CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

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BLA 125118/000

Medical Review(s)

Team Leader Memo

FDA Center for Drug Evaluation and Research
Division of Anesthetic, Analgesic and Rheumatic Drug Products

Medical Officer Team Leader Memorandum

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To: File, BLA 125118/0

From: Jeffrey Siegel, M.D. JS
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Re: BLA 125118/0
Orencia ® (abatacept)
Bristol Myers Squibb

1. Background

Abatacept (CTLA-4Ig) is a fully human, recombinant, soluble fusion protein comprised of the extracellular domain of human CTLA-4 and the hinge-CH2-CH3 domain fragment of the Fc domain of human IgG1. The product was designed to bind to CD80 and CD86 on antigen-presenting cells thereby blocking costimulation of T cells and inhibiting the immune response that leads to the signs and symptoms of rheumatoid arthritis (RA). 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 antirheumatic drugs (DMARDs), including TNF-blocking agents. The sponsor also proposes that abatacept may be used in combination with other non-biologic DMARDs.

Currently drug treatment of RA involves therapies aimed at relieving symptoms and disease modification. Because of increasing recognition of the development of disability in patients receiving inadequate treatment of active disease and the ability of early effective treatment to improve physical function, disease modifying treatment is initiating more frequently early in disease. Currently disease modifying therapies include 1)

conventional disease modifying anti-rheumatic drugs (DMARD's), including methotrexate (MTX), hydroxychloroquine, sulfasalazine, leflunomide and others, used alone or in combination, and 2) biologic DMARD's, including TNF blocking agents and less frequently the IL-1 blocking agent anakinra. Biologic DMARD's are frequently used in combination with conventional DMARD's, particularly with MTX. While there are efficacious conventional DMARD's and biologic DMARD's, therapy is nonetheless suboptimal for significant numbers of patients who do not have a complete response to treatment with currently available treatments, including the combination of MTX plus a TNF blocker.

The RA guidance document plays an important role in guiding agency review of products for RA. The RA guidance document recognizes several claims for products for RA and discusses the evidence required to show efficacy for each one. The claims recognized in the RA guidance document include improvement in signs and symptoms, improvement in physical function, inhibition of progression of structural damage, major clinical response, complete clinical response and remission. Demonstration of improvement in signs and symptoms is based on trials of at least 6 months in duration that may use a validated composite index of disease activity such as the ACR20 (American College of Rheumatology 20), which indicates at least a 20% response in a specified set of core measures of signs and symptoms. Demonstration of improvement in physical function is based on trials of at least 2 years in duration using a validated index of physical function such as the Health Assessment Questionnaire (HAQ). Due to ethical concerns about keeping patients on placebo beyond 6 months in controlled trials, the agency has accepted evidence of improvement in the HAQ for 6-12 months in adequately controlled trials followed by demonstration in long-term open-label treatment studies that the benefits are maintained for products that show a large, clinically significant improvement in the controlled portion of the trial. Demonstration of inhibition of progression of structural damage is based on trials of at least 1 year in duration showing a reduction in progression using a validated measure of radiographic progression. The claim of major clinical response is based on demonstration of an ACR70 (defined based on improvement of at least 70% in a specified set of signs and symptom measures) for 6 consecutive months.

Four biologic agents have been approved for the treatment of RA: three TNF blockers etanercept, infliximab and adalimumab and one IL-1 blocker, anakinra. For each of the three TNF blockers radiographic progression has been observed to be reduced by 80-100% compared to controls and significant increases have been observed in the proportion of patients with no radiographic progression – defined as an increase of ≤ 0 units – over one year. The effects of the approved TNF blockers have been described in the Indications section of the package inserts as inhibition of progression of structural damage. A lower rate of progression of structural damage has been observed in a trial of anakinra as well with anakinra-treated patients showing a reduction of approximately one-third in their rate of progression of structural damage. This effect is described as slowing of progression of structural damage in that structural damage is observed to progress in anakinra-treated patients, but at a lower rate.

The clinical development plan for abatacept was designated Fast Track based on the promising approach to treatment of RA and a commitment on the part of the sponsor to

study a serious aspect of the disease in a population with an unmet medical need. The sponsor committed to studying improvement in physical function, which was agreed by the agency to represent a serious aspect of disease. The proposed population with unmet medical need consisted of RA patients with active disease despite treatment with a TNF blocker, a population for which there are no proven effective therapies. The sponsor submitted this study for a Special Protocol Assessment and this application was approved.

2. Review of Efficacy

2.1. Clinical development program

Efficacy was assessed in three phase 3 trials enrolling a total of 2484 patients as well as three phase 2 trials, as shown in Table 1 copied from the review by Dr. Keith Hull. Each of the studies was randomized, double-blind and placebo-controlled. The primary endpoint to assess signs and symptoms for each of the efficacy trials was the ACR20, a validated and well-accepted endpoint. Radiographic progression was assessed using the Genant modified Sharp score, a validated scoring method that assesses both joint erosions and joint space narrowing. Improvement in physical function was assessed using the HAQ. In brief, study IM101102 was a 1-year trial comparing the efficacy of abatacept to placebo when used in combination with MTX in patients with active RA despite treatment with MTX. IM101029 was a 6-month trial comparing abatacept to placebo in combination with MTX in patients who had failed a TNF blocking agent. Study IM101031 was a 1-year trial comparing addition of abatacept or placebo to background DMARD therapy in patients with active disease despite the DMARD regimen they were currently receiving.

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
				10mg/kg/fixed 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.

2.2. Signs and Symptoms

The phase 2 study IM101100 assessed the efficacy of abatacept at 2 or 10 mg/kg IV at 0, 2 and 4 weeks and then q4wks in combination with MTX for the treatment of signs and symptoms of RA. The primary endpoint of the trial was the ACR20 response at 6 months. As shown in Table 2, treatment with abatacept 10 mg/kg was associated with a statistically significantly greater proportion of patients achieving an ACR20 response. Though the response to abatacept 2 mg/kg was numerically higher than with placebo the difference was not statistically significant. The treatment effect (defined as the response to active treatment minus the response to placebo) was 26%.

Table 2: ACR20 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

Efficacy of abatacept in combination with MTX was also assessed in the phase 3 study IM101102, in which patients received weight-adjusted dosing 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

As shown in Table 3 copied from the review of Dr. Keith Hull, treatment with abatacept was associated with a statistically significant increase in the proportion of responders at month 6. The treatment effect was 28%.

Table 3: 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	

Study IM101029 assessed the efficacy of weight-adjusted dosing of abatacept in combination with MTX in patients who had had an inadequate response to TNF blockers. Patients were stratified according to whether they 1) had active disease despite TNF

blocker therapy at some earlier time or 2) had active disease despite TNF blocker therapy at the time of study enrollment, in which case they began abatacept or placebo following a wash-out period. As shown in Table 4 copied from the review of Dr. Keith Hull, treatment with abatacept was associated with a statistically significant increase in the proportion of ACR20 responders at month 6. The treatment effect was 30%. Similar results were seen whether patients had failed TNF blocker therapy at an earlier time or at the time of enrollment.

Table 4. 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	

Responses to abatacept were observed within weeks of initiation of therapy. As shown in Table 5 copied from the review by Dr. Keith Hull, a greater proportion of responders were observed among abatacept-treated patients as early as week 2 in study IM101102. Responses to abatacept were maintained out to one year.

Table 5. 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

ACR20 responses assess the proportion of patients achieving a 20% or greater improvement in a range of core ACR outcome variables. The ACR 50 and ACR 70 responses measure the proportion of patients achieving a 50% or 70% improvement in the same set of core outcome variables. As shown in Table 6 copied from the review by Dr. Keith Hull, a greater proportion of patients in the abatacept treated group achieved an ACR 50 and ACR 70 response in study IM101102 than in the control group both at month 6 and month 12. Responses were seen among all the core ACR components, as shown in Table 7 copied from the review by Dr. Keith Hull.

Table 6. 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

Table 7. 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

Extensive analysis of patients subsetted by baseline demographics and baseline disease activity uncovered no subgroup of patients lacking a treatment response to abatacept (data not shown).

2.3. Major Clinical Response

Major clinical response is defined as an ACR 70 response attained for six consecutive months. The proportion of patients achieving a major clinical response was assessed in study IM101102 over one year of treatment. As shown in Table 8 copied from the review by Dr. Keith Hull, a greater proportion patients in the abatacept-treated group attained a major clinical response than in the control group.

Table 8. Number of subjects achieving a 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	

2.4. Efficacy of Abatacept Monotherapy

While most of the clinical trials assessed use of abatacept in combination with MTX or with other conventional DMARD's, Study IM103002 evaluated the safety and clinical efficacy of abatacept monotherapy. A greater proportion of subjects receiving abatacept monotherapy (44%, and 53% with abatacept 2 mg/kg and 10 mg/kg, respectively) achieved an ACR 20 response at 3 months compared to placebo-treated subjects (31%). These data demonstrate that abatacept monotherapy is also efficacious. Abatacept monotherapy was not associated with the development of anti-abatacept antibodies.

2.5. Radiographic Progression

Assessment of radiographic progression is important for determining whether a new therapy has disease-modifying properties. Over long periods of time (5-20 years), high rates of radiographic progression are associated with higher rates of disability. Study IM101102 assessed radiographic progression over one year using the Genant-Modified Sharp score. In that study bone erosions was specified as a co-primary endpoint and joint space narrowing and total Sharp scores as secondary endpoints. As shown in Table 9 copied from the review by Dr. Keith Hull, treatment with abatacept reduced the rate of radiographic progression as assessed by the total Sharp score as well as by the erosion score and the joint space narrowing score. The data indicate that the rate of radiographic progression is reduced by approximately half compared to placebo-treated patients. 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).

Table 9. 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	

2.6. Improvement in Physical Function

Evidence that treatment with abatacept is associated with improvement in physical function is provided by several placebo-controlled trials. In study IM101102, improvement in physical function was assessed based on the percent of patients attaining a clinically meaningful improvement in HAQ – defined as an improvement of at least 0.3 units -- at one year. A change of 0.22 units has been demonstrated to represent the minimal clinically important improvement in HAQ. As shown in Table 10, a greater proportion of abatacept-treated patients attained a clinically meaningful improvement in HAQ at one year than controls. Improvement in physical function was also observed in study IM101100, in which 38% of patients receiving abatacept 10 mg/kg attained an improvement in HAQ of 0.3 u or greater at one year compared to 20% of placebo-treated controls.

Table 10. 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	

The durability of improvement in physical function was assessed in an open-label extension of study IM101100. In this study patients were randomized to receive abatacept 2 mg/kg, 10 mg/kg or placebo. After one year patients were allowed to participate in an open-label extension for an additional year. In that open-label extension, patients originally randomized to each of the three study arms received abatacept 10 mg/kg. In the analysis presented in Figure 1 copied from the review by Dr. Keith Hull only patients participating in the open-label extension trial were included. The data indicate that treatment with abatacept is associated with improvement in physical function that is maintained out to 2 years.

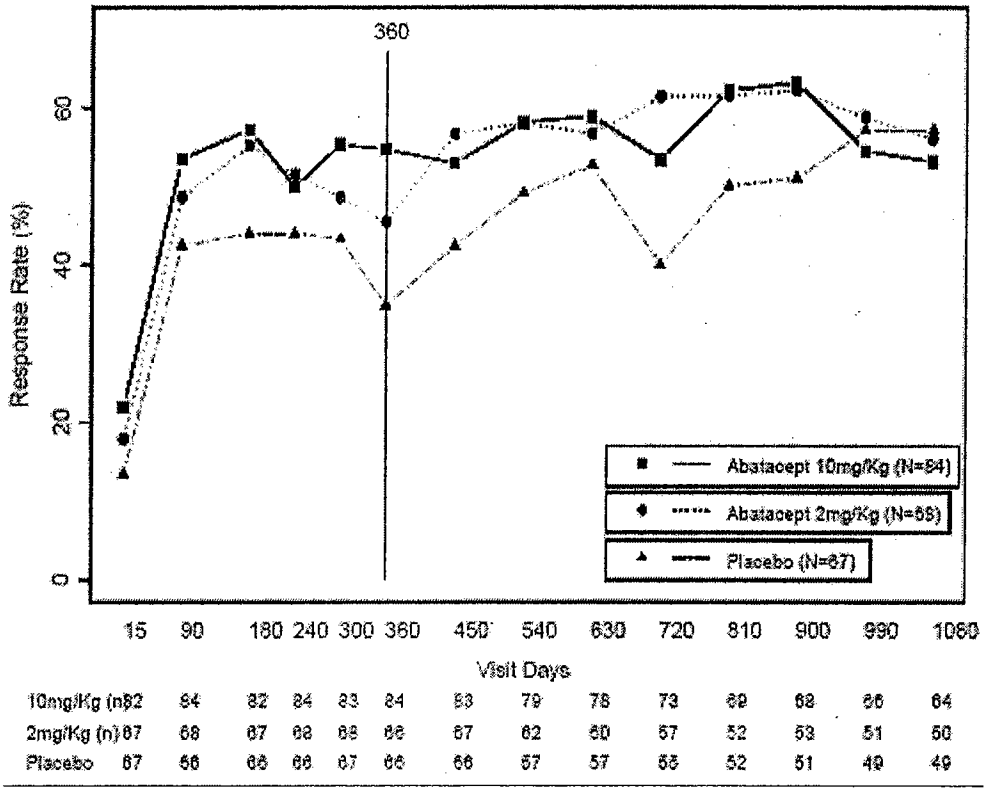

Figure 1: Proportion of Subjects with Clinically Meaningful mHAQ Responses for Subjects Entering Open-Label Therapy; As-Observed Data

3. Review of Safety

3.1. Extent of Exposure

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, as shown in Table 11 copied from the review by Dr. Keith Hull. 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 fixed dose abatacept that approximates ~10 mg/kg) with a mean duration of exposure of 12 months. Just over half the subjects were exposed to 10 mg/kg of abatacept for >12 months.

