in Cumulative Double-Blind and Open-Label Period of Abatacept RA Trials

	Observed Events (95% CI)	**Trial Expected Number of Events (95% CIs) Age and Sex Adjusted Based on Specific RA Cohorts**		
	All Abatacept	BC	NDB	NOAR
Lung Cancer	8 (3.45, 15.76)	9.95 (6.5, 16.3)	3.58 (1.8, 8.3)	4.76 (1.1, 22.8)

While the raw data necessitates increased vigilance and further monitoring for subjects receiving abatacept, there are mitigating factors that need to be taken into account to place these data in the proper perspective.

- The overall rate of malignancy was not increased with abatacept. Looking at many individual types of cancer increases the likelihood that one type will be increased by chance alone.

2 Thomas E, Symmons DP, Brewster DH, Black RJ, Macfarlane GJ. National study of cause-specific mortality in rheumatoid arthritis, juvenile chronic arthritis, and other rheumatic conditions: a 20 year follow-up study. J Rheumatol. 30(5):958-965, 2003.

3 P Geborek, A Bladström, C Turesson, A Gulfe, I F Petersson, T Saxne, H Olsson and L T H Jacobsson. Tumour necrosis factor blockers do not increase overall tumour risk in patients with rheumatoid arthritis, but may be associated with an increased risk of lymphomas. *Ann. Rheum. Dis.* 64:699-703,2005.

4 Askling J, Fored M, Brandt L, Baecklund E, Bertilsson L, Feltelius N, Coster L, Geborek P, Jacobsson L, Lindblad S, Lysholm J, Rantapaa-Dahlqvist S, Saxne T, Klareskog L. Risks of solid cancers in patients with rheumatoid arthritis and following treatment with tnf-antagonists. Ann Rheum Dis. Apr 13, 2005 [Epub ahead of print]

- The frequency of any individual tumor type should be interpreted with caution given the low event rate, and as an increased risk of lung cancer has been observed in patients with RA (see above).
- 2 of the 8 cases (and perhaps a third case) of lung cancer were retrospectively seen on baseline chest X-rays prior to subjects receiving abatacept.
- The comparison SEER database is comprised of subjects from the US. Of the 8 subjects with lung cancer, 4 subjects were from the US, 1 subject from Argentina, 1 subject from Brazil, 1 subject from Belgium, and 1 subject from Hungary.
- The incidence rate of lung cancer in the abatacept group adjusted for exposure is approximately 0.2 events/100 person-years, which is within the range expected based on epidemiologic analysis of the RA observational cohorts discussed above.
- The observed number of lung cancers in the abatacept-treated subjects for the combined double-blind and open-label period was within the expected range of lung cancers based on the reference RA cohorts

5.3.5 Breast Cancers

As noted above, during preclinical testing an increased incidence of lymphomas and mammary tumors was identified in the mouse carcinogenicity study. Subsequent testing of these mice by the sponsor confirmed that the 2 murine retroviruses MLV and MMTV, respectively, were responsible for these tumors as a result of sustained immunosuppression that occurred at all dose levels of abatacept. There was no evidence of lymphomas, solid organ tumors, or pre-neoplastic morphologic changes observed during long-term studies in primates despite immunosuppressive doses up to 1 year in monkeys known to be infected with a number of viruses including LCV, a virus associated with B-cell lymphomas in immunosuppressed primates. Nonetheless, because of the preclinical data in mice, female subjects enrolled into clinical trials with abatacept received mammograms at baseline and at 1 year.

During the double-blind period there was 1/1955 abatacept-treated subjects (<0.1%) reported to have breast cancer compared with 2/989 placebo-treated subjects (0.2%). Although there were no cases of breast cancer reported during the open-label portion of the studies there was 1 additional case noted above that occurred 4 months after discontinuation of abatacept.

It is difficult to attribute this case of breast carcinoma solely to abatacept as the subject had received 7 doses of low dose (2 mg/kg) abatacept and was on concomitant etanercept that was continued after discontinuation of abatacept. Cases of colon, breast, lung, and prostate cancer have been observed in clinical trials with etanercept. However, to be conservative we have included the case in calculating the total number of breast cancer cases reported in the abatacept trials. Thus, a total of 2/1956 abatacept-treated subjects (0.1%) who developed breast cancer compared to placebo-treated subjects (0.2%). Thus the evidence to date does not suggest that abatacept increases the rate of breast cancer in subjects with RA.

5.3.6 Lymphomas

During the double-blind period 1 subject developed lymphoma compared to none in the placebo group. The occurrence of non-Hodgkin's lymphoma in the setting of Hashimoto's thyroditis has been well documented and probably accounts for this case of lymphoma, although the exact role of abatacept is not known. During the open-label period a single subject developed lymphoma.

Given the temporal relationship and mechanisms of action, abatacept and/or etanercept could have contributed to the occurrence of this lymphoma. Thus, although the preclinical data suggested that abatacept might predispose to lymphomas the available data do not demonstrate an increased risk of lymphoma in RA patients treated with abatacept. However, firm conclusions regarding the risk of lymphoma with abatacept would require data on larger numbers of patients and longer periods of abatacept exposure.

5.3.7 Most Frequently Observed Malignancies

Table 76 shows the observed versus expected number of malignancies and standardized incidence ratios compared to the general US population for all RA clinical trials including the 4-month safety update report. Although the number of overall observed malignancies was less than expected, there was a higher incidence of lung cancer and lymphoma compared to that expected. As discussed above, the number of observed cases of lung cancer is within the range observed in RA cohort database. The rate of lymphomas is also higher than that expected based on the general US population but is in the same range as that observed in epidemiologic studies of RA. In those epidemiologic studies a 2-fold higher rate has been reported for the general RA population, a 4-5 fold higher rates for subjects with moderately active disease and higher rates for subjects with highly active disease.[5,6] Therefore it is difficult to determine whether the 3.7 fold higher rate of lymphoma observed in abatacept-treated subjects compared to the general US population is due to the treatment with abatacept or to the underlying disease.

[5] Baecklund E, Ekbom A, Sparen P, Feltelius N, Klardskog, L. Disease activity and risk of lymphoma in patients with rheumatoid arthritis: nested case-control study BMJ 1998; 517:180-181.
[6] Abstract. Wolfe F. Inflammatory activity, but not methotrexate or prednisone use predicts non-Hodgkin's lymphoma in rheumatoid arthritis: a 25-year study of 1767 RA patients. ACR Plenary II 1998: 931.

Table 76. Most Frequently Observed vs. Expected Number of Events and SIR by Malignancy Type

Malignancy[a]	Observed	Expected[b]	SIR	SIR (95% CI)
Overall	26	30.2	0.9	0.6, 1.3
Lung	8	4	2.0	0.9, 4.0
Lymphoma	4	1.1	3.7	1.0, 9.5
Breast	2	7.7	0.3	0.03, 0.9
Prostate	2	3.2	0.6	0.07, 2.2
Thyroid	2	0.6	3.5	0.40, 12.5
Ovarian	2	0.7	2.7	0.3, 9.7
Endometrial	2	1.5	1.3	0.2, 4.9

[a]Excludes non-melanoma skin malignancies; [b]Age- and gender adjusted to US population based on SEER database

5.4 Infections

5.4.1 Serious Infections

During the double-blind periods a higher proportion of abatacept-treated subjects (3%) reported serious infections compared with placebo-treated subjects (2%; Table 77).

Table 77. Serious Infections in Double-Blind Periods occurring more frequently in abatacept-treated subjects and in ≥ 2 subjects

Serious Infection Preferred term	Abatacept (n=1955)	Placebo (n=989)
Total Subjects with Serious Adverse Events	58 (3%)	19 (2%)
All Pneumonia	14 (0.7%)	5 (0.5%)
Pneumonia	9 (0.5%)	5 (0.5%)
Bronchopneumonia	2 (0.1%)	0
Pneumonia bacterial	1 (<0.1%)	0
Pneumonia haemophilus	1 (<0.1%)	0
Pneumonia influenza	1 (<0.1%)	0
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
Acute Pyelonephritis	3 (0.2%)	0
Localized infection	2 (0.1%)	0
Sinusitis	2 (0.1%)	0
Subcutaneous abscess	2 (0.1%)	0

Pneumonia was seen in similar proportions in subjects from both treatment groups with 0.7% for abatacept-treated subjects and 0.5% for placebo-treated subjects. As demonstrated in Table 77, a higher proportion of abatacept-treated subjects had cellulitis (0.3%), urinary tract infections (0.2%), bronchitis (0.2%), diverticulitis and pyelonephritis (0.2%). Most of the reported serious infections presented in a typical manner, responded to conventional treatment, and resolved in an expected manner. Three subjects died (1 abatacept-treated subject and 2 placebo-treated subjects) due to an infection of special interest. Narratives can be found under the discussion of study deaths.