Table 11. 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

3.2. Deaths

In the controlled portions of the abatacept trials, a total of 15 deaths were observed: 9 (0.5%) occurring in abatacept-treated subjects and 6 (0.6%) among placebo-treated subjects. In addition, 8 subjects died during the open-label periods. The deaths were of a type expected in this patient population.

3.3. Serious adverse events

A total of 14% of all abatacept-treated patients experienced a serious adverse event, compared to 12% of placebo-treated controls. As shown in Table 12 copied from the review by Dr. Keith Hull infections was the only category of serious adverse event observed more frequently in abatacept-treated patients than controls.

Table 12. Most Frequently Reported (>1%) SAE in the Double-Blind Periods

System Organ Class Preferred term	Abatacept (n=1955)	Placebo (n=989)
Total Subjects with SAE	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%)

A more detailed analysis of serious infections is provided in Table 13, copied from the review by Dr. Keith Hull, in which serious infections are shown that occurred in more abatacept-treated patients than controls and where the total number of subjects experiencing that infection exceeds 2. The data indicate that the higher rate of serious infection with abatacept is attributable to a variety of common infections, with no one type of infection predominating.

Table 13. Serious Infections in Double-Blind Periods where abatacept-treated subjects > Placebo-treated subjects and total subjects > 2

Serious Infection Preferred term	Abatacept (n=1955)	Placebo (n=989)
Total Subjects with SAE	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

3.4. Malignancies

Overall, 10 malignancies were observed among abatacept-treated patients in the double-blind portions of the trials compared to 5 among placebo-treated patients. The 10 solid organ malignancies occurring in abatacept-treated patients consisted of 4 cases of lung cancer and one case each of cervical carcinoma, papillary thyroid, rectal, prostate, uterine, and ovarian cancer.

Three types of malignancy were analyzed in particular detail: lung cancer because of the higher rate of that malignancy in the double-blind portions of the trials; breast cancer and lymphoma because of a finding of mammary tumors and lymphoma during preclinical studies of mice treated with abatacept. Subsequent testing of these mice suggested that the murine retroviruses, MMTV and MLV, were responsible for these tumors as a result of sustained immunosuppression that occurred at all dose levels of abatacept. In addition there is concern that some immunosuppressives may increase the risk of lymphoma (e.g., MTX, azathioprine, and TNF blockers).

Table 14 (copied from the review by Dr. Keith Hull) shows the crude malignancy incidence rates in the double-blind portions of the trials. Overall the rate of malignancy excluding non-melanoma skin cancers is not higher among abatacept-treated patients than controls (0.59 vs. 0.63 cases/100 patient-years). The rate of breast cancer in particular is not higher in the abatacept-treated group. The rate of lung cancer was higher with abatacept (0.24 cases vs. 0/100 patient-years) than controls. A single case of lymphoma was observed in an abatacept-treated patient for a rate of 0.06 vs. 0/100 patient-years in the abatacept and placebo groups, respectively.

Since the overall rate of malignancy is not higher in the abatacept-treated group than controls it is difficult to assess the significance of the finding of a higher rate of lung cancer among abatacept-treated patients in the controlled trials. It could be a chance observation related to the large number of types of malignancies examined. Examination of the individual cases showed that 3 of the 4 patients had a substantial smoking history. In addition, re-examination of screening chest radiographs revealed that the lung cancer was pre-existing in one patient and there was strong evidence of a pre-existing malignancy in another case.

Several studies have reported a higher rate of lung cancer among RA patients than in the general population. The rate of lymphoma has also been reported to be elevated in patients with RA, particularly those with active disease. To further examine the significance of the 4 cases of lung cancer and the higher rate of lymphoma in the abatacept group the sponsor provided estimates of the rate of malignancy in sex and gender matched controls in the general population (SEER database) and in four RA observational cohorts. As shown in Table 14, the rate of lung cancer was higher in the abatacept-treated group but similar to rates observed in two of the RA observational cohorts. In would be informative to adjust these rates for the rate of smoking but unfortunately data on the rate of smoking in the RA observational cohorts are not available. Regarding lymphoma, the rates among abatacept-treated patients was higher than that expected in the general population but similar to that expected based on each of the four RA observational cohorts.

Table 14. 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

In summary, the rate of malignancy overall was not higher among abatacept-treated patients than among controls. Regarding specific types of malignancy there was a higher rate of lung cancer in the abatacept group. However most of the patients who developed lung cancer had a significant smoking history and two of the four cases appeared to have pre-existing disease. Comparison to RA observational cohorts suggests that the rate of lung cancer is similar to that seen in some other RA populations. A single case of lymphoma was observed in an abatacept-treated patient. The rate calculated based on

this single occurrence is higher than that expected in the general population but similar to rates expected in patients with RA.

3.5. Safety in patients with co-morbidities

Study IM101031 allowed enrollment of patients with co-morbidities. Examination of data from this trial, though limited, allows some initial assessment of the safety of use of abatacept in patients with diabetes mellitus (n=96), asthma (n=83), chronic obstructive pulmonary disease (COPD, N=54) and congestive heart failure (CHF, N=18). No safety signals were seen among patients with diabetes mellitus, asthma or CHF treated with abatacept. However, adverse events (AEs) were more frequent among patients with COPD receiving abatacept than controls (97% compared to 88%). Infections occurred in similar proportions of patients in both groups. Analysis of AEs categorized as respiratory disorders occurred approximately 2-fold more frequently in abatacept-treated subjects (43%) than placebo-treated subjects (24%). The most commonly reported respiratory AEs among abatacept-treated subjects included cough, rhonchi, COPD exacerbation, COPD, dyspnea and nasal congestion. More SAEs were reported in abatacept-treated subjects (10/37; 27%) than 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. The majority of abatacept-treated subjects with COPD who reported SAEs either continued treatment without dose interruption or resumed treatment after dose interruption.

3.6. Combination with TNF Blocking Agents

Rheumatologists in clinical practice commonly combine different DMARD's to improve control of disease. Given the widespread use of TNF blocking agents it is possible that rheumatologists might combine a TNF blocking agent with abatacept if it is approved. The sponsor assessed the safety of combination use of abatacept with TNF blocking agents in two of their clinical trials. Study IM101101 studied a dose of abatacept (2 mg/kg) less than the proposed dose for marketing in combination with an approved dose of etanercept (25 mg biw sc) in patients with an inadequate response to etanercept. Study IM101029 studied the addition of weight-adjusted abatacept to a variety of background DMARD's based on whatever DMARD's the patient was receiving at the time of enrollment. Study IM101029 allowed combination use of abatacept with TNF blocking agents or anakinra. A total of 103 subjects in study IM101031 received abatacept in combination with biologic DMARD's. Approximately 90% of these subjects were receiving a TNF blocker (87% receiving etanercept) and the remainder anakinra.

Use of biologic DMARD's in the randomized controlled trials was associated with a higher rate of AEs and SAEs. As shown in Table 15 copied from the review by Dr. Keith Hull although the rate of SAEs in patients receiving concomitant non-biologic DMARD's was similar for abatacept-treated and placebo-treated groups (13% for both) the rate for patients receiving biologic DMARD's was higher among abatacept-treated patients (20%

compared to 9% for placebo-treated controls). The types of SAEs that account for this higher rate (Table 16 copied from review by Dr. Keith Hull) include infections (4% vs. 2%) and neoplasms.

Table 15. 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%)
SAEs	40 (20%)	12 (9%)	226 (13%)	110 (13%)
Discontinuations	9 (4%)	3 (2%)	44 (3%)	13 (2%)
Related SAEs	11 (5%)	3 (2%)	47 (3%)	14 (2%)
AEs	192 (94%)	113 (84%)	1544 (88%)	727 (85%)
Discontinuations	19 (9%)	6 (5%)	88 (5%)	33 (4%)
Related AEs	124 (61%)	67 (50%)	889 (51%)	389 (46%)

Table 16. 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 SAEs	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)

In summary, the data indicate that there is a safety signal for infections and possibly malignancies among patients receiving abatacept with concomitant TNF blockers. Thus the safety of concomitant use is unproven and these agents should not be used together outside of an investigational setting until further data are available.

3.7. Immunogenicity

Antibodies to abatacept were assessed based on reactivity to the whole molecule as well as to the CTLA-4 (CTLA4-T) portion. 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 two subjects (< 1%) seroconverted for CTLA4- T-specific antibodies during the treatment period of 180 days.

4. Chemistry, Manufacturing and Controls

4.1. General properties

Abatacept drug substance is a 50 mg/ml aqueous solution in 25 mM sodium phosphate, 50 mM sodium chloride, pH 7.5 ± 0.5, pI 4.5.-5.5. The final abatacept for injection drug product is supplied at 250 mg/vial. Each vial contains [ ] contains [ ] mg of abatacept, [ ] maltose monohydrate, [ ] sodium phosphate, monobasic, [ ] sodium chloride and hydrochloric acid/sodium hydroxide as necessary to adjust pH.

4.2. Manufacturing Process

Abatacept is produced as a secreted protein in [ ] cell culture using a Chinese hamster ovary (CHO) cell line. A [ ] bioreactor is harvested, concentrated and subjected to a series of chromatography and filtration steps. The downstream purification steps remove high molecular weight abatacept species, process-related impurities, allow for clearance of adventitious virus and control of the sialic acid content of the drug substance. Control of the manufacturing process is maintained by implementation of in-process testing and acceptance criteria for release test specifications. The sponsor has provided acceptable release test specifications for drug substance and drug product. The agency requested the sponsor add specifications for [ ]

The CMC review consisted of review of the abatacept drug substance and drug product manufacturing process including evaluation of methods and process validation, product characterization, data regarding manufacturing consistency, drug substance and product specifications and stability data. Issues of concern identified during review included justification of a number of release specifications, monitoring of impurities during drug substance manufacture, inadequate functional characterization of the Fc portion of abatacept, the need for justification/clarification of a number of the methods validation studies and inadequate data allowing for evaluation of drug substance and drug product stability. Responses to questions raised regarding these issues are currently under review. The CMC reviewer at this time does not anticipate that any of these issues will delay the approval process. It should be noted that the product reviewers are still in the process of reviewing recently received information from the Sponsor.

5. Pharmacology/Toxicology Issues

5.1. Carcinogenesis, mutagenesis, and impairment of fertility

No mutagenic potential of abatacept was observed in the in vitro reverse Ames or Chinese hamster ovary/hypoxanthine guanine phosphoribosyl-transferase (CHO/HGPRT) forward point mutation assays, and no chromosomal aberrations were

observed in human lymphocytes (with or without metabolic activation) treated with abatacept. In rats, abatacept had no adverse effects on male or female fertility at doses up to 10.9-fold the human exposure at 10 mg/kg based on AUC.

In a mouse carcinogenicity study, abatacept was injected weekly for up to 84 weeks. Increases were observed in the incidence of malignant lymphomas (all doses) and mammary gland tumors (intermediate- and high-dose in females). The increased incidence of lymphomas and mammary tumors observed in mice treated with abatacept may have been associated with the decreased control of murine leukemia virus and mouse mammary tumor virus, respectively, in the presence of long-term immunomodulation. The doses used in these studies were 0.8-, 1.9- and 3.0-fold, respectively, the human exposure at 10 mg/kg based on AUC.

In a one-year toxicity study in cynomolgus monkeys, abatacept was administered intravenously once weekly at doses up to 50 mg/kg (9.2-fold the human exposure at 10 mg/kg based on AUC). No significant drug-related toxicity was observed. Reversible pharmacological effects consisted of minimal transient decreases in serum IgG and minimal to severe lymphoid depletion of germinal centers in the spleen and/or lymph nodes. No evidence of lymphomas or preneoplastic changes was observed.

5.2. Reproductive toxicology

The pharmacology/toxicology reviewer recommends pregnancy category C. Abatacept has been shown to cross the placenta. Reproductive toxicology studies in rats at doses that were 11-fold the proposed dose in patients demonstrated inflammation of the thyroid in 1 female offspring out of 10 males and 10 females and a 9-fold increase in the mean T-cell-dependent antibody response. In view of evidence that CTLA-4 signaling may be critical for development of regulatory T cells (Treg) this evidence suggests that high doses of CTLA4-Ig in fetal development may have lasting effects on the developing immune system that could predispose to autoimmunity and exaggerated immune responses. At lower doses (3 times the human exposure) no effects were seen.

5.3. Nursing mothers

Abatacept has been shown to be present in rat milk. The toxicology reviewer recommends that because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from ORENCIA, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

5.4. Other Non-Clinical Findings

Toxicology studies were conducted in rats, mice and monkeys administered subcutaneously and/or intravenously with durations of exposure ranging from a single dose to 1-year of weekly dosing. Abatacept was pharmacologically active in all of the toxicology species used. In a pivotal single-dose intravenous toxicity study performed in monkeys at doses ranging from 10 to 100 mg/kg abatacept was well tolerated at 100 mg/kg dose (x10 human dose) with no target organ toxicity identified. In the pivotal

repeat-dose studies, reversible pharmacologic changes related to the immune system were observed. The NOEL and NOAEL in the 1-year monkey study were <10 and 50 mg/kg/weekly, respectively providing estimated human exposure multiples of <1.9 and 9.2, respectively. The changes in immune parameters were not associated with any clinical manifestation of infection.