Of the 58 abatacept-treated subjects who reported a serious infection 9 (16%) received abatacept + a biologic RA therapy compared to 2 of 19 placebo-treated subjects (11%) who developed a serious infection. Since 204/1955 (10%) of the subjects treated with abatacept were receiving a concomitant biologic RA therapy, the frequency of reported serious infections in this group is 9/204 (4%) subjects compared to the rate of serious infections in the remainder of subjects treated with abatacept 49/1751 (3%). Since the risk (3%) is still higher than the rate of serious

infection among placebo-treated subjects the higher rate of serious infection in subjects receiving abatacept plus a biologic RA therapy does not fully account for the higher rate in abatacept-treated subjects compared to placebo-treated subjects. Thus, there appears to be a higher rate of serious infection both when abatacept is given concomitantly with biologic RA therapy and when it is given with other RA therapies.

The incidence rate of serious infections, infections of special interest, and pneumonia by 6-month intervals is shown in Table 78. Although there is limited exposure beyond 2 years, there does not appear to be a trend to higher incidence of serious infections, infections of special interest or pneumonia with continued abatacept exposure. The low number of subjects and total person-years of exposure for later 6-month intervals was associated with a few events resulting in fluctuating incidence rates.

Table 78. Incidence Rates by 6 Month Intervals of Serious Infections, Infections of Special Interest, and Pneumonia

	All Abatacept Exposure Subjects with Event (rate/100 person-years)					
Preferred Term **(95% CI)**	Days 1-180	Days 181-360	Days 361-540	Days 541-720	Days 721-900	Days >901
Total Exposure (p-y)	1285	1032	795	399	117	198
All Serious Infections	50 (3.92) (2.9, 5.2)	39 (3.81) (2.7, 5.2)	22 (2.78) (1.7, 4.2)	9 (2.26) (1.0, 4.3)	4 (3.45) (0.9, 8.8)	3 (1.53) (0.3, 4.5)
Infections of Special Interest	26 (2.03) (1.3, 3.0)	28 (2.73) (1.8, 3.9)	12 (1.51) (0.8, 2.6)	6 (1.51) (0.6, 3.3)	3 (2.58) (0.5, 7.5)	2 (1.02) (0.1, 3.7)
Pneumonia	8 (0.62) (0.3, 1.2)	11 (1.07) (0.5, 1.9)	2 (0.25) (0.03,0.9)	3 (0.75) (0.2, 2.2)	1 (0.85) (0.02,4.8)	1 (0.51) (0.01,2.8)

5.4.2 Infections of Special Interest

Infections of special interest are a subset of all infections that were pre-defined by the sponsor to include those infections thought to be significant in the development of a biologic immunomodulatory molecule such as abatacept. The subset of infections includes 377 MedDRA preferred terms that includes fungal (e.g., aspergillosis), viral (e.g., Herpes zoster), and bacterial infections (e.g., pneumonia and TB). As shown in

Table 79, a higher proportion of abatacept-treated subjects (10%) reported an infection of special interest compared to placebo-treated subjects (7%). Abatacept-treated subjects had a higher incidence of Herpes infection, pneumonia, abscess, and pyelonephritis.

Table 79. Infections of Special Interest during Double Blind Period occurring more frequently in abatacept-treated subjects and in ≥ 2 subjects

Infection Preferred term	Abatacept (n=1955)	Placebo (n=989)
Total Subjects with Adverse Events	187 (10%)	70 (7%)
All Herpes infection	72 (4%)	28 (3%)
Herpes simplex	37 (2%)	10 (1%)
Herpes zoster	30 (2%)	16 (2%)
Herpes Virus	5 (0.3%)	2 (0.2%)
All Pneumonia	40 (2%)	8 (1%)
Pneumonia	33 (2%)	8 (1%)
Bronchopneumonia	5 (0.3%)	0
Pneumonia bacterial	2 (0.1%)	0
All Abscess	36 (2%)	22 (2%)
Abscess	2 (0.1%)	0
Tooth Abscess	28 (2%)	14 (2%)
Abscess limb	3 (0.2%)	4 (0.4%)
Subcutaneous abscess	3 (0.2%)	4 (0.4%)
All Pyelonephritis	9 (0.5%)	0
Pyelonephritis	6 (0.3%)	0
Pyelonephritis Acute	3 (0.2%)	0
Bursitis infectious	4 (0.2%)	0
Oral fungal infection	3 (0.2%)	0
Mycetoma mycotic	2 (0.1%)	0
Cellulitis	21 (1%)	9 (1%)

All 3 infection-related deaths were due to infections of special interest. One abatacept-treated subject died from pulmonary aspergillosis, which occurred in a subject with pulmonary scarring and bronchiectasis secondary to previous TB infection. Of the 2 placebo-treated subjects who died of an infection, 1 subject died of PCP and , and 1 subject died of pneumonia and sepsis.

The median time to first onset of infection and the median duration for the 5 most common infections of special interest are illustrated in Table 80.

Table 80. Time to First Onset and Duration for the 5 Most Common Infections of Special Interest

	Abatacept (n=1955)			**Placebo (n=989)**		
		Median Days			Median Days	
Adverse Events	%	Time to Onset	Duration	%	Time to Onset	Duration
Herpes simplex	1.9	118	8	1	227	17
Pneumonia	1.7	161	12	0.8	223	14
Herpes Zoster	1.5	176	27	1.6	180	20
Tooth Abscess	1.4	135	9	1.4	137	9
Cellulitis	1.1	211	14	0.9	154	10

The time to onset of pneumonia and Herpes simplex infection was less in abatacept-treated subjects compared to placebo-treated subjects but there was a shorter mean duration in abatacept-treated subjects compared to placebo-treated subjects, supporting the idea that abatacept-treated subjects respond adequately to conventional therapies. It should be noted that abatacept therapy was discontinued during the treatment of an infection and restarted following resolution of symptoms.

5.4.2.1 Bacterial infections

Pneumonias were the most common bacterial infection and occurred at twice the rate in abatacept-treated subjects (2%) as compared to placebo-treated subjects (1%). All subjects responded to treatment with resolution of symptoms. Tuberculosis (TB) is of particular interest given the risk of TB in subjects receiving anti-TNF drugs. All subjects participating in the abatacept trials were screened at baseline for latent TB infection. There were 2 cases of TB reported, 1 subject from each of the 2 treatment arms.

5.4.2.2 Viral infections

Herpes simplex occurred at a higher frequency among abatacept-treated subjects (2%) compared to placebo-treated subjects (1%). All presented typically and responded to treatment with appropriate resolution of symptoms.

5.4.2.3 Fungal infections

Two subjects developed fungal infections. One abatacept-treated subject developed pulmonary aspergillosis, which occurred in the setting of pulmonary scarring and bronchiectasis secondary

to previous TB infection. One placebo-treated subject developed pneumocystis carinii pneumonia.

5.4.3 All Infections

Table 81 shows that a higher proportion of abatacept-treated subjects (54%) developed infections compared to placebo-treated subjects (48%).

Table 81. Most Frequently reported infections in double-blind study periods

Infection Preferred Term	Abatacept (n=1955)	Placebo (n-989)
Total Subjects with Adverse Events	1051 (54%)	478 (48%)
URI	248 (13%)	119 (12%)
Nasopharyngitis	225 (12%)	90 (9%)
Sinustitus	125 (6%)	68 (7%)
UTI	113 (6%)	45 (5%)
Influenza	111 (6%)	52 (5%)
Bronchitis	101 (5%)	45 (5%)
Pharyngitis	59 (3%)	27 (3%)
Rhinitis	53 (3%)	17 (2%)
Herpes simplex	37 (2%)	10 (1%)
Pneumonia	33 (2%)	8 (1%)
Gastroenteritis	31 (2%)	19 (2%)
Herpes zoster	30 (2%)	16 (2%)
Tooth Abscess	28 (1%)	14 (1%)
Bronchitis	28 (1%)	10 (1%)
Otitis media	23 (1%)	8 (1%)
Fungal infection	22 (1%)	11 (1%)
Cellulitis	21 (1%)	9 (1%)
Cystitis	16 (1%)	11 (1%)
Fungal skin infection	16 (1%)	10 (1%)

There were several types of infections that occurred at a rate at least 1% higher among subjects in the abatacept group compared to the placebo group: upper respiratory infections (13% vs. 12%), nasopharyngitis (12% vs. 9%), urinary tract infections (6% vs. 5%), influenza (6% vs. 5%), rhinitis (3% vs. 2%), Herpes simplex (2% vs. 1%), and pneumonia (2% vs. 1%). Infection led to study discontinuation in similar proportions (1%) of abatacept-treated subjects and placebo-treated subjects with the most common infection in abatacept-treated subjects being pneumonia (0.2%) and bronchitis in placebo-treated subjects.

Antibiotic use can serve as a crude measure of infection severity. In the first 6 months of study IM101102, 26% of abatacept-treated subjects received an antibiotic compared to 32% of placebo-treated subjects. In the next 6 months of the blinded period of the study, 33% of subjects from both treatment arms received antibiotics. In study IM101031, 45% of abatacept-treated subjects received an antibiotic compared to 42% of placebo-treated subjects. In study Im101029, 32% of abatacept-treated subjects received an antibiotic compared to 24% of placebo-treated subjects. Furthermore, in each of the studies, equal proportions of subjects from both treatment arms received IV antibiotics. In general, these data did not demonstrate a greater severity of infections among abatacept-treated subjects.

There were no new types of infections of special interest reported during the open-label periods and in general these data were similar to that seen during the double-blind periods (data not shown).

5.5 Dropouts and Other Significant Adverse Events

5.5.1 Overall profile of dropouts

The total number of dropouts for the 5 major abatacept RA trials (IM101100, IM101101, IM101102, IM101029, and IM101031) is shown in Table 82. The largest proportion of subjects in the placebo arm dropped out due to lack of efficacy (15%) while the largest proportion of subjects in the abatacept arm dropped out due to AEs (6%). The larger percentage of total dropouts in the placebo arm was due to lack of efficacy. This difference may be partly explained as subjects enrolled in current RA trials may be less tolerant to AEs or perceived lack of efficacy than during previous clinical trials due to the availability of more effective therapies, e.g., anti-TNF drugs.

Table 82. Total Number of Dropouts from the 5 Major RA Trials

	Abatacept (n=1955)	**Placebo (n=989)**
Number Discontinued	275 (14%)	233 (24%)
Death	7 (0.4%)	4 (0.4%)
Adverse Events	107 (6%)	39 (4%)
Lack of Efficacy	92 (5%)	151 (15%)
Lost to Follow-up	20 (1%)	5 (0.5%)
Withdraw of Consent	46 (2%)	22 (2%)
Other	22 (1%)	4 (2%)

5.5.2 Adverse events associated with dropouts

The overall frequency of AEs that led to discontinuation of study drug during the double-blind periods was higher in the abatacept group (6%) compared to the placebo group (4%). Infections were the most common reason for study discontinuation and were reported by similar proportions (1%) of subjects in both treatment groups. No pattern of AEs was identified in

abatacept-treated subjects leading to discontinuation more frequently than in placebo-treated subjects.

5.5.3 Common Adverse Events

During the double-blind periods 89% of abatacept-treated subjects reported an AE compared to 85% of placebo-treated subjects (Table 83). Subjects treated with abatacept reported a higher frequency of infections (54% vs. 48%), gastrointestinal disorders (38% vs. 36%), and nervous system disorders (32% vs. 27%) compared to subjects treated with placebo. Infections are discussed separately above.

Table 83. Common Adverse Events with Incidence of >1% in Abatacept Group of the RA studies

System Organ Class Preferred Term	Abatacept N=1955	Placebo N=989
Total Subjects with Adverse Events	1736 (89%)	840 (85%)
Infections	1051 (54%)	478 (48%)
URI	248 (13%)	119 (12%)
Nasopharyngitis	225 (12%)	90 (9%)
UTI	113 (6%)	45 (5%)
Influenza	111 (6%)	52 (5%)
Rhinitis	53 (3%)	17 (2%)
Herpes Simplex	37 (2%)	10 (1%)
Pneumonia	33 (2%)	8 (1%)
Gastrointestinal Disorders	750 (38%)	351 (36%)
Nausea	224 (12%)	105 (11%)
Dyspepsia	126 (6%)	42 (4%)
Abdominal Pain	74 (4%)	30 (3%)
Mouth Ulceration	50 (3%)	14 (1%)
Aphthous Stomatitis	30 (2%)	4 (<1%)
Nervous System Disorders	623 (32%)	268 (27%)
Headache	356 (18%)	125 (13%)
Dizziness	183 (9%)	69 (7%)
Somnolence	48 (3%)	24 (2%)
Paraesthesia	38 (2%)	14 (1%)
Musculoskeletal and CT Disorders	589 (30%)	304 (31%)
Back Pain	144 (7%)	58 (6%)
Arthralgia	77 (4%)	34 (3%)
Pain in Extremity	60 (3%)	19 (2%)
Respiratory, Thoracic & Mediastinal Disorders	443 (22%)	192 (19%)
Cough	162 (8%)	71 (7%)
Skin and Subcutaneous Tissue Disorders	443 (22%)	179 (18%)
Rash	85 (4%)	32 (3%)
Investigations	265 (14%)	126 (13%)
Blood Pressure Increased	54 (3%)	13 (1%)
Weight Increased	33 (2%)	7 (1%)
Aspartate Aminotransferase Increased	30 (2%)	11 (1%)
Vascular Disorders	252 (13%)	93 (9%)
Hypertension	129 (7%)	43 (4%)
Insomnia	69 (4%)	29 (3%)
Eye Disorders	181 (9%)	82 (8%)
Keratoconjunctivitis Sicca	31 (2%)	10 (1%)

Dyspepsia was the only gastrointestinal event reported by >3% more subjects in the abatacept group compared with the placebo group. The higher frequency of nervous system disorders was due in large part to the higher frequency of headache (18% vs. 13%) and dizziness (9% vs. 7%) with approximately half of these events being reported within 24 hours of study drug infusion.

Hypertension was the only other commonly reported AE that occurred in >2% more subjects in the abatacept group compared with the placebo group. Hypertension was reported by 7% of subject in the abatacept group and 4% of subjects in the placebo group and increased blood pressure was reported by 3% and 1% of subjects, respectively. It should be noted that MedDRA coding conventions assign the preferred term of hypertension for the AE text of "elevated blood pressure" and may not always be consistent with more objective diagnostic criteria. Additionally, many subjects had pre-existing hypertension or elevated blood pressure. During treatment the number of subjects with blood pressure values exceeding 120 mmHg systolic or 90 mmHg diastolic was comparable between groups. Antihypertensive usage was comparable between the abatacept and placebo groups and antihypertensive use was stable among abatacept-treated subjects suggesting that changes in blood pressure were transient or subclinical. One subject in each group discontinued the study due to hypertension. The occurrence of hypertension or increased blood pressure did not predispose abatacept-treated subjects to AEs such as headache or dizziness.

These data do not suggest a clinically important difference between abatacept-treated subjects and placebo-treated subjects for common AEs, apart from infections.

5.6 Identifying common and drug-related adverse events

Adverse events that occurred in greater frequency than 1% of the abatacept group is shown in Table 83. AEs that were more common in the abatacept group included upper respiratory infection, nasopharyngitis, urinary tract infection, influenza, rhinitis, Herpes simplex, pneumonia, nausea, dyspepsia, abdominal pain, mouth ulceration, aphthous stomatitis, headache, dizziness, somnolence, parasthesia, back pain, arthralgia, pain in extremity, cough, rash, asthenia, chest pain, fall, increased blood pressure, increased weight, elevated aspartate aminotransferase, hypertension, insomnia, keratoconjunctivitis sicca, seasonal allergy, malignancy, and infusion reactions.

Most of these adverse events occurred with an incidence only slightly (i.e., 1-3%) higher in the abatacept group than the placebo group. Of primary concern are the increased rate of infections and malignancies.

Infusion reactions were also more commonly associated with abatacept infusions. Abatacept was administered intravenously as a 30-minute infusion without a protocol requirement for pretreatment for hypersensitivity reactions in the core RA studies. Infusion reactions that occurred within 1 hour after study drug infusion were more common in the abatacept group (9%) compared to the placebo group (6%). The most commonly reported events were of mild to

moderate intensity and included dizziness (2% vs. 1%), headache (2% vs. 1%), and hypertension (1% vs. <1%). Severe events reported by 2 or more subjects in the abatacept group included: flushing (3 subjects), dizziness (2 subjects), and hypersensitivity (2 subjects). The placebo group had no severe events reported by 2 or more subjects. Six (0.4%) abatacept-treated subjects and 2 (0.2%) placebo-treated subjects discontinued the study due to an acute infusion reaction.

A higher proportion of abatacept-treated subjects experienced infusion reactions within 24 hours after the start of the infusion compared to placebo-treated subjects (23% vs. 19%, respectively). The most frequently reported events that occurred in the abatacept group compared to the placebo group were of mild to moderate intensity and included headache (9% vs. 5%), dizziness (5% vs. 4%), nausea (5% vs. 4%), hypertension (2% vs. 1%), flushing (1% vs. <1%), and arthralgia (1% vs. <1%). Severe infusion-related events were reported in a larger percentage of abatacept-treated subjects (1.3%) compared to placebo-treated subjects (0.7%) with the most frequently severe events in the abatacept group being arthralgia (0.3%), headache (0.2%), dizziness (0.2%), nausea (0.2%), flushing (0.2%),and vomiting (0.2%). Twelve (0.6%) abatacept-treated subjects and 2 (0.2%) placebo-treated subjects discontinued the study due to an infusion reaction within 24 hours after receiving study drug.

There was 1 case of anaphylactic/anaphylactoid reaction in the double-blind period and 1 case in the open-label period. The case of anaphylactic/anaphylactoid reaction during the open-label period occurred after the first dose of abatacept as the subject had been randomized to placebo during the double-blind portion of the study. Both subjects were discontinued from the study and not rechallenged with abatacept. Three percent of abatacept-treated subjects and 4% of placebo-treated subjects experienced infusion-reaction symptoms following re-treatment with study drug during the double-blind portion of the study, suggesting that there does not appear to be an increased risk of infusion reaction after restarting abatacept after missing a dose.