The local tolerance of abatacept was assessed after single IV, intra-arterial, and paravenous injections at concentrations similar to or greater than those to be used in humans in New Zealand White rabbits. No injection-site irritation was observed with any route of parenteral administration. In addition, no adverse effects at the injection site were seen in repeat-dose studies up to 1 year in monkeys.

6. Clinical Pharmacology

Pharmacokinetics of single dose administration was studied in normal volunteers and in patients with psoriasis. Population PK studies were carried out in multiple-dose studies in the RA population. 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. After multiple intravenous infusions, 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 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 have 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.

7. Facilities inspections

As of the time of writing of this review there remained a few issues to be resolved regarding facilities inspections.

8. Conclusions

The clinical development program has provided evidence from adequate and controlled trials to support efficacy of abatacept for improving signs and symptoms of RA in

patients with moderately to severely active RA and inducing major clinical responses. The data also support slowing of radiographic progression and improvement in physical function based on 1-year and 2-year data, respectively. Efficacy was demonstrated in patients receiving concomitant MTX and other conventional DMARD's and as monotherapy. Efficacy was demonstrated among patients with an inadequate response to a TNF blocking agent.

Abatacept was generally well tolerated but several safety signals were observed. A slightly higher rate of serious infections was observed, a finding that is not unexpected in view of the immunosuppressive properties of this product. However, when used concomitantly with TNF blocking agents a considerably higher rate of SAEs was observed, particularly serious infections. Use of abatacept in combination with TNF blockers should be recommended against. Among patients with comorbidities a higher rate of AEs and SAEs were observed among patients with COPD, particularly adverse events that were respiratory in nature.

Overall the rate of malignancies was not higher with abatacept than in placebo-treated controls. However a higher rate of lung cancer was seen, consisting of 4 cases in the abatacept group and none in controls. The significance of this finding is unclear given that 1) the rate of malignancies overall was not elevated; 2) 3 of the 4 patients had histories of heavy smoking exposure; 3) 2 of the 4 had evidence of a pre-existing lung cancer upon study enrollment; 4) a higher rate of lung cancer has been reported in RA patients. In summary the evidence supporting a link between abatacept treatment and lung cancer is not strong. Nonetheless vigilance is warranted in evaluating further evidence of lung cancer in exposed populations.

Evidence of autoimmunity and exaggerated immune responses in offspring of pregnant rats exposed to high doses of CTLA4-Ig suggest that a pregnancy category C is warranted. No other major issues were identified in CMC, pharm/tox or clinical pharmacology. Assuming all remaining issues are resolved as expected there do not appear to be any issues that would hold up an approval. Some facilities inspections are ongoing.

9. Recommendations

I recommend approving abatacept with appropriate labeling.

CLINICAL REVIEW

Application Type	BLA
Submission Number	125118/0
Submission Code	Not Applicable
Letter Date	December 31, 2005
Stamp Date	December 22, 2004
PDUFA Goal Date	December 31, 2005
Reviewer Name	Keith M Hull, MD, PhD KMH
Team Leader	Jeffrey Siegel, MD JS
Division Director	Robert A Rappaport, MD
Review Completion Date	November 22, 2005
Established Name	Abatacept
(Proposed) Trade Name	Orencia
Therapeutic Class	Fusion Protein
Applicant	Bristol-Myer-Squibb
Priority Designation	P
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 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

This licensing application is for approval of abatacept (proposed trade name: Orencia) 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 (RA) who have had an inadequate response to one or more Disease Modifying Anti-Rheumatic Drugs (DMARDs), including TNF blocking agents. The licensing application proposes that abatacept may be used in combination with methotrexate or other non-biologic DMARD therapy. Six multicenter, randomized, double-blind, placebo-controlled studies (IM101100, IM101101, IM101102, IM101029, IM10131, and IM103002) provide evidence of the safety and efficacy of abatacept. Each of the studies enrolled subjects with moderately to severely active RA. The majority of these subjects had failed one or more non-biologic or biologic DMARDs.

This submission proposes that abatacept is efficacious in the specific subset of patients who have failed a TNF blocking agent. Such a claim would require evidence that the new drug provides meaningful therapeutic benefit over existing treatment. Recently, TNF blockers have been added to the therapeutic armamentarium for the treatment of RA, and when added to background non-biologic DMARDs, demonstrate superior efficacy than non-biologic DMARDs alone. However, 30-45% of subjects receiving a TNF blocker fail to achieve an adequate clinical benefit as assessed by an ACR 20 response. There are currently no approved therapies for patients who fail TNF blockers. Study IM101029 provides evidence that abatacept is effective in subjects with moderate to severe RA who are on background non-biologic DMARDs and have had an inadequate response to TNF blockers, thus addressing this unmet medical need.

This clinical reviewer recommends approval of abatacept for reducing signs and symptoms, inducing major clinical response, slowing the progression of structural damage, and improving physical function in patients with moderately to severely active RA who have had an inadequate response to one or more DMARDs, including TNF blocking agents.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

No special risk management actions are recommended for the marketing of abatacept.

1.2.2 Required Phase 4 Commitments

There are no required Phase 4 commitments.

1.2.3 Other Phase 4 Requests

The sponsor submitted a pharmacovigilance plan on April 6, 2005 that commits to follow over 2000 patients currently enrolled in the open-label extension portion of the studies discussed in this review for at least 5 years. The sponsor also proposes 2 additional studies:

- Protocol IM101045A is designed as a nested case-control study to assess the risk of hospitalization due to infection (all hospitalized infections, hospitalized pneumonia, and all opportunistic infections) among patients with RA treated with abatacept in comparison to other DMARDs within a large cohort of individuals with commercial health insurance.

- Protocol IM101045B is designed as a cohort study to assess the risk of malignancies and infection in patients with RA treated with abatacept in comparison to other DMARDs within 2 existing registries containing patients with rheumatoid arthritis.

This reviewer recommends a Phase 4 commitment to complete the above two studies and the 5-year study of the over 2000 patients enrolled in the open-label extension studies.

This reviewer also recommends the sponsor commit to:

1. Collecting and analyzing data on the incidence rate of lung cancer in smokers and non-smokers of RA subjects treated with abatacept.

2. Conducting a pregnancy registry, with concurrent controls, for women who become pregnant while exposed to abatacept to identify the pregnancy outcome and postnatal health status of the children.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Abatacept is a fully human, recombinant, soluble fusion protein comprised of the extracellular domain of human CTLA-4 and the hinge-CH2-CH3 domain fragment of the Fc domain of human IgG1 that inhibits T-cell activation by blocking signaling of the co-stimulatory molecule CD28. Abatacept is administered as an intravenous infusion with tiered-based dosing dependent on the patient's weight.

The clinical development program for RA consists of six multicentered, randomized, double-blind, placebo-controlled studies that provide evidence of the safety and efficacy of abatacept. Each of the studies enrolled subjects with moderately to severely active RA. The majority of these subjects had failed one or more non-biologic or biologic DMARDs. The safety database consists of 2760 subjects treated with abatacept for a median of 14 months duration.

1.3.2 Efficacy

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

1.3.2.1 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 receiving 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 of signs and symptoms. In studies IM101100, IM101102, and IM101029, a statistically significant 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 criteria 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% with abatacept 2 mg/kg and 10 mg/kg, respectively) achieved an ACR 20 response at 3 months compared to placebo-treated subjects (31%). These data support the findings in the larger trials discussed above and also demonstrate that abatacept monotherapy demonstrates efficacy compared to placebo. Abatacept monotherapy was not associated with the development of anti-abatacept antibodies.

Overall, the data support the claim that abatacept therapy reduces the signs and symptoms of RA in subjects who have failed DMARDs and/or a TNF blocker. The data support the use of abatacept as monotherapy. The results of study IM101029 support its use in patients who have had an inadequate clinical response to TNF-blocking drugs.

1.3.2.2 Improvement of Physical Function

The claim of improvement in physical function described in the RA guidance document is intended to recognize clinical benefits in trials of two years or longer regarding the disabling changes that occur over time in untreated patients.

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 percent 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 indicate 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 and the effect appears to be maintained at 2 years.

1.3.2.3 Inhibition of Progression 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 change in mean erosion score from baseline to one year for abatacept-treated subjects of 0.63u compared to 1.14u for placebo-treated subjects. This represents an approximately 45% reduction in erosions for subjects treated with abatacept.

1.3.3 Safety

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 and form the primary evidence of safety. Adverse events (AE) related to abatacept include hypersensitivity reactions

and infections. Hypersensitivity reactions within 24 hours of infusion were more common with subjects receiving abatacept than placebo subjects. Infections were also seen more frequently in subjects with abatacept (54%) than placebo (48%) and included upper respiratory tract infection (13% vs. 12%), nasopharyngitis (12% vs. 9%), urinary tract infection (6% vs. 5%), rhinitis (3% vs. 2%), herpes simplex (2% vs. 1%), and pneumonia 2% vs. 1%). Serious infections were also more frequent in abatacept-treated subjects (3%) compared to placebo-treated subjects (2%) and included cellulitis, urinary tract infection, bronchitis, diverticulitis, and acute pyelonephritis, all occurring in fewer than 1% of subjects.

The overall frequency of benign and malignant neoplasms was similar for the abatacept and placebo arms (3% for both) 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 events/100 person-years), placebo group (0.63 events/100 person-years), and the SEER database (0.47 events/100 person-years) 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 duration of abatacept exposure. There were a disproportionate number of cases of lung cancer in subjects receiving abatacept (4 cases during the double-blind period and 4 cases during the open-label period) compared to none of the subjects receiving placebo. While the safety signal suggested by 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.
- The frequency of any individual tumor type should be interpreted with caution given the low event rate.
- An increased risk of lung cancer has been observed in patients with RA in observational databases.
- 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. Malignancy rates in other countries may differ, especially in countries with different rates of smoking. 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 RA observational cohorts.

1.3.4 Dosing Regimen and Administration

The proposed dose of abatacept is a tiered-dose regimen whereby patients will receive approximately 10 mg/kg by intravenous infusion over 30 minutes. This dosing 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, and appears to be adequate regarding the safety and efficacy of abatacept. The infusion should be discontinued if there are any signs or symptoms suggestive of a hypersensitivity reaction. These symptoms include urticaria, dizziness, fever, rash, rigors, pruritis, nausea, flushing, hypotension, dyspnea, and chest pain.

1.3.5 Drug-Drug Interactions

Subjects treated with abatacept with concomitant biologic RA therapy (64%) reported infections more frequently (64%) than subjects receiving placebo and a biologic RA therapy (43%), as well as serious infections (4 % vs. 2%, respectively). Given that there are insufficient data to support use of abatacept in combination with biologic DMARDs, this reviewer recommends that the label not recommend use of this combination until there is adequate supporting data.

1.3.6 Special Populations

A higher proportion of subjects with COPD who received abatacept reported a SAE compared to subjects with COPD receiving placebo (27% vs. 6%). The safety and efficacy of abatacept have not been adequately studied in patients with renal or hepatic insufficiency, of the subjects <18 years of age. There is very limited data of the effects of abatacept during pregnancy and/or lactation, and consequently, this reviewer would recommend that abatacept be used in pregnancy only if clearly needed.

2 INTRODUCTION AND BACKGROUND

RA is a chronic systemic inflammatory disease that primarily affects diarthrodial joints but frequently involves other organs as well. Approximately 1% of the general population is affected worldwide and although RA may occur at any age, the peak incidence of onset is usually between the 4th and 6th decades with females being 2-3 times more likely affected than males. The etiology of RA is unknown but there clearly appears to be a combination of both genetic and environmental factors that allow for the onset and progression of the disease. Evidence suggests that a major portion of the pathogenesis of RA is mediated by antigen-driven T cells and macrophages which produce proinflammatory cytokines including IL-1 and tumor necrosis factor-α (TNFα). This process contributes to osteoclast activation and proliferation of synoviocytes surrounding the joint that can ultimately expand and resorb cartilage and bone and present radiographically as erosions.

The initial clinical presentation of RA can be extremely variable but the majority of patients develop symmetrical polyarticular pain and/or stiffness of the proximal interphalangeal (PIP), metacarpophalangeal (MCP), wrist, shoulder, knee, ankle, and metatarsophalangeal (MTP) joints over the course of weeks to months which then develop into frank synovitis and joint swelling. As the disease progresses most patients develop joint deformities caused by bone erosions and tendon/ligament damage that limit physical function resulting in deformity, early disability, and even death.

Diagnosis of RA, especially for inclusion in clinical trials, has relied on the 1987 revised American Rheumatism Association criteria. Using these criteria, a patient is said to have RA if he or she has satisfied at least 4 of the following 7 criteria:

1. **Morning Stiffness** lasting > 1 hour before maximal improvement.
2. **Arthritis of ≥3 joints** having soft tissue swelling or fluid (not bony overgrowth alone) observed by a physician; the 14 possible joint areas are right or left proximal interphalangeal (PIP) joints, metacarpophalangeal (MCP) joints, wrist, elbow, knee, ankle, and metatarsophalangeal (MPT) joints.
3. **Arthritis of hand joints** with ≥1 area swollen in a wrist, MCP or PIP joint.
4. **Symmetric arthritis** of the same joint areas on both sides of the body.
5. **Rheumatoid nodules.**
6. **Serum rheumatoid factor positive.**
7. **Radiographic changes** typical of RA on posteroanterior hand and wrist radiographs, which must include erosions or unequivocal bony decalcification localized to or most marked adjacent to the involved joints (osteoarthritis changes alone do not qualify).

Criteria 1 through 4 must have been present for at least 6 weeks. Patients with 2 clinical diagnoses are not excluded. Designation as classic, definite, or probable RA is not to be made.

2.1 Product Information

Abatacept (CTLA-4Ig) is a fully human, recombinant, soluble fusion protein comprised of the extracellular domain of human CTLA-4 and the hinge-CH2-CH3 domain fragment of the Fc domain of human IgG1.