5.7 Additional analyses and explorations

5.7.1 Abatacept and Concomitant non-Biologic and Biologic RA Therapy

In light of the possibility that abatacept could be used concomitantly with other commercially available biologic RA therapies (i.e., TNF blockers and anakinra), additional safety analyses were performed examining the safety of abatacept on a background of biologic RA therapy. Five of the 6 RA trials were conducted with subjects receiving background DMARDs (non-biologic and/or biologic). Study IM103002 compared abatacept- to placebo-treated subjects without concomitant background DMARDs but enrolled small numbers of subjects in each individual DMARD treatment group (approximately 30 subjects/treatment group). Consequently, it is difficult to compare the true drug-drug interactions between abatacept alone and abatacept with concomitant background DMARDs. However, there are adequate data to compare abatacept with concomitant non-biologic DMARDs versus biologic DMARDs.

A total of 204 subjects were treated with abatacept while receiving concomitant biologic RA therapy during the double-blind periods representing 173 person-years of exposure. Subjects were included if they had taken a biologic RA therapy at any time during the study, including up to 2 months after discontinuation of the study or the beginning of the open-label period. The majority of subjects participated in study IM101101 (n=85), in which subjects received only 2 mg/kg abatacept compared to the proposed dose of 10 mg/kg, and study IM101031 (n=103) with approximately 90% of those subjects receiving a TNF antagonist (87% of subjects received etanercept) and the remainder receiving anakinra.

Approximately 20% of subjects receiving abatacept + biologic RA therapy experienced a SAE compared to 9% of subjects receiving placebo + biologic RA (Table 84). The frequencies of all AEs and discontinuation due to AEs were also higher in abatacept-treated subjects (Table 84). There were no reported deaths.

Table 84. Adverse events in subjects on biologic RA therapy during double-blind periods

	Number (%) of Subjects			
	Biologic RA Therapy		Non-Biologic RA Therapy	
	Abatacept (n=204)	Placebo (n=134)	Abatacept (n=1751)	Placebo (n=855)
Deaths	0	0	9 (1%)	6 (1%)
Serious Adverse Events	40 (20%)	12 (9%)	226 (13%)	110 (13%)
Discontinuations	9 (4%)	3 (2%)	44 (3%)	13 (2%)
Related Serious Adverse Events	11 (5%)	3 (2%)	47 (3%)	14 (2%)
Adverse Events	192 (94%)	113 (84%)	1544 (88%)	727 (85%)
Discontinuations	19 (9%)	6 (5%)	88 (5%)	33 (4%)
Related Adverse Events	124 (61%)	67 (50%)	889 (51%)	389 (46%)

As shown in Table 85, the most common AEs in subjects receiving abatacept + biologic RA therapy compared to subjects receiving placebo + biologic RA therapy included headache (21% vs. 11%) and dizziness (11% vs. 8%). Additionally, nausea (16% vs. 10%), fatigue (14% vs. 9%), and diarrhea (14% vs. 10%) were more common in the abatacept + biologic RA therapy compared to the abatacept + non-biologic RA therapy group, respectively. Upper respiratory tract infection (20% vs. 11%), sinusitis (16% vs. 8%), and cough (10% vs. 3%) were more frequent in the abatacept + biologic RA therapy compared to abatacept + non-biologic RA therapy group, an effect not seen in the non-biologic RA subgroup suggesting an increased risk of upper respiratory tract infections in the abatacept + biologic RA therapy group.

Table 85. Most frequently reported AE in subjects of biologic- and non-biologic RA therapy during the double-blind periods

Number (%) of Subjects				
	Biologic RA Therapy		Non-Biologic RA Therapy	
	Abatacept	Placebo	Abatacept	Placebo
	(N=204)	(N=134)	(N=1751)	(N=855)
Total with Adverse Events	192 (94)	113 (84)	1544 (88)	727 (85)
Headache	42 (21)	15 (11)	314 (18)	110 (13)
Upper Resp. Tract Infection	40 (20)	15 (11)	208 (12)	104 (12)
Nausea	32 (16)	13 (10)	192 (11)	92 (11)
Sinusitis	32 (16)	11 (8)	93 (5)	57 (7)
Fatigue	29 (14)	12 (9)	97 (6)	56 (7)
Diarrhea	28 (14)	13 (10)	161 (9)	80 (9)
Dizziness	22 (11)	11 (8)	161 (9)	58 (7)
Cough	20 (10)	4 (3)	142 (8)	67 (8)
Nasopharyngitis	13 (6)	7 (5)	212 (12)	83 (10)

A higher proportion of subjects treated with abatacept + biologic RA therapy (20%) experienced a SAE compared to subjects treated with abatacept + non-biologic RA therapy (13%). Table 86 shows the SAEs reported in ≥2 subjects in the biologic RA therapy groups. Although limited conclusions can be drawn due to the small sample size, the greatest differences between the abatacept + biologic RA therapy group compared to placebo + biologic RA therapy group were in total SAEs, infections and neoplasms.

Table 86. SAEs reported in 2 or more subjects in the biologic RA therapy groups during the double-blind period

	Number (%) of Subjects			
	Biologic RA Therapy		Non-Biologic RA Therapy	
	Abatacept (n=204)	Placebo (n=134)	Abatacept (n=1751)	Placebo (n=855)
Total Serious Adverse Events	40 (20)	12 (9)	226 (13)	110 (13)
Infections	9 (4)	2 (2)	49 (3)	17 (2)
Cellulitis	3 (2)	0	2 (0.1)	2 (0.2)
Neoplasms (benign & malignant)	5 (3)	1 (1)	23 (1)	10 (1)
Basal Cell CA	2 (1)	0	7 (0.4)	3 (0.4)
General Disorders	1 (1)	2 (2)	15 (1)	7 (1)
Chest Pain	1 (1)	2 (2)	10 (0.6)	2 (0.2)

As illustrated in Table 87, a higher proportion of subjects in the abatacept + biologic RA therapy group (9%) discontinued study due to an AE than the placebo + biologic RA therapy group (6%). This was largely due to the increased number of infections in the abatacept + biologic RA therapy group.

Table 87. AEs that led to study discontinuation in subjects receiving biologic RA therapy during the double-blind periods

	Number (%) of Subjects			
	Biologic RA Therapy		Non-Biologic RA Therapy	
	Abatacept (n=204)	Placebo (n=134)	Abatacept (n=1751)	Placebo (n=855)
Total with Serious Adverse Events	19 (9)	6 (5)	88 (5)	33 (4)
Infections	7 (3)	2 (2)	17 (1)	8 (1)
Pneumonia	1 (<1)	0	3 (<1)	1(<1)
Localized infection	1 (<1)	0	2 (<1)	0
Bronchitis	2 (1)	1 (1)	0	1 (<1)
General Disorders	3 (2)	1 (<1)	7 (<1)	5 (<1)
Asthenia	1 (<1)	0	2 (<1)	0

A higher proportion of subjects receiving abatacept + biologic RA therapy (64%) reported infections compared to those subjects receiving placebo + biologic RA therapy (43%), which is a larger difference than that seen in subjects receiving abatacept versus placebo in the setting of non-biologic RA therapy (53% vs. 49%; Table 88). This further supports the conclusion that abatacept increases the risk of infection more when it is given with biologic RA therapy than with non-biologic RA therapies.

The majority of infections experienced by subjects in the abatacept + biologic RA therapy group were mild to moderate in severity. However, approximately 5% of abatacept-treated subjects receiving biologic RA therapy reported severe infections. Bacterial and viral infections were more common among subjects receiving abatacept + biologic RA therapy compared to the respective placebo control group. No opportunistic infections were noted, except for Herpes zoster.

Table 88. Most common infections in subjects receiving biologic RA therapy during double-blind periods

	Number (%) of Subjects			
	Biologic RA Therapy		Non-Biologic RA Therapy	
	Abatacept (n=204)	Placebo (n=134)	Abatacept (n=1751)	Placebo (n=855)
Infections	130 (64)	58 (43)	921 (53)	420 (49)
Upper Respiratory Tract Infection	40 (20)	15 (11)	208 (12)	104 (12)
Sinusitis	32 (16)	11 (8)	93 (5)	57 (7)
Bronchitis	20 (10)	7 (5)	81 (4)	38 (4)
Influenza	16 (8)	7 (5)	95 (5)	49 (6)
Nasopharyngitis	13 (6)	7 (5)	212 912)	83 (10)
Urinary Tract Infection	8 (4)	9 (6)	105 (6)	37 (4)

Analysis of the occurrence of neoplasms in abatacept-treated subjects on concomitant biologic RA therapy and placebo-treated subjects on concomitant biologic RA therapy is difficult given the small sample size. However, 10 of 204 (5%) abatacept + biologic RA therapy subjects reported a neoplasm, of which 3 of the 10 were malignant and consisted of non-melanoma skin cancers. Two subjects in the respective placebo control group developed a neoplasm of which none were malignant.

A higher proportion of subjects receiving abatacept + biologic RA therapy (5%) reported autoimmune symptoms and disorders compared to those subjects receiving placebo + biologic RA therapy (2%), which is more pronounced than that seen in subjects receiving abatacept versus placebo on non-biologic RA therapy (3% vs. 2%). Similar to the subjects on non-biologic RA therapy, the most common autoimmune events were keratoconjunctivitis sicca and psoriasis. Two subjects discontinued due to an autoimmune symptom or disorder: 1 subject due to leukocytoclastic vasculitis (mentioned above) and 1 subject due to cutaneous vasculitis.

During the open-label periods, 85 subjects were exposed to abatacept + biologic RA therapy for approximately 2 years in IM101101 and 103 subjects exposed to abatacept for approximately 3 months in IM1010031, and the safety profile was similar to that during the double-blind periods (data not shown).

The above discussion concerns the safety of combining biologic or non-biologic therapy with abatacept in the entire safety database. Closer analyses of study IM101031 were performed to better understand the incidence of SAEs and serious infections when abatacept is combined with biologic RA therapies. IM101031 was designed to evaluate the safety of abatacept in subjects with RA typically seen in a clinical practice, i.e., a heterogeneous patient population with active RA who are receiving background non-biologic and/or biologic RA therapies. A total of 1441 subjects were randomized to abatacept (n=949) or placebo (n=482). A subgroup of the total subject population were randomized to receive abatacept (n=103) or placebo (n=64) while on background biologic therapy, with approximately 90% of subjects receiving etanercept.

Of subjects receiving background biologic RA therapy the abatacept-treated subjects had a higher overall frequency of SAEs compared with abatacept-treated subjects in the total non-biologic subgroup (Table 89). The overall frequency of SAEs was almost 2-fold higher in abatacept + biologic DMARD treated subjects compared with placebo treated subjects (Table 89). This effect was almost entirely due to the etanercept subgroup of subjects since they accounted for the vast majority of subjects in the subgroup. The number of subjects receiving other biologics who reported SAEs was small (1-2 subjects), making it difficult to draw meaningful conclusions of risk within these subgroups.

Table 89. Study IM101031: Serious Adverse Events in Double-Blind Period

	Number of Subjects (%; n of subgroup)	
Background RA Therapy	Abatacept	Placebo
Total in Biologic Subgroup	23 (22%; n=103)	8 (13%; n=64)
Etanercept	17 (26%; n=66)	5 (12%; n=42)
Infliximab	4 (12%; n=34)	0(0%; n=9)
Adalimumab	3 (27%; n=11)	1 (10%; n=10)
Anakinra	2 (15%; n=13)	2 (20%; n=10)
Total in Non-Biologic Subgroup	100 (12%; n=856)	51 (12%; n=418)
MTX	73 (11%; n=691)	37 (11%; n=336)
Hydroxycholoquine/Chloroquine	23 (12%; n=194)	10 (8%; n=123)
Sulfasalazine	15 (11%; n=137)	9 (13%; n=72)
Leflunomide	25 (24%; n=106)	9 (15%; n=59)
1 DMARD	66 (11%; n=598)	36 (14%; n=257)
2 DMARDs	27 (13%; n=202)	14 (11%; n=123)
3 DMARDs	6 (13%; n=45)	0 (0%; n=31)
4 DMARDs	1 (10%; n=10)	1 (17%; n=6)

In the total non-biologic subgroup, there was no increase in the frequency of SAEs with abatacept compared with placebo (Table 89). However, abatacept-treated subjects on a background of leflunomide had a higher frequency of SAEs compared with placebo-treated subjects. Further analysis of these SAEs showed that the most medically serious of these events was due to infection in which both abatacept-treated and placebo-treated subjects had a 33% incidence rate. It is difficult to draw conclusions about the safety of leflunomide in combination with abatacept because of the problem of multiple comparisons and because of the lack of any comparisons and because of the lack of any pattern to the AEs observed. There was no evidence for an increase in the frequency of SAEs when abatacept was added to a regimen with multiple DMARDs

In the subgroup receiving non-biological DMARDs, serious infections were reported more frequently with abatacept compared with placebo, but the difference between abatacept and

placebo in the non-biologic subgroup was smaller than that observed in the total subgroup receiving biologics. Abatacept-treated subjects receiving background leflunomide or hydroxychloroquine/chloroquine had a higher frequency of serious infections compared with placebo-treated subjects. There was also a trend in the 3 non-biologic DMARDs subgroup toward a higher frequency of serious infections in abatacept-treated subjects compared with placebo-treated subjects.

The efficacy results of study IM101101 demonstrated that abatacept 2 mg/kg plus etanercept 25 mg BIW was associated with a trend to higher ACR 20 response rates at Day 180 that fell short of statistical significance as compared to placebo + etanercept 25 mg BIW (48% vs. 31%, p=0.072). An additional analysis of study IM101031 was conducted to determine whether adding abatacept 10 mg/kg to background biologic RA therapies produced a clinical benefit as assessed by the change from baseline in HAQ scores. In general, subjects treated with abatacept and concomitant biologic RA therapy in study IM101031 had more improvement in HAQ scores than those treated with placebo, but the magnitude of the improvement was approximately half that observed in subjects treated with abatacept plus non-biologic DMARDs (Table 90).

Table 90. Study IM101031: Mean Change from Baseline in HAQ Scores during Double-Blind Period

	Number of Subjects (%; n of subgroup)			
Background RA Therapy	Abatacept	95% CI	Placebo	95% CI
Total in Biologic Subgroup	-0.33 (n=103)	-0.44,-0.21	-0.23 (n=64)	-0.38,-0.07
Etanercept	-0.34 (n=66)	-0.49,-0.19	-0.22 (n=42)	-0.30,-0.08
Infliximab	-0.12 (n=34)	-0.40,-0.15	-0.56 (n=9)	-1.58,0.58
Adalimumab	-0.14(n=11)	-0.55,-0.27	-0.20 (n=10)	-0.48,-0.09
Anakinra	-0.40 (n=13)	0.70,-0.09	-0.59 (n=10)	-1.06,-0.13
Total in Non-Biologic Subgroup	-0.47 (n=856)	-0.52,-0.43	-0.26 (n=418)	-0.32,-0.20
MTX	-0.49 (n=691)	-0.54,-0.44	-0.26 (n=336)	-0.33,-0.19
Hydroxycholoquine/ Chloroquine	-0.47 (n=194)	-0.56,-0.38	-0.36 (n=123)	-0.46,-0.25
Sulfasalazine	-0.46 (n=137)	-0.56,-0.36	-0.24 (n=72)	-0.39,-0.10
Leflunomide	-0.39 (n=106)	-0.50,-0.28	-0.21 (n=59)	-0.42,-0.00
1 DMARD	-0.48 (n=598)	-0.53,-0.43	-0.24 (n=257)	-0.32,-0.16
2 DMARDs	-0.46 (n=202)	-0.55,-0.37	-0.29 (n=123)	-0.42,-0.17
3 DMARDs	-0.49 (n=45)	-0.65,-0.33	-0.20 (n=31)	-0.39,-0.01
4 DMARDs	-0.55 (n=10)	-0.89,-0.21	-0.75 (n=6)	-1.68,0.18

In summary, the combination of abatacept and concomitant biologic RA therapies, especially TNF-blockers, appears to increase the incidence of AE, SAEs, and infections. Efficacy data with the proposed dose of abatacept 10 mg/kg in combination with a biologic RA therapy is limited. Thus, the combination of abatacept with other biologic DMARDs is associated with an increased safety signal and unproven efficacy.

5.7.2 Abatacept Monotherapy

Additional analyses were performed for abatacept monotherapy as outlined in the study design for Study IM103002 (section 4.6). This section discusses only analysis of the safety of abatacept monotherapy. A total of 122 subjects were randomized to receive study drug with 90 subjects receiving abatacept (0.5 mg/kg, n= 26; 2 mg/kg, n=32, 10 mg/kg, n=32) and 32 subjects receiving placebo. Of the original 122 subjects randomized, 90 (74%) subjects completed the active treatment period through Day 85, and 160 (68%) subjects completed the study. The primary reason for discontinuation was lack of efficacy, which occurred more frequently in subjects treated with placebo (31%) than with abatacept (13%). Four subjects from the abatacept group, and no subjects in the placebo group, discontinued due to AEs. Peri-infusional AEs occurred with similar frequency among those who received placebo (31%) or abatacept (29%). During the treatment period, 14% of subjects treated with abatacept experienced SAEs compared with 19% of subjects in the placebo arm. No deaths were reported. Review of the safety of abatacept monotherapy did not identify additional safety concerns.

5.8 Autoimmune Symptoms and Disorders

Exploratory analyses were performed to evaluate the incidence of autoimmune symptoms and disorders associated with abatacept in light of the increased incidence of autoimmune phenomenon with the TNF blockers. Autoimmune symptoms and disorders were reported in 52/1955 (3%) subjects in the abatacept group compared to 18/989 (2%) of subjects in the placebo groups with the most common symptom/disorder reported in both groups being keratoconjunctivitis (1.6% vs. 1%), psoriasis (0.5% vs. 0.1%), vasculitis (0.3% vs. 0.2%) and Sjogren's syndrome (0.2% vs. 0.3%). It should be noted that except for psoriasis, each of these symptoms are commonly reported in subjects with RA. The majority of symptoms in both groups were of mild to moderate intensity; however 3 (0.2%) abatacept-treated subjects and 1 (0.1%) placebo-treated subjects reported AEs that were considered severe. The 3 severe AE in the abatacept treated subjects were keratoconjunctivitis sicca, psoriasis, and leukocytoclastic vasculitis. The placebo-treated subject was reported with severe vasculitis.