Abatacept was initially prepared in a lyophilized form as a 50mg/vial lyophile (Process A) and subsequently a 200 mg/vial lyophile (Process B, C, and D) for the Phase I and II studies. The manufacturing process was further modified for the Phase III clinical program which included growth of cell lines in animal component-free medium (Process E). Process E is the formulation that will be marketed and will be manufactured at the same site where study drug for the Phase III studies was produced. Abatacept will be supplied as a sterile, white, preservative-free, lyophilized powder for parenteral administration. Following reconstitution with 10 mL of Sterile Water for Injection, USP, the solution of abatacept is clear, colorless to pale yellow, with a pH range of 7.0 to 8.0. 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 tiered-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 antirheumatic drugs (DMARDs), including TNF-blocking agents. The sponsor also proposes that abatacept may be used in combination with other non-biologic DMARDs.

2.2 Currently Available Treatment for Indications

Pharmacologic therapy for RA depends on the severity of disease and may include a combination of DMARDs, non-steroidal anti-inflammatory drugs (NSAIDs), and/or corticosteroids. While corticosteroids and NSAIDS are commonly used in the management of RA, they do not tend to alter the course of the disease as do the non-biologic and biologic RA DMARD therapies. Since abatacept is of the latter category, we will limit our discussion to the DMARDs that are available for treatment of RA. DMARD therapies for RA can be divided into 2 categories: non-biologic RA therapies; and biologic RA therapies, which include the currently FDA approved TNF-blockers (Enbrel®, Remicade®, and Humira®) and the IL-1 blocker, Kineret®.

2.2.1 Non-Biologic RA Therapies

The non-biologic RA therapies commonly used in the treatment of RA include methotrexate (MTX), sulfasalazine (SSZ), hydroxychloroquine (HCQ), and leflunomide. Less commonly utilized are azathioprine (AZA), D-penicillamine (D-Pen), gold salts, minocycline, and cyclosporine. These medications suppress immune function to varying

degrees and are used alone or in combination. Controlled clinical trials have demonstrated the clinical benefit of some of the non-biologic DMARDs (e.g., leflunomide) to improve the signs and symptoms of joint involvement, improve functional status and health-related quality of life, and inhibit structural damage as evidenced by decreased progression of erosions on radiographs. Which particular drug(s) are used depends on the physician and the needs of the individual patient but includes relative efficacy, convenience of administration, cost of the medication and monitoring, frequency of monitoring for adverse events, and the toxicity profile of the drug. Many rheumatologists choose MTX as the initial drug because of its favorable risk-benefit ratio.

2.2.2 Biologic RA Therapies

The FDA approved biologic RA therapies include three TNF-blocking drugs and one IL-1 blocking drug. The TNF-blockers are generally used in subjects with moderate to severe RA who have failed non-biologic RA therapies; however, Enbrel® in combination with MTX or alone and Remicade® in combination with MTX has been approved to be used as initial therapy in this population as well. Controlled trials have demonstrated TNF-blocking drugs with concomitant MTX to be superior to MTX alone as measured by a greater proportion of subjects demonstrating improved signs and symptoms, improved physical function, and inhibition of structural damage. The TNF-blockers demonstrate a profound effect on the inhibition of structural damage with minimal progression of erosions over the course of at least 1 year. The IL-1-blocking agent in combination with MTX also demonstrates improvements in signs and symptoms, improved physical function, and slowing of progression of structural damage. The major concerns with the biologic RA therapies are the adverse events (e.g., infections, possible increased rate of lymphoma) and cost of therapy. Despite the improved efficacy observed with the biologic RA therapies, a significant minority of subjects does not respond. Thus, abatacept provides a possible alternative to subjects with an inadequate response to currently approved biologic RA therapies and this is the reason that the sponsor was granted priority review.

2.3 Availability of Proposed Active Ingredient in the United States

Abatacept is a new molecular entity that is not currently marketed in the United States

2.4 Important Issues With Pharmacologically Related Products

Currently, no pharmacologically-related products are marketed. Accordingly, it is not possible to draw upon experience from pharmacologically related products.

Abatacept's proposed mechanism of action is via inhibition of T-cell activation; therefore, safety concerns include the potential for increased risk of infections and/or malignancy. Furthermore, abatacept is a biologic product and consequently immunogenicity is a concern. Safety issues of infection, malignancy, and immunogenicity are discussed in Section 7 of this review.

2.5 Presubmission Regulatory Activity

2.5.1 Special Protocol Assessment

The Agency granted the sponsor a Special Protocol Assessment for study IM101029 as the study was expected to provide information to determine whether abatacept is efficacious in subjects who have had an inadequate response to TNF-blocking agents. Subsequently, the Agency indicated that inclusion of subjects who had failed adalimumab (Humira®) therapy would not be allowed under the terms of the existing Special Protocol Assessment but that this would not limit the scope of the target indication. The 2 parties also agreed that no more than 2/3 of the subjects would be enrolled in either the current anti-TNF user or the prior anti-TNF user group.

2.5.2 Fast Track Designation

The Agency granted the sponsor Fast Track when the sponsor agreed to extend study IM101029 to a total of 2 years in order to obtain data on improvement in physical function, thus having efficacy data for an important aspect of RA in subjects who had had an inadequate response to TNF-blocking drugs. The data are analyzed in this review.

2.5.3 Core Statistical Analysis Plan

The sponsor submitted a core statistical analysis plan with prespecified endpoints, data imputation methods, and analysis methods that would be used to conduct the statistical analyses of the Phase III studies.

2.5.4 Pharmacokinetic (PK) and Pharmacodynamic (PD) Program

The sponsor discussed its PK and PD program with the agency, which agreed that the planned analyses should be sufficient to support the target labeling. An amendment to this agreement was agreed to by both parties after technical issues with an assay were discovered.

2.5.5 Other Issues for Filing

The FDA and the sponsor agreed on the properties of the radiograph review tool, the format of theelectronic submission, the cut-off dates for safety data, the types of CRFs to be submitted. At a separate meeting the agency confirmed that there were sufficient data to file a BLA.

2.6 Other Relevant Background Information

Neither abatacept nor any other selective T-cell co-stimulation modulators are currently marketed anywhere in the world.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

The CMC review concludes that the data submitted in this application support the conclusion that the manufacture of abatacept is well controlled, and leads to a product that is pure and potent. The product is free from endogenous or adventitious infectious agents in a way that meets or exceeds the parameters recommended by FDA. The conditions used in manufacturing have been validated, and a consistent product is produced from different production runs. Animal Pharmacology/Toxicology. See the CMC review by Dr. Joy Williams

3.2 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. There were no unresolved toxicology issues. See the non-clinical pharmacology/toxicology review by Dr. Hanan Ghantous.

3.3 Diagnostic Imaging

171 of 586 total subject joint radiographs (29%) from study IM101102 were reviewed for the quality and completeness of the images. The 171 images were specifically chosen by the clinical and imaging reviewers.

Imaging readers were able to validate the reading score of the independent reading scores for all of the patients queried. The cited minor protocol violations and artifacts including 1 case of inconsistent reading score did not affect the evaluation of the radiographic data set for efficacy. The submitted radiographic database supports the approval of abatacept for the proposed indication – use 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. See the diagnostic imaging review by Dr.Hsien Ju.

3.4 Biostatistics

The Biostatistic review confirmed the results of the primary and major secondary endpoints. See the Biostatistics review by Dr. Kyung Lee.

4 INTEGRITY

4.1 Sources of Clinical Data

This review is based on data from clinical trials conducted by the sponsor, Bristol-Myers-Squibb Company.

Significant Submission(s) Reviewed	Document Date
STN 125118/0.001	20-Dec-2004
STN 125118/0.002	02-Feb-2005
STN 125118/0.004	25-Mar-2005
STN 125118/0.005	31-Mar-2005
STN 125118/0.006	01-Apr-2005
STN 125118/0.007	12-May-2005
STN 125118/0.008	12-May-2005
STN 125118/0.009	10-June-2005

4.2 Tables of Clinical Studies

Table 1 summarizes the completed, double-blind RA clinical trials of abatacept that form the primary basis for this review. Studies IM101100, IM101101, IM101102, IM101029, and IM101031 also have uncontrolled, open-labeled studies currently ongoing.

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
				10mg/kg/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.

4.3 Review Strategy

The primary focus of the efficacy review is the 3 RA clinical studies IM101100, IM101102, and IM101029, with supporting evidence of efficacy provided by studies IM1011031 and IM103002. Study IM101101 tested the combination of abatacept 2 mg/kg and etanercept 25 mg BIW but did not reach statistical significance on the primary efficacy endpoint. Although the trial is discussed, the efficacy data were not considered relevant to the overall conclusion regarding abatacept's efficacy since the dose of abatacept used was 5-fold less than the proposed dose and it was used in combination with etanercept.

The principal studies reviewed are large randomized, placebo-controlled, double-blind studies of the efficacy of abatacept in the proposed target population. Studies IM101102, IM101029, and IM101031 administered abatacept using the proposed tiered-dose/subjects' weight recommended dose, which approximates 10 mg/kg. Because they were conducted earlier in the clinical development of abatacept, studies IM101100 and IM103002 used weight-based dosing (mg/kg) of abatacept. Each of the studies was adequately powered and had appropriate pre-specified primary endpoints from which conclusions could be drawn. The collective data from individual trials was ultimately considered as a whole to assess whether the sponsor's proposed indications and claims are substantiated by the data.

The safety review is based primarily on 5 of the RA studies: IM101100, IM101101, IM101102, IM101029, and IM010031. These 5 studies provided an adequate amount of drug exposure for evaluation of the safety of abatacept in subjects with RA. In addition to evaluating the data for safety signals, deaths, AEs, and SAEs, special attention was focused on the incidence of infections, opportunistic infections, and malignancies given abatacept's immunosuppressant mechanism of action. Study IM103002, which evaluated abatacept monotherapy, is discussed separately.

4.4 Data Quality and Integrity

In general, the data quality and integrity of the studies were good. The amount of missing data was small and did not interfere with reaching conclusions on safety and efficacy. Issues regarding data quality and integrity of the studies are described below.

A total of 32 subjects in studies IM101102, IM101029, and IM101031 were treated at sites under the supervision of [redacted] for which integrity issues were raised pertaining to entry criteria, source documents, incomplete CRFs, AE reporting, and staff training. All subject data were excluded for efficacy analyses but were included for all safety analyses.

In study IM101029, 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 anti-TNF 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.

At the time of start-up for studies IM101031 and IM101102 printed CRFs for the VAS and the disability or fatigue index of the HAQ were not yet available in the local language for some countries. The final translated electronic forms were printed on local site printers and copied for use by the subjects; however, it was discovered that the VAS lines for subjects' assessment of pain and global assessment of disease activity were occasionally reduced from the standard 100-mm length and in some instances, the length was increased. The degree of line length reduction/increase was variable depending on the printer and copier used. The CRF originals of all suspect CRF pages were retrieved from archive storage and the line was re-measured. The baseline distance was normalized to a 100-mm scale to account for the difference in overall line length, and a correction factor was used so that the baseline versus on-treatment comparison correctly reflected the subject's pain assessment. This correction was applied prior to database lock and unblinding, with the sole intent of identifying and correcting all affected forms in an unbiased manner.

In study IM101031 subjects were suppose to be randomized to abatacept or placebo in a 3:1 ratio with the protocol estimating that 1000 patients randomized to abatacept group would allow detection of at least 1 case of an uncommon (> 0.2% incidence) AE with 87% probability. However, due to an error, the IVRS randomized subjects in a 2:1 ratio, resulting in 948 subjects to the abatacept group instead of the proposed 1000 subjects. Due to the double-blind nature of the study, the error was not discovered until the database was unlocked and the results were unblinded. Though the chance of a subject receiving abatacept decreased from the specified 3/4 to 2/3, the study remained adequately well controlled and blinded, preserving the integrity of the study.

The division of Scientific Investigations is currently conducting a Bioresearch Monitoring Inspection (BIMO) of 3 study sites.

4.5 Compliance with Good Clinical Practices

All studies were conducted in accordance with the ethical principles in the Declaration of Helsinki and Good Clinical Practice. The studies were conducted in compliance with the protocols. Informed consent, protocol, amendments, and administrative letters form for each study received Institutional Review Board/Independent Ethics Committee approval prior to implementation.

4.6 Financial Disclosures

The sponsor has adequately disclosed financial arrangements with clinical investigators as recommended in the FDA guidance for industry (Financial Disclosure by Clinical Investigations, CDER, March, 20, 2001). There were 2 investigators identified with potential conflict of interest.

Dr. [ ] was a principal investigator in study [ ], a study primarily designed to assess safety. Dr. [ ] spouse is a Bristol-Myers Squibb employee and therefore via — compensation and retirement account(s), has a significant equity interest in Bristol-Myers Squibb. Dr. [ ] enrolled — the — subjects in the trial translating to [ ] of subjects. The overall contribution of subjects enrolled by Dr. [ ] did not make a significant contribution to the demonstration of efficacy for abatacept.

Potential for bias was further minimized by using a double blind, placebo-controlled study design. Additionally, investigational sites are routinely monitored following established procedures and guidelines that are designed to detect questionable data.

Dr. [ ] entered into a contract with Bristol-Myers Squibb to provide consultation regarding protocol development and study conduct that will exceed $25,000. Dr. [ ] is one of six [ ] radiologists performing evaluations for the [ ] study and one of five [ ] radiologists performing evaluations for the [ ] studies. All radiographic evaluations were performed with the readers blinded to subject treatment and blinded to the sequence of the radiographs. Potential for bias was further minimized by using a double blind, placebo-controlled study design. Additionally, investigational sites are routinely monitored following established procedures and guidelines that are designed to detect questionable data.