Autoimmune symptoms and disorders led to discontinuation in 6 (0.3%) abatacept-treated subjects and included psoriasis, vasculitis, leukocytoclastic vasculitis and systemic lupus erythematosus. None of the placebo-treated subjects discontinued the study due to an autoimmune symptom and disorder. Abatacept-treated subjects developed anti-nuclear antibodies and antibodies to double-stranded DNA at rates equal to or below that observed in placebo-treated subjects.

5.8.1 Psoriasis

During the double-blind periods of the RA studies, 10 (0.5%) abatacept-treated subjects and 1 (0.1%) placebo-treated subject reported new onset or worsening of psoriasis. The time of onset relative to the initiation of abatacept varied between 2 to 12 months. Of the 10 abatacept-treated

subjects, 4 had new onset of psoriasis and 6 had a flare in their disease. Four subjects did not require treatment, 3 subjects were given topical therapy, and 3 subjects required systemic therapy. Of the 3 subjects requiring systemic therapy, 1 subject required methylprednisolone, 1 subject had an increase in their dose of MTX, and 1 subject was treated with Augmentin.

Two of the 10 subjects discontinued the study due to psoriasis. One of the subjects discontinued due to a severe psoriasis flare which necessitated treatment with systemic corticosteroids that occurred 2 months into the double-blind study and resolved approximately 7 months after discontinuation of abatacept. The second subjects discontinued due to development of new onset psoriasis approximately 3 months into the double-blind portion of the study but was not treated with specific therapy for psoriasis.

Thus, placebo-controlled data from the double-blind portion of the RA studies suggests that abatacept therapy may be associated with new or worsening psoriasis in subjects with RA. This is interesting in light of the studies evaluating abatacept in subjects with psoriasis that have demonstrated that 46% of subjects had at least a 50% improvement in their psoriasis following abatacept treatment. Additionally, in another study evaluating abatacept in subjects with psoriasis that was prematurely terminated due to severe infusion reactions, there was approximately equal worsening of psoriasis in abatacept-treated subjects (33%) and placebo-treated subjects (36%) and there was 1 abatacept-treated subject that discontinued due to worsening psoriasis but there were no reports of worsening psoriasis as a SAE.

Additional analyses were conducted to determine to what degree subjects were enrolled with pre-existing psoriasis and/or psoriatic arthritis. As neither of these conditions were included in the exclusion criteria nor specifically inquired for, the data were collected by retrospectively noting the number of subjects who had psoriasis or psoriatic arthritis entered as free text on their CRFs. A total of 46/1955 (2.4%) abatacept-treated subjects reported psoriasis and 4/1955 (0.2%) abatacept-treated subjects reported psoriatic arthritis at the time of enrollment compared to 21/989 (2.1%) placebo-treated subjects who reported psoriasis and 1/989 (0.1%) who reported psoriatic arthritis. Thus, the number of subjects with psoriasis and/or psoriatic arthritis was small and balanced between the 2 arms. It is unlikely that the number of subjects with psoriasis and/or psoriatic arthritis affected the interpretation of these studies in regards to the efficacy or safety of abatacept in RA.

5.9 Laboratory Findings

On the whole, there were no clinically significant changes in ALT, AST, alkaline phosphatase, and serum creatinine in either the abatacept or placebo groups at 6 and 12 months. Overall, there were no meaningful differences between the abatacept and placebo groups with respect to changes from baseline for blood chemistry.

On the whole there was a small increase in hemoglobin levels observed at 6 months for subjects in the abatacept group (+0.28 gm/dL) compared to the placebo group (-0.19 gm/dL) and at 12 months (+0.37 gm/dL vs -0.14 gm/dL, respectively). The small increase in hemoglobin may be

accounted for by the ability of abatacept to decrease the systemic inflammation associated with RA and thereby allowing for increased erythropoeisis. There were no appreciable changes in platelet counts in either group. Both the WBC counts and absolute neutrophil counts were similar between the abatacept and placebo groups.

5.9.1 Analyses focused on outliers or shifts from normal to abnormal

During the double-blind period a similar proportion of subjects in the abatacept and placebo groups had elevations in alanine transferase (ALT; 2% vs. 2%), aspartate aminotransferase (AST; 1% vs. 1%), or serum creatinine (4% vs. 5%). Of abatacept-treated subjects, 3 subjects had elevated ALT values ≥3x the upper limit of normal (ULN) at 6 months and 2 subjects at 12 months, compared with 2 placebo-treated subjects at 6 months and 12 months. The majority of these subjects were on concomitant MTX or leflunomide, and one subject had ALT elevation associated with acute cholelithiasis. Elevation of ALT and AST levels between 3x and ≤5 x ULN and levels ≥5x ULN were uncommon and equally distributed between both abatacept- and placebo-treated treated subjects at 6 and 12 months. There were no significant differences between the abatacept and placebo groups for the mean change from baseline at both 6 and 12 months for alkaline phosphatase.

During the double-blind period there was no increase in the rate of hematologic abnormalities in abatacept-treated subjects.

There were small decreases in serum Ig levels in abatacept-treated subjects at 6 and 12 months compared with placebo-treated subjects but no abatacept-treated subject developed clinically significant immunodeficiency. No clinically significant safety signal was identified related to changes in immunoglobulin levels.

5.10 Immunogenicity

Immunogenicity of abatacept has been determined in all Phase I and II studies. It became apparent that human serum contained an endogenous, preexisting reactivity to abatacept. Additional studies were carried out in serum obtained from normal individuals as well as those with psoriasis and RA. These studies determined that the reactivity was to the Ig portion of the molecule and not to the CTLA4 portion. In the Phase II RA studies, the antibody response to the whole molecule, the CTLA4 and immunoglobulin (Ig) portion as well as the antibody response to only the CTLA4 portion (CTLA4-T) was determined. Out of a total of 385 subjects receiving multiple intravenous doses of 2 or 10 mg/kg of abatacept, no subject seroconverted for abatacept antibodies, and only two subjects (< 1%) seroconverted for CTLA4- T-specific antibodies during the treatment period of 180 days. The clinical significance of this is not known.

5.11 Special Safety Studies

Study IM101031 permitted enrollment of subjects with comorbid conditions allowing for analysis of AEs in 4 commonly occurring comorbid conditions found in the RA population and also reported with anti-TNF medication (Table 91): diabetes mellitus (n=96), asthma (n=83), COPD (N=54), and CHF (N=18).

Table 91. AE Occurring During the Double-Blind Period for Subjects with Co-Morbidities

	Number (%) of Subjects							
	All Abatacept				All Placebo			
Adverse Events	Diabetes n=65	COPD n=37	CHF n=9	Asthma n=54	Diabetes n=31	COPD n=17	CHF n=9	Asthma n=29
Deaths	1 (2)	0	0	1 (2)	1 (3)	1 (6)	1 (11)	1 (3)
Serious Adverse Events	14 (22)	10 (27)	3 (33)	7 (13)	4 (13)	1 (6)	4 (44)	3 (10)
Discontinuation from study	3 (5)	2 (5)	1 (11)	3 (6)	1 (3)	1 (6)	2 (22)	1 (3)
Adverse Events	61 (94)	36 (97)	8 (89)	52 (96)	28 (90)	15 (88)	9 (100)	26 (90)
Discontinuation from study	6 (9)	4 (11)	2 (22)	4 97)	3 (10)	4 (24)	2 (22)	3 (10)

5.11.1 Diabetes Mellitus

AEs were reported in 94% of abatacept-treated subjects and 90% of placebo-treated subjects with diabetes mellitus. Infections were the most commonly reported AE with 51% of abatacept-treated subjects reporting an infection compared with 58% of placebo-treated subjects. The type and pattern of infections that occurred were similar to those observed in abatacept-treated patients without diabetes. Although the sample size was small, there was no evidence of an increased risk of infection in abatacept-treated subjects with diabetes mellitus. There was no evidence to support an increased risk of loss of diabetes control in subjects receiving abatacept. A higher proportion of abatacept-treated subjects with diabetes reported a SAE compared to placebo-treated subjects, which was largely accounted for by an increase in the number of musculoskeletal disorders and injuries in the abatacept group. The only SAE reported by more than 1 subject in the abatacept group was RA, with most of these events associated with hospitalizations for elective joint replacement surgery. Discontinuation due to AEs occurred in a similar proportion of abatacept- and placebo-treated subjects with diabetes mellitus.

5.11.2 COPD

AEs were reported in 97% of abatacept-treated subjects and 88% of placebo-treated subjects with COPD. Infections were the most commonly reported AE and occurred in approximately 59% of subjects from both groups. The type and pattern of infections that occurred were similar to those observed in abatacept-treated patients without COPD. Analysis of AEs categorized as respiratory disorders occurred approximately 2-fold higher in abatacept-treated subjects (43%) compared to placebo-treated subjects (24%). The most commonly reported respiratory AEs among abatacept-treated subjects included cough, rhonchi, COPD exacerbation, COPD, dyspnea and nasal congestion. Overall, common AE were comparable between abatacept- and placebo-treated subjects with COPD. More SAEs were reported in abatacept-treated subjects (10/37; 27%) compared with placebo-treated subjects (1/17; 6%) with COPD. SAEs reported for abatacept-treated subjects with COPD include: intestinal ischemia, colon adenoma, COPD, exacerbated COPD, squamous cell carcinoma of the skin, RA (2 cases), bronchitis, basal cell carcinoma (2 cases), cellulitis, cataract and eye operation. There were no reported deaths in the 10 abatacept-treated subjects with COPD who had a SAE. Discontinuation due to AE occurred in (11%) of abatacept-treated subjects and 24% of placebo-treated subjects. The majority of abatacept-treated subjects who reported SAEs either continued treatment without dose interruption or resumed treatment after dose interruption.

5.11.3 Asthma and CHF

Overall the frequency of SAEs and discontinuation due to AEs with abatacept and placebo were comparable between groups.

5.12 Human Reproduction and Pregnancy Data

Pregnant or lactating women were excluded from participating in all abatacept RA trials. The following exclusion criteria were included in each protocol:

- Women who were pregnant or breast-feeding were excluded
- Women with a positive pregnancy test at enrollment or prior to study drug administration were excluded
- Women of child bearing potential who were unwilling or unable to use an acceptable method to avoid pregnancy for the entire study period and up to 10 weeks after the last infusion of study medication were excluded
- Urine or serum pregnancy tests were conducted throughout the study, within 48 hours prior to dosing for all women of child bearing potential.

Despite the requirement for contraception, 4 women in the abatacept group became pregnant during the double-blind period of the RA trials, and 3 of the 4 subjects experienced a spontaneous abortion during the first trimester. All 4 women were also receiving concomitant MTX. One subject had a history of 2 previous spontaneous abortions; one subject had a history

of a previous unsuccessful pregnancy, and another had no prior history of pregnancy; one subject electively terminated the pregnancy.

Preclinical reproductive studies conducted with abatacept in mice, rats, and rabbits demonstrated that abatacept was able to cross the placenta and that doses up to 20 to 30 times the human dose of 10 mg/kg had no evidence of fetal harm.

There is conflicting evidence concerning whether or not females with RA have an increased risk for fetal wastage and spontaneous abortions. There have been concerns that women on MTX may have an increase in spontaneous abortions since higher doses of MTX can be used as an abortifactant. Additionally, MTX has been implicated in the development of congenital defects or neural tube developmental abnormalities due to folate deficiency.

Since there are no adequate and well-controlled studies in pregnant women, and since animal reproduction studies are not always predictive of human response, it would be appropriate for abatacept to be considered a pregnancy category B and used in pregnancy only if clearly needed.

6. ADDITIONAL ANALYSES

6.1 Dosing Regimen and Administration

The sponsor conducted 2 clinical studies (IM101100 and IM103002) that explored the dose-response relationship of abatacept in subjects with RA, which form the basis for the choice of the 10 mg/kg dose.

6.1.1 Study IM101100

Study IM101100 randomized subjects with active RA on background non-biologic DMARDs to receive either abatacept 2 mg/kg, abatacept 10 mg/kg, or placebo infusions at Days 1, 15, 29, the every 28 days thereafter. Table 92 shows the dose-response relationship of abatacept which was evident at Day 180 as assessed by the proportion of subjects achieving an ACR 20, ACR 50 and ACR 70.

Table 92. Study IM101100: Number of Subjects Achieving an ACR 20, ACR 50 and ACR 70 at Day 180 and Day 360

	Abatacept 10 mg/kg + MTX (n=115)	Abatacept 2 mg/kg + MTX (n=105)	Placebo + MTX (n=119)
Day 180			
ACR 20	70 (61%)*	44 (42%)	42 (35%)
ACR 50	42 (37%)*	24 (23%)**	14 (12%)
ACR 70	19 (17%)*	11 (11%)****	2 (2%)
Day 360			
ACR 20	72 (63%)*	44 (42%)	43 (36%)
ACR 50	48 (42%)*	24 (23%)	24 (20%)
ACR 70	24 (21%)****	13 (12%)	9 (8%)
* p<0.001; **p=0.03; ***p=0.005; ****p=0.003			

A dose-response relationship could also be appreciated in the proportion of subjects achieving a major clinical response: 8% and 6% of the of the abatacept 10 mg/kg and 2 mg/kg subjects, respectively, achieved the endpoint compared to 1% of placebo-treated subjects. Additionally, a higher proportion of subjects in the 10 mg/kg group than in the 2 mg/kg group achieved an improvement in physical function as assessed by an improvement in baseline HAQ score ≥0.3u at Day 360 (38% and 30%, respectively, compared to 20% for the placebo-treated subjects).

Overall, study IM101100 demonstrated a dose-response relationship of abatacept with the 10 mg/kg dose being more effective than the 2 mg/kg dose. Safety review of study IM101100 did not demonstrate a dose-response relationship to the incidence of deaths, AEs, SAEs, infections or malignancies, although active treatment groups as a whole had a higher incidence of AEs.

6.1.2 Study IM103002

Study IM103002 randomized subjects with active RA, not receiving concomitant DMARDs, to receive either abatacept (0.5 mg/kg, 2 mg/kg or 10 mg/kg) or placebo infusions at Days 1, 15, 29, and Day 57. Table 93 shows the dose-response relationship of abatacept as assessed by the proportion of subjects achieving an ACR 20, ACR 50, and ACR 70 at Day 85.

Table 93. Study IM103002: Number of Subjects Achieving an ACR 20 Response on Day 85

	Placebo	Abatacept		
	(n=32)	0.5 mg/kg (n=26)	2 mg/kg (n=32)	10 mg/kg (n=32)
ACR 20 Responders N (%)	10 (31%)	6 (23%)	14 (44%)	17 (53%)
ACR 50 Responders N (%)	2 (6%)	0	6 (19%)	5 (16%)
ACR 70 Responders N (%)	0	0	4 (13%)	2 (6%)

Details of the efficacy of study IM101100 are discussed in Section 6.1.4.1, but overall, the study demonstrated a dose-response relationship of abatacept with the 10 mg/kg dose being clearly more effective than the 2 mg/kg dose. Safety review of study IM101100 did not demonstrate a dose-response relationship to the incidence of deaths, AEs, SAEs, infections or malignancies, although active treatment groups as a whole had a greater incidence of AEs.

6.2 Proposed Abatacept Tiered-dose Regimen

The sponsor intends to market abatacept using a tiered-dose regimen whereby patients will receive approximately 10 mg/kg. This dosing regimen was used in Phase III trials whereby subjects weighing <60 kg received abatacept 500 mg/kg, ≥60 kg to ≤100 kg received abatacept 750 mg, and >100 kg received abatacept 1000 mg. Thus, patients at the extremes of the weight categories will be receiving substantially different doses of abatacept. For example, a patient weighing 60 kg and a patient weighing 100 kg will both receive 750 mg of abatacept but this translates to 12.5 mg/kg versus 7.5 mg/kg, respectively. Consequently, analyses have been conducted to determine that the safety and efficacy of the tiered-dose regimen are similar to the 10 mg/kg dose across a range of weights.

Two analyses have been conducted to determine the safety of the tiered-dose regimen. First is the comparison of tiered-dose abatacept compared to abatacept dosed specifically at 10 mg/kg., and the second analysis consists of evaluating AE and SAE by weight in 10 kg intervals.

The AE profile of abatacept 10 mg/kg used in study IM101100 was compared with that for abatacept tiered-dose that approximated 10 mg/kg used in the similarly designed study IM 101102. Both studies were randomized, placebo-controlled studies that enrolled subjects with the similar severity of RA who were taking concomitant MTX treatment without additional DMARDs during the first 6 months of the double-blind period of the studies. After 6 months, subjects in both studies were permitted to add on DMARD. One major difference between the

studies was the reporting of worsening of RA as an AE. In study IM101100 investigators were to report worsening of RA as an AE, while in study IM101102 investigators were instructed not to report worsening of RA as an AE.

AEs were comparable between the 2 studies. The most common AEs were comparable between the 10 mg/kg and tiered-dosing abatacept: nasopharyngitis (15% vs. 15%), headache (14% vs. 18%), nausea (14% vs. 12%), diarrhea (11% vs. 11%), and upper respiratory tract infection (11% vs. 11%). The frequency of cough was higher in the subjects receiving abatacept 10 mg/kg compared with subjects receiving abatacept tiered-dosed (14% vs. 7%, respectively); however, the frequency of cough in the abatacept groups was similar compared to their respective placebo groups in each of the studies.