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5 CLINICAL PHARMACOLOGY

Abatacept interferes with T-cell co-stimulation by binding to CD80 and CD86 (also known as B7.1 and B7.2, respectively) on antigen presenting cells and preventing their interaction with CD28 on 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. The combination of the CD28 activation and the T-cell-antigen-MHC complex results in the T-cell becoming fully activated which then in turn activates the antigen presenting cell which can then mediate inflammation via the production of cytokines (e.g., TNFα or IL-1 via macrophages) or antibodies via B-cells.

CTLA-4 is an endogenous 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 either CD80 or CD86. Consequently, CTLA-4 is able to "out-compete" CD28 for binding to CD80 or CD86 and thereby inhibits further T-cell activation. CTLA-4 cross-linking also generates a negative signal in T-cells, which also inhibits T-cell activation.

Abatacept contains the extracellular domain of human CTLA-4. It derives its immunosuppressant activity by binding to CD80/86 on antigen presenting cells thereby inhibiting binding to CD28 on T-cell surfaces and preventing T-cell activation. Therefore, abatacept decreases antigen presenting cell-mediated inflammation by decreasing T-cell activity, which in and of itself has been implicated in the pathogenesis of RA.

5.1 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.

For additional discussion of abatacept pharmacokinetics see Dr. Anil Rajpal's Clinical Pharmacology review of this application.

5.2 Pharmacodynamics

In clinical trials with abatacept using the tiered-dosing schedule approximating 10 mg/kg, inhibition of T-cell activation, decreases in products of macrophages, fibroblast-like synoviocytes, and B cells, and reductions in acute phase reactants of inflammation were observed. Decreases were seen in: serum levels of soluble IL-2 receptor, a marker of T-cell activation; serum IL-6, a product of activated macrophages and fibroblast-like synoviocytes; RF, and CRP. In addition, serum levels of matrix metalloproteinase-3, which produces cartilage destruction and tissue remodeling, were decreased. Reductions in serum TNF were also observed. These changes are consistent with the mechanism of action of this selective co-stimulation modulator.

For additional discussion of abatacept pharmacokinetics see Dr. Anil Rajpal's Clinical Pharmacology review of this application.

5.3 Exposure-Response Relationships

The sponsor submitted an analysis of PK/PD relationship based on data from subjects dosed in phase 2 at 2 mg/kg (N=128) and 10 mg/kg (N=77) as well as from patients dosed at 10 mg/kg in phase 3. The analysis included data from the phase 2 studies IM101100 and IM101101 and from the phase 3 studies IM101102 and IM101029. As shown in Figure 1, when the data from the 2

mg/kg and 10 mg/kg doses were included there was a dose-response relationship between trough serum levels of abatacept and the likelihood of clinical response. The nominal p value was less than 0.05 (p=0.0125) for this analysis. The relationship was not linear. Rather, at higher trough levels there was a lesser increment in clinical response for a given increase in trough serum level. When the analysis was restricted to patients receiving the proposed dose of 10 mg/kg (Figure 2) there was a trend toward dose-response relationship, although the curve is flatter. For this analysis the nominal p value exceeded 0.05 (p=0.1584). How much of an effect would variation in trough serum levels be expected to have among patients receiving the 10 mg/kg dose? In the phase 2 study, IM101100, the range of trough serum concentrations was from 22.0 to 28.7 mcg/ml. In this range the exposure-response model would suggest only a modest effect of serum levels on clinical responses.

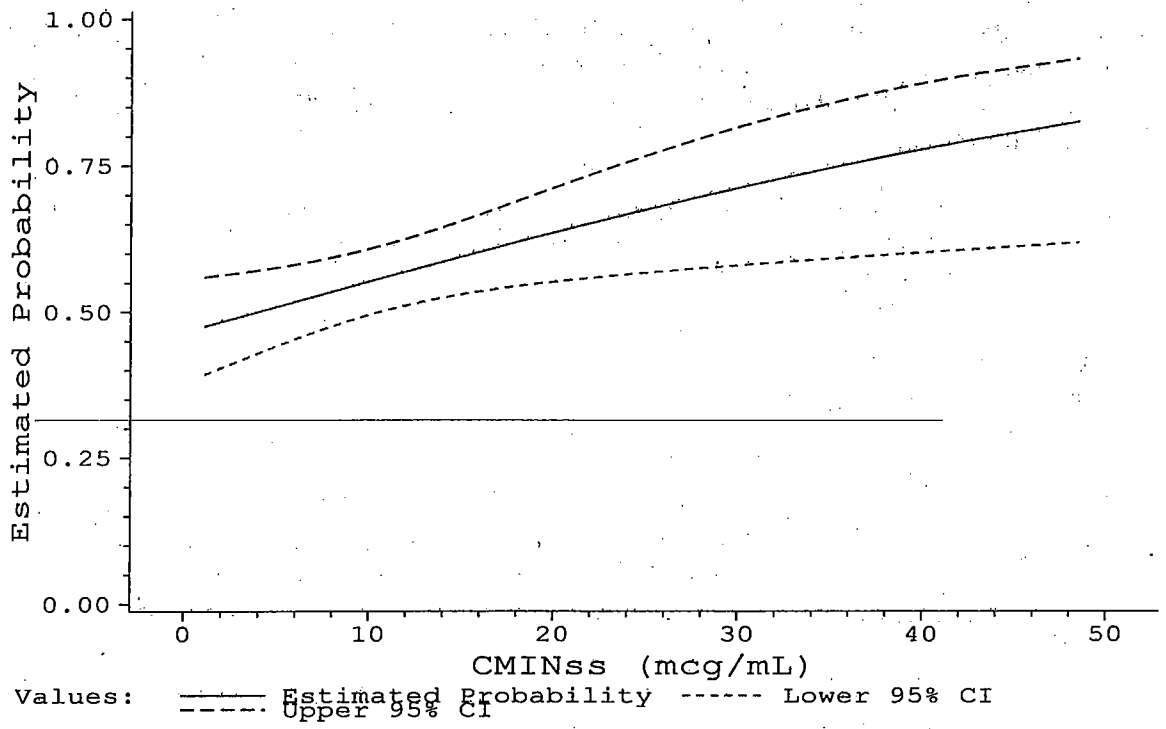


Figure 1: Estimated probability of achieving ACR20 at 6 mo. Vs. predicted steady-state Cmin concentrations (data from 2 and 10 mg/kg dosing)

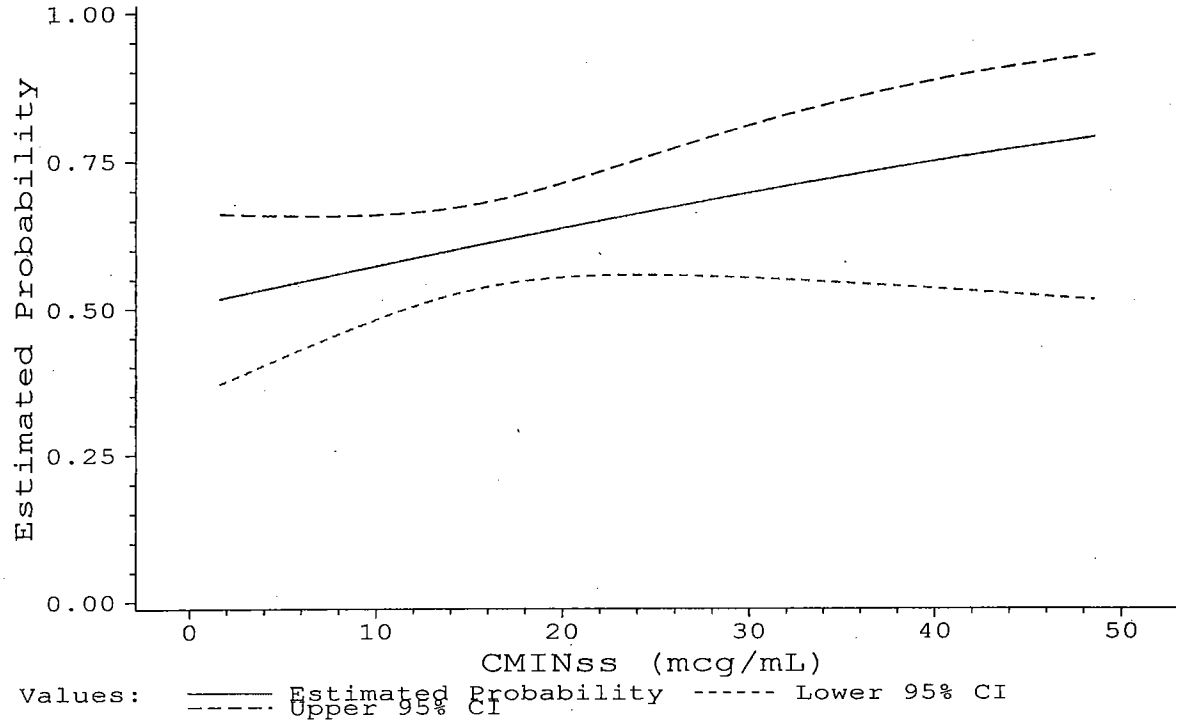


Figure 2: : Estimated probability of achieving ACR20 at 6 mo. Vs. predicted steady-state Cmin concentrations (data from 10 mg/kg dose only)

6 INTEGRATED REVIEW OF EFFICACY

6.1 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.

6.1.1 Methods

There were a total of 6 well-designed and conducted, double-blind, randomized, placebo-controlled studies (see Section 4) 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 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%).

6.1.2 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 ≥ 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.

6.1.3 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, respectively, 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) occurred 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.

6.1.3.1 Study 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.

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%.

6.1.3.2 Study IM101102

Study IM101102 was a 12-month, randomized (2:1), double blind, placebo-controlled, parallel-arm, Phase-3 study evaluating ababatacept + 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.

Subjects had assessments for safety and disease activity on Days 1, 15, 29, 57, 85, 113, 145, 169, 197, 225, 253, 281, 309, and 337. Independent blinded joint assessors determined joint counts and scores. ACR core data set consisted 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, ACR 50, and ACR 70 definitions of response correspond to a 20%, 50%, and 70% improvement, respectively, over baseline swollen and tender joints and in 3/5 of the remaining core data set measures. 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 $\geq$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.

6.1.3.3 Study 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. ACR core data set consisted 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, ACR 50, and ACR 70 definitions of response correspond to a 20%, 50%, and 70% improvement, respectively, over baseline swollen and tender joints and in 3/5 of the remaining core data set measures.

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%.

6.1.3.4 Study 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.

6.1.3.5 Study 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, 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.

6.1.3.6 Study IM103002

Study IM103002 was a 6-month, multicenter, randomized, double-blind, placebo-controlled, parallel dosing, Phase-2 study evaluating 3 different doses of ababatacept monotherapy (0.5 mg/kg, 2 mg/kg, and 10 mg/kg) and 3 different doses of BMS-224818 (a closely related molecule with the same mechanism of action as abatacept) compared with placebo in subjects with active rheumatoid arthritis. The study randomized 216 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 etantercept
- 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 8 treatment arms with study drug administered by IV infusion at Day 1, 15, 29 and 57:

Abatacept

- 0.5 mg/kg (n=26)
- 2 mg/kg (n=32)
- 10 mg/kg (n-32)

BMS-224818

- 0.5 mg/kg (n=32)
- 2 mg/kg (n=29)
- 10 mg/kg (n-31)

Placebo (n=32)

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.

6.1.4 Efficacy Findings

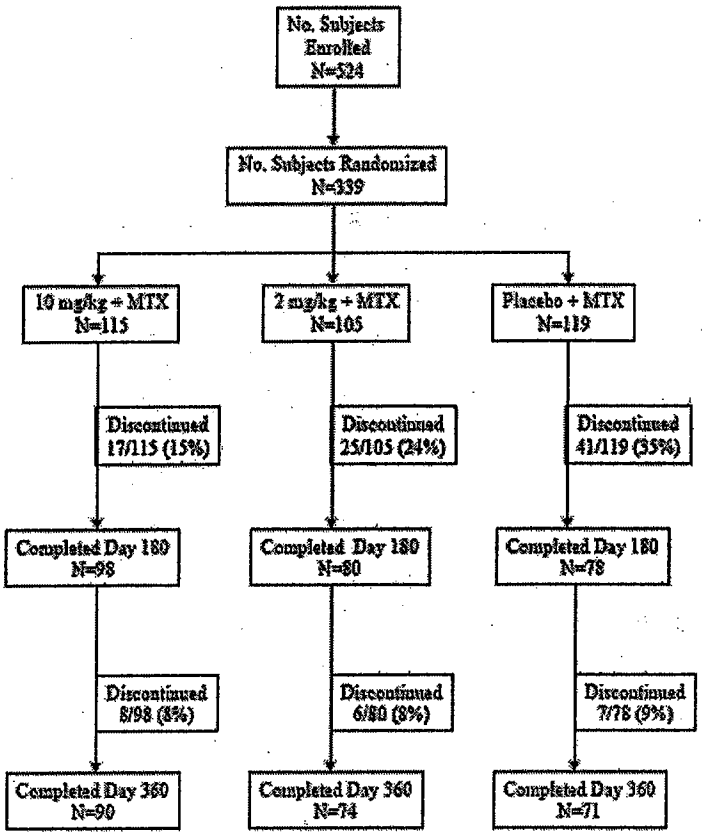
The efficacy review is focused on studies IM101100, IM101102, and IM101029, with supportive data from study IM103002 and IM101101. Study IM101031 was primarily conducted for analysis of safety with a minor secondary efficacy outcome of improvement as assessed by HAQ score, which was supportive of the 3 principal efficacy studies.

6.1.4.1 Study IM101100

6.1.4.1.1 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 3). The most frequent reason for not being randomized was subjects not meeting inclusion/exclusion criteria.

Figure 3. Subject Disposition for Study IM101100



During study Days 1-180, 12 subjects had protocol violations that could potentially be clinically important.

3 subjects from the abatacept 10 mg/kg + MTX arm:

- 2 subjects with Day 15 visit> 7days from the ideal window or visits after Day15 >14 days from ideal window
- 1 subject with >1 intra-articular/intra-muscular steroid injection between Days 1-180

5 subjects from the abatacept 2 mg/kg + MTX arm:

- 2 subjects with Day 15 visit> 7days from the ideal window or visits after Day15 >14 days from ideal window
- 2 subjects did not receive stable dose of oral corticosteroids within 14 days of Day 1 or within 14 days of ≥2 assessments
- 1 subject never received MTX

4 subjects from the placebo + MTX arm

- 2 subjects with Day 15 visit> 7days from the ideal window or visits after Day15 >14 days from ideal window
- 1 subject with >1 intra-articular/intra-muscular steroid injection between Days 1-180
- 1 subject did not receive stable dose of oral corticosteroids within 14 days of Day 1 or within 14 days of ≥2 assessments

The total number of subjects from each group with protocol violations was small and relatively balanced between treatments arms. Consequently these subjects were included in all analyses and are not expected to adversely affect the conclusions drawn from the study.

During Days 181 to 360, 17 subjects had protocol violations (note some subjects may have had >1 protocol violation):

7 subjects from the abatacept 10 mg/kg + MTX arm:

- 5 subjects with visit outside allowed window (>7 days from ideal window)
- 7 subjects with x-rays taken outside of allowed window

5 subjects from the abatacept 2 mg/kg + MTX arm:

- 4 subjects with visit outside allowed window (>7 days from ideal window)
- 4 subjects with x-rays taken outside of allowed window
- 1 subject missed >1 study infusion

5 subjects from the placebo + MTX arm

- 3 subjects with visit outside allowed window (>7 days from ideal window)
- 2 subjects with x-rays taken outside of allowed window
- 1 subject received a DMARD other than MTX, hydroxychloroquine, sulfasalazine, gold, or azathioprine between Days 181-360

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
AE	3 (3%)	7 (7%)	9 (8%)
LOE	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.

A total of 92% of abatacept 10 mg/kg + MTX subjects, 91% of abatacept 2 mg/kg + MTX subjects, and 96% of placebo + MTX subjects received all study infusions. The mean duration of exposure for the abatacept 10 mg/kg group was 325 days, the abatacept 2 mg/kg group was 308 days, and the placebo group was 277 days reflecting the respective time subjects from each group remained in the study (Table 3).

Table 3. Extent of Exposure

Days	Abatacept 10 mg/kg + MTX (n=115)	Abatacept 2 mg/kg + MTX (n=105)	Placebo + MTX (n=119)
1-90	4 (4%)	6 (6%)	14 (12%)
91-180	12 (10%)	13 (12%)	23 (19%)
181-270	1 (1%)	6 (6%)	5 (4%)
271-360	59 (51%)	40 (38%)	39 (33%)
>360	39 (34%)	40 (38%)	38 (32%)
Mean Duration of Exposure	328	308	277

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 analaysis for inhibition of radiographic progression was assessed.

6.1.4.1.2 Study Demographics of IM101100

The baseline characteristics were generally similar across all 3 arms of the study and are shown in Table 4. The majority of subjects were white and female, with a mean age of 55 years, and a mean weight of 79 kg.

Table 4. Baseline Demographic Characteristics

	Abatacept 10 mg/kg + MTX (n=115)	Abatacept 2 mg/kg + MTX (n=105)	Placebo + MTX (n=419)
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 5.
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.

Table 5. 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 6.

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Table 6. Medication Use Prior to Enrollment

	Abatacept 10 mg/kg + MTX (n=115)	Abatacept 2mg/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 7).

Table 7. 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 8) with only a minority of subjects having an additional DMARD added to their therapy.

Table 8. 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%)
Azathioprine	1 (1%)	0	0
Hydroxychloroquine	0	0	1 (1%)
Leflunomide	0	0	1 (1%)
Quinine	1 (1%)	0	0

6.1.4.1.3 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 9). 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 9. 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.

6.1.4.1.4 Secondary Analyses of Study IM101100

6.1.4.1.4.1 Improvement of Signs and Symptoms

Table 10 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 11).

Table 10. 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 11). 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 shwn).

Table 11. 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 12).

Table 12. 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 13).

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Table 13. % 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%

6.1.4.1.4.2 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.

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 subjects who 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 4 and Table 14).

Figure 4. Proportion of Subjects with Clinically Meaningful mHAQ Responses for Subjects Entering Open-Label Therapy; As-Observed Data

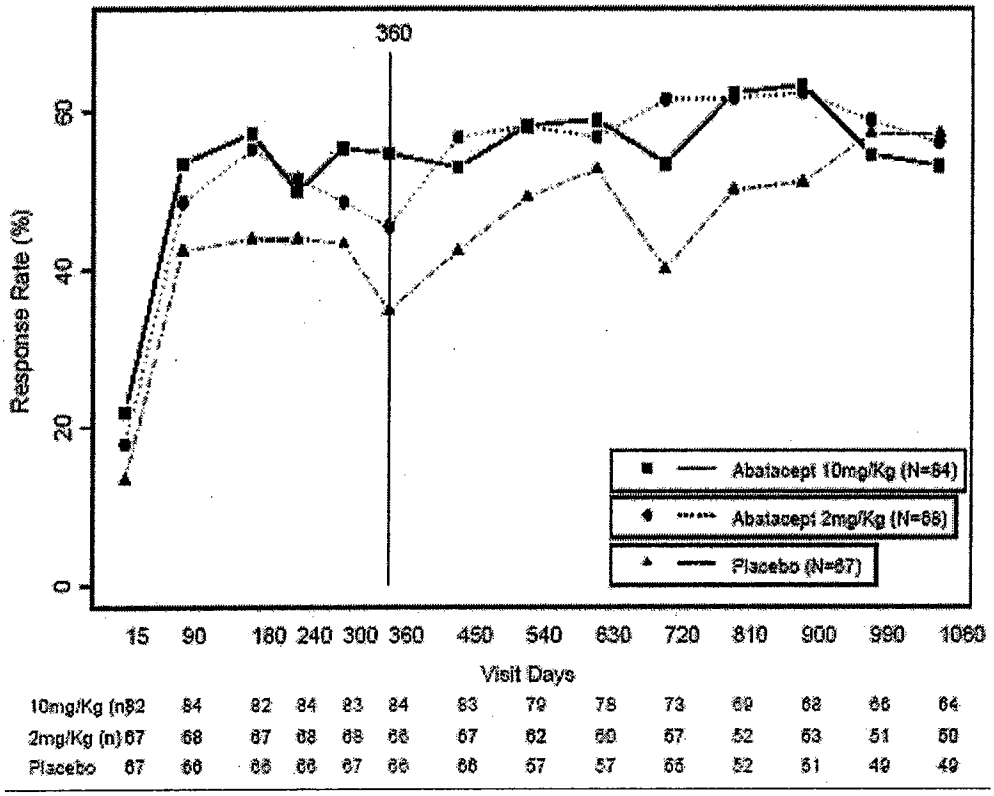


Table 14. Proportion of Subjects with Clinically Significant mHAQ (≥0.3u) Responses for Subjects Who Entered the Open-Label Period; As-Observed Data

	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 4 and Table 14). 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 4 and Table 14). 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.

6.1.4.1.4.3 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 15. 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

6.1.4.2 Study IM101102

6.1.4.2.1 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 5).

Site 39 enrolled 14 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 had protocol violations that could potentially be clinically important. These did not affect the conclusions of the study and were included in all analyses.

10 subjects from the abatacept + MTX arm:

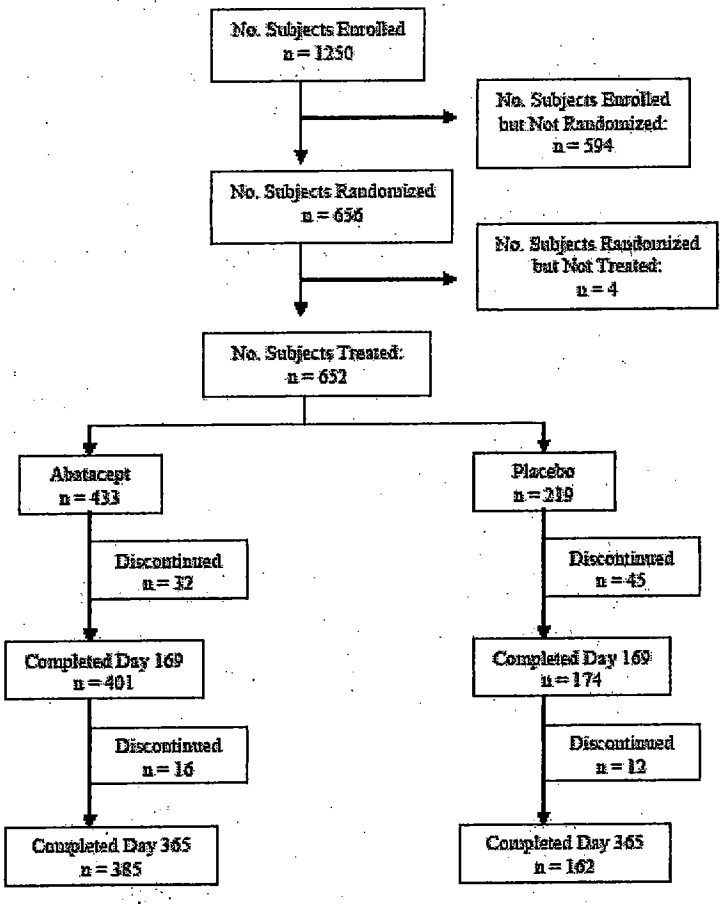
- 6 subjects with joint count at randomization: < 10 swollen joints and <12 tender joints
- 2 subjects with CRP<0.8 mg/dL
- 2 subjects received an intra-articular injection < 1 month prior to Day 169

8 subjects from the placebo + MTX arm

- 3 subjects with joint count at randomization: < 10 swollen joints and <12 tender joints
- 2 subjects received an intra-articular injection < 1month prior to Day 169
- 1 subject received >2 intra-articular injections prior to Day 169
- 1 subjects entered study with surgeries on >5 joints

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 5.

Figure 5. 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 16)

Table 16. Day 1-169: reasons for discontinuation

	Abatacept + MTX (n=433)	Placebo + MTX (n=219)
Number Discontinued	32 (7%)	45 (21%)
Death	0	0
AE	11 (3%)	3 (1%)
LOE	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 17.

Table 17. 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%)
AE	7 (2%)	1 (<1%)
LOE	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%)

The majority of subjects in each treatment group did not miss study drug infusions with approximately 85% of abatacept + MTX subjects and 89% of placebo + MTX subjects receiving all study infusions. Five subjects (1%) in the abatacept arm and 4 subjects (2%) in the placebo arm missed 2 non-consecutive infusions of study medication. No subject missed ≥3 infusions of study drug. Subjects received the same median (14) number of infusions for both treatment arms with a greater proportion of subjects in the abatacept group (75%) receiving ≥14 infusion compared with the placebo group (66%; Table 18). There were approximately 25% of subjects in the abatacept arm and approximately 33% of subjects in the placebo arm who did not receive all pre-specified infusions.

Table 18. Number of infusions by subject

	Abatacept + MTX (n=433)	Placebo + MTX (n=219)
Number of infusions		
≤3	9 (2%)	17 (8%)
4-7	20 (5%)	26 (12%)
8-13	80 (19%)	31 (14%)
≥14	324 (75%)	145 (66%)
Median infusion/subject	14	14

Table 19 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 19. 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%)

6.1.4.2.2 Study Demographics of Study IM101102

The baseline characteristics of the study subjects are shown in Table 20. 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 20. 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 21. 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 21. 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

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The use of DMARDs prior to enrollment and randomization were generally comparable in both treatment groups and are shown in Table 22. Similar numbers of subjects were taking corticosteroids and NSAIDs at baseline.

Table 22. 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 23). Doses of corticosteroids remained stable at approximately 5 mg day and were evenly balanced between arms.

Table 23. 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%)

6.1.4.2.3 Primary Analysis of Study IM101102

6.1.4.2.3.1 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 24). Missing data were imputed using non-responder imputation for the primary analysis.

Table 24. 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.

6.1.4.2.3.2 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 25). Missing data were imputed using non-responder imputation.

Table 25. 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.

6.1.4.2.3.3 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 26). This represents an approximately 45% reduction in erosions for subjects treated with abatacept + MTX.

Table 26. 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 27 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 27. 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 (0-102)	0.27 (0-130)

*Subjects without baseline radiographs were not included

6.1.4.2.4 Secondary Analyses of Study IM101102

6.1.4.2.4.1 Improvement of Signs and Symptoms

Table 28 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 28. 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 29). 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 29. 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 30). Additionally a greater percentage of subjects (6%) in the abatacept + MTX achieved an extended major clinical response, defined as maintenance of an ACR 70 response over a 9-month period, compared to subjects in the placebo + MTX arm (<1%; Table 13).

Table 30. 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 31).

Table 31. 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 32). These results were maintained through Day 365.