For the second analysis, safety data was integrated across the 3 Phase III core RA studies. Table 94 shows the number of AEs by 10 kg weight intervals in the double-blind periods. These data demonstrate that the frequency of AE was similar for each 10 kg weight interval within each respective treatment group. For the most common AEs, as defined as at least 10% of subjects in any weight interval, the frequencies of AEs were similar for each 10 kg weight interval (data not shown).

Table 94. Adverse Events by Weight Intervals in the Double-Blind Periods

	Abatacept		Placebo	
Weight Intervals (kg)	N	Number (%) of Subjects	N	Number (%) of Subjects
<50	126	113 (90)	49	45 (92)
50-<60	319	279 (88)	163	133 (82)
60-<70	373	322 (86)	207	179 (87)
70-<80	328	285 (87)	168	130 (77)
80-<90	231	203 (88)	110	96 (87)
90-<100	124	112 (90)	54	44 (82)
100-<110	73	65 (89)	35	29 (83)
>110	75	69 (92)	47	39 (83)

Table 95 shows the overall frequency of SAEs by weight interval in the double-blind periods. These data demonstrate that the frequency of SAE was similar for each 10 kg weight interval within each respective treatment group.

Table 95. Overall Frequency of SAEs by Weight Interval in the Double-Blind Periods

	Abatacept		Placebo	
Weight Intervals (kg)	N	Number (%) of Subjects	N	Number (%) of Subjects
<50	126	20 (16)	49	8 (16)
50-<60	319	39 (12)	163	15 (9)
60-<70	373	41 (11)	207	30 (15)
70-<80	328	44 (13)	168	17 (10)
80-<90	231	30 (13)	110	12 (11)
90-<100	124	19 (15)	54	9 (17)
100-<110	73	10 (14)	35	7 (20)
>110	75	12 (16)	47	2 (4)

Table 96 shows the number of reported serious infections by 10 kg weight intervals in the double-blind periods. These data demonstrate that the frequency of serious infections was similar for each 10 kg weight interval within each respective treatment group. Additionally, as noted above, abatacept-treated subjects had a greater proportion of serious infections than placebo-treated subjects.

Table 96. Number of Reported Serious Infections by 10 kg weight intervals in the Double-Blind Periods

	Abatacept		**Placebo**	
Weight Intervals (kg)	N	Number (%) of Subjects	N	Number (%) of Subjects
<50	126	6 (5)	49	0 (0)
50-<60	319	6 (2)	163	2 (1)
60-<70	373	12 (3)	207	6 (3)
70-<80	328	13 (4)	168	4 (2)
80-<90	231	3 (1)	110	0 (0)
90-<100	124	3 (2)	54	2 (4)
100-<110	73	4 (6)	35	1 (3)
>110	75	4 (5)	47	1 (2)

Table 97 shows the number of malignancies by 10 kg weight intervals in the double-blind period. These data demonstrate that the frequency of serious neoplasms was similar for each 10 kg weight interval within each respective treatment group.

Table 97. Number of Malignancies by 10 kg Weight Intervals in the Double-Blind Period

	Abatacept		Placebo	
Weight Intervals (kg)	N	Number (%) of Subjects	N	Number (%) of Subjects
<50	126	0 (0)	49	0 (0)
50-<60	319	5 (2)	163	0 (0)
60-<70	373	2 (<1)	207	3 (1)
70-<80	328	3 (1)	168	0 (0)
80-<90	231	3 (1)	110	2 (2)
90-<100	124	4 (3)	54	2 (4)
100-<110	73	3 (4)	35	0 (0)
>110	75	2 (3)	47	1 (2)

In studies IM101102 and IM101029, ACR 20 responses were generally similar at Day 169 in the respective treatment groups independent of weight (Table 98 and Table 99, respectively).

Table 98. Proportion of Subjects with ACR 20 Responses at Day 169 During the Double-Blind Period of IM101102 by Weight

	Abatacept		Placebo		
Weight Intervals (kg)	N	N(%) Response	N	N(%) Response	Estimate of the Difference
<50	30	19 (63%)	10	5 (50%)	13
50 to <60	77	50 (65%)	47	12 (26%)	39
60 to <70	113	74 (66%)	62	28 (45%)	20
70 to <80	87	62 (71%)	45	16 (36%)	36
80 to <90	64	48 (75%)	26	16 (62%)	14
90 to <100	24	19 (79%)	12	5 (42%)	38
100 to <110	11	8 (73%)	7	2 (29%)	44
>110	18	8 (44%)	5	1 (20%)	24

Table 99. Proportion of Subjects with ACR 20 Responses at Day 169 During the Double-Blind Period of IM101029 by Weight

	Abatacept		Placebo		
Weight Intervals (kg)	N	N(%) Response	N	N(%) Response	Estimate of the Difference
<50	10	3 (30%)	0	0	30
50 to <60	34	16 (47%)	19	3 (16%)	31
60 to <70	48	27 (56%)	26	5 (19%)	37
70 to <80	52	31 (60%)	33	6 (18%)	41
80 to <90	49	22 (45%)	14	2 (14%)	31
90 to <100	28	11 (39%)	16	6 (38%)	2
100 to <110	15	8 (53%)	8	3 (38%)	16
>110	19	10 (53%)	11	1 (9%)	44

Clinically meaningful HAQ responses (≥0.3u improvement from baseline) were generally similar in the respective treatment groups independent of weight for studies IM101102, IM101029, and IM101031 (Table 100, Table 101, and Table 102, respectively).

Table 100. Proportion of Subjects with a Clinically Meaningful HAQ Response at Day 365 During the Double-Blind Period of IM101102 by Weight

	Abatacept		Placebo		
Weight Intervals (kg)	N	N(%) Response	N	N(%) Response	Estimate of the Difference
<50	30	19 (63%)	10	4 (40%)	23
50 to <60	77	46 (60%)	47	17 (36%)	24
60 to <70	113	68 (60%)	62	27 (44%)	17
70 to <80	87	65 (75%)	45	18 (40%)	35
80 to <90	64	47 (73%)	26	15 (58%)	16
90 to <100	24	13 (54%)	12	2 (17%)	38
100 to <110	11	7 (64%)	7	1 (14%)	49
>110	18	5 (28%)	5	0	28

Table 101. Proportion of Subjects with a Clinically Meaningful HAQ Response at Day 169 During the Double-Blind Period of IM101029 by Weight

	Abatacept		Placebo		
Weight Intervals (kg)	N	N(%) Response	N	N(%) Response	Estimate of the Difference
<50	10	0	5	2 (40%)	-40
50 to <60	34	15 (44%)	19	3 (16%)	28
60 to <70	48	25 (52%)	26	5 (19%)	33
70 to <80	52	25 (48%)	33	9 (27%)	21
80 to <90	49	26 (53%)	14	13 (21%)	32
90 to <100	28	13 (46%)	16	4 (25%)	21
100 to <110	15	6 (40%)	8	3 (38%)	3
>110	19	10 (53%)	11	2 (18%)	34

Table 102. Proportion of Subjects with a Clinically Meaningful HAQ Response at Day 365 During the Double-Blind Period of IM101031 by Weight

	Abatacept		Placebo		
Weight Intervals (kg)	N	N(%) Response	N	N(%) Response	Estimate of the Difference
<50	85	37 (44%)	33	11 (33%)	11
50 to <60	207	99 (48%)	95	38 (40%)	8
60 to <70	208	107 (51%)	119	48 (40%)	11
70 to <80	184	89 (48%)	86	25 (29%)	19
80 to <90	115	52 (45%)	70	22 (31%)	14
90 to <100	69	32 (46%)	25	7 (28%)	18
100 to <110	45	20 (44%)	19	5 (26%)	18
>110	35	12 (34%)	30	9 (30%)	4

Overall, there does not appear to be a difference regarding the safety or efficacy of the tiered-dosing regimen proposed by the sponsor with respect to subject weight as assessed by analysis of 10 kg weight-intervals and the proportion of subjects with AEs, SAEs, serious infections, serious neoplasms, ACR 20 responses, and subjects achieving a clinically meaningful increase in physical function.

7. OVERALL ASSESSMENT

7.1 Summary and Conclusions

1. The data submitted by the sponsor suggest clinical activity of abatacept for the treatment of patients with moderately to severely active RA who have had an inadequate response to one or more DMARDs, including TNF blocking agents. This assessment is based on data from 3 adequate and well controlled studies and additional Phase 2 trials. Abatacept demonstrated effects on signs and symptoms of RA, including major clinical response, inhibition of structural damage, and improvement in physical function.

2. The safety of abatacept was assessed in subjects with moderately to severely active RA who have had an inadequate response to one or more DMARDs, including TNF blocking agents. Data were submitted from 2760 subjects exposed to abatacept for a median of 14 months.

3. Adverse events most clearly related to abatacept include hypersensitivity reactions and infections.

4. The data submitted suggest that the use of abatacept with concomitant biologic RA therapy (i.e., etanercept, infliximab, adalimumab, anakinra) may be associated with a greater incidence of infections.

5. The safety and efficacy of abatacept have not been established in patients with renal or hepatic insufficiency, and in women who are pregnant or nursing.