Table 32. 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 low disease activity (DAS ≤3.2)	82 (22%)	7 (4%)
Subjects in 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 low disease activity (DAS ≤3.2)	103 (28%)	7 (4%)
Subjects in remission (DAS <2.6)	65 (17%)	4 (2%)

*p<0.001

6.1.4.2.4.2 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 6). 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 33).

Table 33: 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

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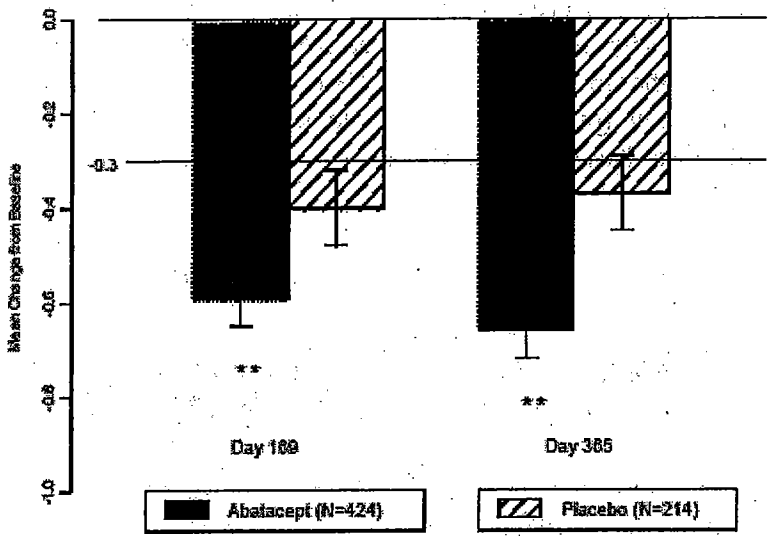
Figure 6. HAQ index: change from baseline



**p<0.001

6.1.4.2.4.3 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 34) of the Genant-modified Sharp score.

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Table 34. 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)	0.88u ± 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).

6.1.4.2.5 Subgroup Analysis of Study IM101102

6.1.4.2.5.1 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 35). 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 35. 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 index. Analysis of disease duration demonstrated a clinical benefit as assessed by ACR 20 in subjects receiving abatacept regardless of disease duration (Table 36). 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 36).

Table 36. 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%)

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6.1.4.2.5.2 Improvement of Physical Function

Responses for improvement in physical function at Day 365 as assessed by HAQ scores were analyzed in relation to baseline demographics. Subjects receiving abatacept + MTX demonstrated a greater improvement in physical function as assessed by HAQ compared to subjects receiving placebo + MTX regardless of age, sex, race, geographical region, and weight (Table 37). One exception appeared to be with Black subjects; however, the total number of subjects in each group is extremely small and makes interpretation of the data difficult, especially in light of the fact that Black subjects benefited from abatacept in terms of achieving an ACR 20 (Table 35) and inhibition of radiographic progression (Table 34).

Table 37. Subgroup analysis of HAQ responses by baseline demographics

	n	Abatacept + MTX	n	Placebo + MTX
Age (years)				
≤65	359	234 (65%)	188	76 (40%)
>65	65	36 (55%)	26	8 (31%)
Sex				
Female	331	210 (63%)	176	71 (40%)
Male	93	60 (65%)	38	13 (34%)
Race				
White	370	241 (65%)	189	72 (38%)
Black	10	3 (30%)	4	3 (75%)
Asian	18	10 (56%)	10	4 (40%)
Other	26	16 (62%)	11	5 (46%)
Geographical Region				
North America	84	42 (50%)	41	7 (17%)
South America	173	127 (73%)	93	48 (52%)
Europe	143	89 (62%)	67	22 (33%)
ROW	24	12 (50%)	13	7 (54%)
Body Weight (kg)				
<60	107	65 (61%)	57	21 (37%)
60-100	288	193 (67%)	145	62 (43%)
>100	29	12 (41%)	12	1 (8%)

Subjects receiving abatacept + MTX also demonstrated a greater improvement in physical function as assessed by HAQ compared to subjects receiving placebo + MTX regardless of disease duration, swollen and tender joints, CRP, Genant-modified Sharp score, and baseline HAQ (Table 38).

Table 38. Subgroup analysis of HAQ responses by baseline disease characteristics

	n	Abatacept + MTX	n	Placebo + MTX
Disease Duration (years)				
≤2	95	67 (71%)	41	16 (39%)
>2 to ≤5	91	61 (67%)	46	22 (48%)
>5 to ≤10	105	65 (62%)	54	18 (33%)
>10	133	77 (58%)	73	28 (38%)
# Swollen Joints				
Upper Quartile	91	62 (68%)	52	21 (40%)
Other Quartiles	333	208 (63%)	162	63 (39%)
# Tender Joints				
Upper Quartile	92	65 (71%)	56	25 (45%)
Other Quartiles	332	205 (62%)	158	59 (37%)
CRP				
Upper Quartile	112	78 (70%)	46	23 (45%)
Other Quartiles	312	192 (62%)	168	61 (36%)
Genant-modified Sharp Score				
Upper Quartile	104	60 (58%)	48	20 (42%)
Other Quartiles	302	198 (66%)	156	60 (39%)
HAQ				
Upper Quartile	93	70 (75%)	38	17 (45%)
Other Quartiles	329	200 (61%)	176	67 (38%)

6.1.4.2.5.3 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 39). 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 36) and improvement in physical function (Table 38).

Table 39. 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 40).

Table 40. Subgroup analysis of total Genant-modified Sharp score by baseline disease activity

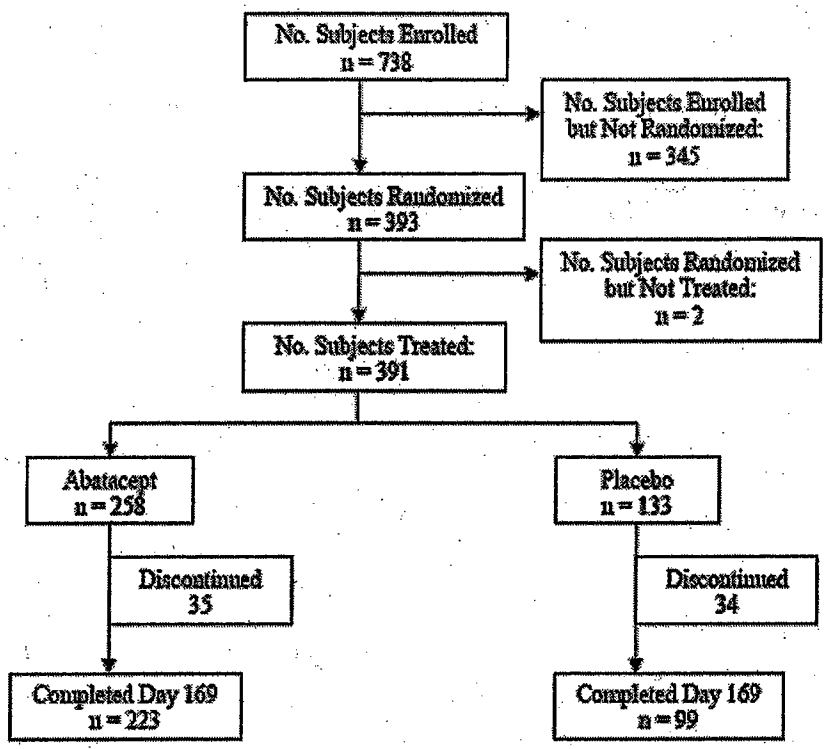
Mean Change from Baseline (SD)	n	Abatacept + MTX	n	Placebo + MTX
Disease Duration (years)				
≤2	91	1.13 (2.88)	35	4.03 (8.2)
>2 to ≤5	83	2.05 (4.36)	42	2.99 (5.72)
>5 to ≤10	99	0.91 (2.77)	51	1.49 (2.96)
>10	118	0.93 (2.11)	67	1.64 (3.22)
# Swollen Joints				
Upper Quartile	85	1.38 (4.14)	48	3.37 (5.76)
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)

6.1.4.3 Study IM101029

6.1.4.3.1 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 7**).

Figure 7. Study Disposition for IM101029



Site 95 enrolled 2 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.

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During the double-blind period, 20 subjects had protocol violations that could potentially be clinically important.

15 subjects (1 subject had 2 protocol violations) from the abatacept arm:

- 8 subjects with joint count at randomiztion: < 10 swollen joints and <12 tender joints
- 1 subject with CRP<1 mg/dL
- 1 subject with ACR functional class IV
- 1 subject with addition of another DMARD prior to Day 169

5 subjects from the placebo arm

- 3 subjects with joint count at randomiztion: < 10 swollen joints and <12 tender joints
- 2 subjects received TNF blocker drug for <3 months or did not fail TNF blocker therapy

Since <10% of subjects had significant protocol violations a "per-protocol" data set was not performed. These protocol violations 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 41). The higher rate of discontinuation in the placebo group was attributable to a higher rate of discontinuation due to lack of efficacy.

Table 41. Day 1-169: Reasons for Discontinuation

	Abatacept (n=258)	Placebo (n=133)
Number Discontinued	35 (14%)	34 (26%)
Death	0	0
AE	9 (4%)	5 (4%)
LOE	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%)

Approximately 89% of abatacept subjects and 93% of placebo subjects received all of their respective study infusions. There were 2 abatacept treated subjects (~1%) who missed 2 infusions of study medication and no subjects missed ≥3 infusions of study drug. Subjects received the same median (7) number of infusions for both treatment arms with a greater proportion of subjects in the abatacept group (93%) receiving ≥4 infusion compared with the placebo group (81%; Table 42). The mean duration of exposure for the abatacept group was 163 days compared to 146 days for the placebo group, consistent with higher frequency of discontinuations observed in the placebo group.

Table 42. Number of Infusions by Subject

	Abatacept (n=258)	Placebo (n=133)
Number of infusions		
≤3	18 (7%)	26 (20%)
4-7	240 (93%)	107 (81%)
Median infusion/subject	7	7

6.1.4.3.2 Study Demographics of IM101029

The baseline characteristics of the study subjects are shown in Table 43. 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 43. Baseline Demographic Characteristics

	Abatacept + MTX (n=258)	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 44. 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 44. Baseline Disease Characteristics

	Abatacept + MTX (n=258)	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 45).

Table 45. Duration of TNF blocker Use Prior to Randomization

	Abatacept (n=258)		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 46. Similar numbers of subjects were taking corticosteroids and NSAIDs at baseline.

Table 46. Previous RA Medication History

	Abatacept (n=258)	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.

6.1.4.3.3 Primary Analysis of Study IM101029

6.1.4.3.3.1 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 47). Missing data were imputed using non-responder imputation for the primary analysis.

Table 47. 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 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 were the same as the primary analysis with 50% of subjects in the abatacept arm achieving an ACR 20 compared to 20% of subjects in the placebo arm. The results of the worst-case scenario sensitivity analysis demonstrated that a greater proportion of subjects in the abatacept arm achieved an ACR 20 compared to the placebo arm (50% versus 45%, respectively). The results of the sensitivity analyses indicate that the favorable effect of abatacept on ACR 20 responses is unlikely to be attributed to bias due to missing data.

6.1.4.3.3.2 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 48).

Table 48. Proportion of Subjects with Clinically Meaningful HAQ Response at Day 169

	Abatacept (n=258)	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.

6.1.4.3.4 Secondary Analyses

6.1.4.3.4.1 Improvement of Signs and Symptoms

Table 49 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 continued to rise out to Day 141. Responses were maintained from 3 months out to 6 months.

Table 49. Number of Subjects Achieving an ACR 20 Response by Study Visit Day

	Abatacept (n=258)	Placebo (n=133)
Study Visit		
Day 15	45 (18%)*	7 (5%)
Day 29	84 (33%)**	25 (19%)
Day 57	118 (46%)*	32 (24%)
Day 85	118 (46%)*	24 (18%)
Day 113	126 (49%)*	31 (23%)
Day 141	141 (55%)*	26 (20%)
Day 169	129 (50%)*	26 (20%)

* p=0.001; **p=0.05

Additionally, a greater proportion of subjects receiving abatacept achieved an ACR 50 and ACR 70 compared to placebo-treated subjects at Day 169 (Table 50). 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 50. Number of subjects achieving an ACR 50 and ACR 70 at Day 169

	Abatacept (n=258)	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

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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 score (Table 51).

Table 51. Improvement from Baseline of Individual Components of ACR Criteria at Day169

	Abatacept (n=258)	Placebo (n=133)
Swollen Joints (66 total)		
Baseline Median	21	20
Day 169 Median	10	14
Tender Joints (68 total)		
Baseline Median	30	31
Day 169 Median	13	24
Subject Pain Assessment (VAS 100mm)		
Baseline Median	73	74
Day169 Median	43	64
Physical Function (HAQ Index)		
Baseline Median	1.88	2
Day 169 Median	1.38	1.75
Subject Global Assessment (VAS 100mm)		
Baseline Median	71	73
Day 169 Median	44	63
Physician Global Assessment (VAS 100mm)		
Baseline Median	71	69
Day 169 Median	32	54
CRP (mg/dL)		
Baseline Median	3.4	2.8
Day 169 Median	1.3	2.3

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 52).

Table 52. Mean Change from Baseline in DAS 28 at Day 169 (LOCF Analysis)

	Abatacept (n=258)	Placebo (n=133)
Baseline Mean	6.9	6.9
Day 169		
Post-Baseline Mean	4.9*	6.2
Subjects with improvement (DAS28 change ≥1.2)	129 (71%)	311 (32%)
Subjects with low disease activity (DAS ≤3.2)	30 (17%)	4 (4%)
Subjects in remission (DAS <2.6)	19 (10%)	1 (1%)

*p<0.001

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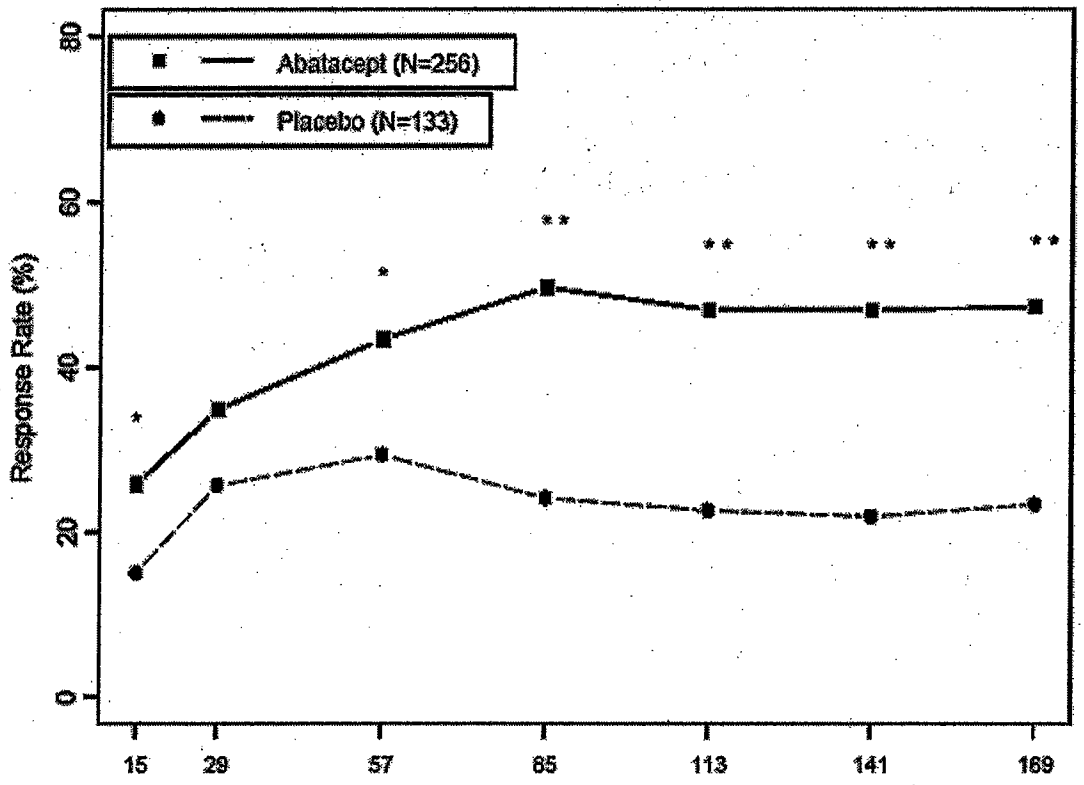
6.1.4.3.4.2 Improvement in Physical Function

A greater proportion of subjects in the abatacept arm achieved a clinically significant improvement (pre-specified as a change >0.3u) as compared to subjects at Days 15, 57, 85, 113, 141 and 169 (Figure 8).

Figure 8. HAQ Response Over Time



6.1.4.3.5 Subgroup Analyses

6.1.4.3.5.1 Improvement in Signs and Symptoms

In order to assess the generalizability of the study results ACR 20 responses at Day 169 were analyzed in relation to baseline demographics. Eighty-one percent of subjects were younger than 65 years of age. The 71 subjects at least 65 years old who received abatacept demonstrated an overall beneficial effect similar to younger subjects (Table 53). Greater clinical responses were seen in males and females receiving abatacept as compared to placebo. Analysis by previous type of TNF blocker use, race, geographical location, and body weight demonstrated that a greater proportion of subjects receiving abatacept achieved an ACR 20 compared to the subjects receiving placebo (Table 53).

Table 53. Subgroup Analysis of ACR 20 responses by Baseline Demographics

	n	Abatacept	n	Placebo
Previous TNF blocker use				
Etanercept	61	28 (40%)	43	8 (19%)
Infliximab	140	80 (57%)	68	14 (21%)
Etanercept + Infliximab	55	21 (38%)	22	4 (18%)
Age (years)				
≤65	205	101 (49%)	113	24 (21%)
>65	51	28 (55%)	20	2 (10%)
Sex				
Female	198	96 (64%)	106	23 (22%)
Male	58	33 (51%)	27	3 (11%)
Race				
White	246	126 (51%)	124	24 (19%)
Geographical Region				
North America	187	95 (51%)	99	19 (19%)
Europe	69	34 (49%)	34	7 (21%)
Body Weight (kg)				
<60	44	19 (43%)	24	3 (13%)
60-100	177	91 (51%)	89	19 (21%)
>100	34	18 (53%)	19	4 (21%)

A variety of baseline disease-activity characteristics could influence the likelihood of clinical responses including disease duration, number of swollen and tender joints, CRP, and level of disability as measured by the HAQ index. Clinical benefit as assessed by ACR 20 was observed in subjects receiving abatacept regardless of disease duration (Table 54). 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, level of CRP, or level of physical function (Table 54).

Table 54. Subgroup Analysis of ACR 20 Responses by Baseline Disease Characteristics

	n	Abatacept	n	Placebo
Disease Duration (years)				
≤2	31	11 (36%)	16	3 (19%)
>2 to ≤5	31	18 (58%)	25	5 (20%)
>5 to ≤10	58	34 (59%)	25	5 (20%)
>10	136	66 (49%)	66	13 (20%)
# Swollen Joints				
Upper Quartile	60	36 (60%)	32	7 (22%)
Other Quartiles	196	93 (48%)	97	19 (20%)
# Tender Joints				
Upper Quartile	58	34 (59%)	36	7 (19%)
Other Quartiles	198	95 (48%)	97	19 (20%)
CRP				
Upper Quartile	64	35 (55%)	31	2 (7%)
Other Quartiles	192	94 (49%)	102	24 (24%)
HAQ				
Upper Quartile	57	27 (47%)	34	4 (12%)
Other Quartiles	194	102 (53%)	99	22 (22%)

6.1.4.3.5.2 Improvement in Physical Function

Responses regarding improvement in physical function at Day 169 as assessed by HAQ scores were analyzed in relation to baseline demographics. Subjects receiving abatacept demonstrated a greater improvement in physical function as assessed by HAQ compared to subjects receiving placebo regardless of age, sex, race, geographical region, and weight (Table 55).

Table 55. Subgroup Analysis of HAQ Responses by Baseline Demographics

	n	Abatacept	n	Placebo
Previous TNF blocker use				
Etanercept	61	25 (41%)	43	11 (26%)
Infliximab	140	77 (55%)	68	15 (22%)
Etanercept + Infliximab	55	19 (35%)	22	5 (23%)
Age (years)				
≤65	205	98 (48%)	113	27 (24%)
>65	51	23 (45%)	20	4 (20%)
Sex				
Female	198	89 (45%)	106	28 (26%)
Male	58	32 (55%)	27	3 (11%)
Race				
White	246	119 (48%)	124	28 (23%)
Geographical Region				
North America	187	82 (44%)	99	26 (26%)
Europe	69	39 (57%)	34	5 (15%)
Body Weight (kg)				
<60	44	15 (34%)	24	5 (21%)
60-100	177	89 (50%)	89	21 (24%)
>100	34	16 (47%)	19	5 (26%)

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Subjects receiving abatacept also demonstrated a greater improvement in physical function as assessed by HAQ compared to subjects receiving placebo regardless of disease duration, swollen and tender joint counts, level of CRP, or baseline HAQ (Table 56).

Table 56. Subgroup Analysis of HAQ Responses by Baseline Disease Characteristics

	n	Abatacept	n	Placebo
Disease Duration (years)				
≤2	31	10 (32%)	16	3 (19%)
>2 to ≤5	81	39 (48%)	25	9 (35%)
>5 to ≤10	58	37 (64%)	25	3 (12%)
>10	136	59 (43%)	66	16 (24%)
# Swollen Joints				
Upper Quartile	60	32 (53%)	32	9 (28%)
Other Quartiles	196	89 (45%)	97	22 (22%)
# Tender Joints				
Upper Quartile	58	35 (60%)	36	8 (22%)
Other Quartiles	198	86 (43%)	97	23 (24%)
CRP				
Upper Quartile	64	34 (53%)	31	4 (13%)
Other Quartiles	192	87 (45%)	102	27 (27%)
HAQ				
Upper Quartile	57	30 (52%)	34	7 (21%)
Other Quartiles	194	91 (47%)	99	24 (24%)

6.1.4.4 Study IM101101

6.1.4.4.1 Study Conduct

6.1.2.1.1 Study Conduct

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 9).

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.

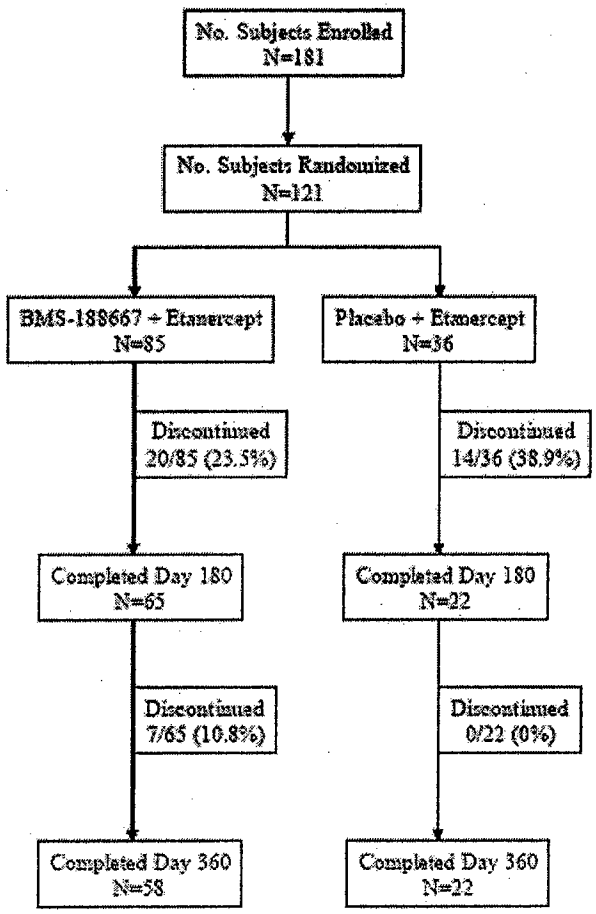
6 subjects from the abatacept 2 mg/kg + etanercept arm:

- 6 subjects with Day 15 visit >7 days form ideal window or visits after Day 15 >14 days of ideal window

1 subjects from the placebo + etanercept arm

- 1 subject did not receive stable dose of oral corticosteroids within 14 days of Day 1 or within 14 days of ≥2 assessments

Figure 9. 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 57).

Table 57. 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
AE	6 (7%)	1 (3%)
LOE	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.

6.1.4.4.2 Study Demographics

The baseline characteristics were generally similar across both treatment arms of the study and are shown in Table 58. The majority of subjects were white and female, mean age of ~51 years, and mean weight of 80 kg.

Table 58. 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 59.
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 59. 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

The use of DMARDs prior to enrollment was generally comparable in both treatment groups as shown in Table 60. At the time of randomization subjects were on etanercept only and approximately 60% of subjects in both arms were on daily oral corticosteroids.

Table 60. Medication Use at Enrollment

Prior Anti-Rheumatic Medications	Abatacept 2 mg/kg + Etanercept (n=85)	Placebo + Etanercept (n=36)
Etanercept	85 (100%)	36 (100%)
MTX	13 (15%)	9 (25%)
Hydroxychloroquine	6 (7%)	0
Sulfasalazine	3 (4%)	0
Gold salts	1 (1%)	0
Azathioprine	1 (1%)	0
Quinine	1 (1%)	1 (3%)
Aurothioglucose	0	1 (3%)
Corticosteroids	52 (61%)	20 (56%)

During Days 1-180 concomitant systemic corticosteroid use was comparable between treatment arms (~70%). Two subjects in the abatacept + etanercept arm received a DMARD (1 subject received hydroxychloroquine and 1 subject received quinine) and 1 subject in the placebo group received quinine. Neither of these protocol violations is expected to affect the validity of the trial. Table 61 shows the concomitant medications administered between Days 181 to 2 months after the end of the double-blind period of the study. All subjects who remained in the study continued etanercept therapy and approximately 10% of subjects in both groups received a concomitant oral DMARD.

Table 61. Medication Use After Day 180 to 2-Months post-Double-Blind Period

Anti-Rheumatic Medications	Abatacept 2 mg/kg + Etanercept (n=65)	Placebo + Etanercept (n=22)
Etanercept	65 (100%)	22 (100%)
MTX	3 (5%)	2 (9%)
Sulfasalazine	2 (3%)	0
Quinine	1 (2%)	0
Corticosteroids	45 (69%)	16 (73%)

6.1.4.4.3 Analysis of Primary Endpoint Study IM101101

6.1.4.4.3.1 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 62).

Table 62. 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	

6.1.4.4.4 Analysis of Secondary Endpoints of Study IM101101

6.1.4.4.4.1 Improvement of Signs and Symptoms

The proportions of subjects achieving a modified ACR 50 and ACR 70 response are shown in Table 63. There was not a statistically significant difference between treatment arms achieving an ACR 50 but there was a significant difference of abatacept-treated subjects achieving an ACR

70. Given that there was no statistically significant difference on the primary endpoints, the interpretation of the finding on ACR 70 responses is uncertain.

Table 63. Modified ACR 50 and ACR 70 Responders at Day 180

	Abatacept 2 mg/kg + Etanercept (n=85)	Placebo + Etanercept (n=36)
Modified ACR 50 (%)		
Number of responders	22 (26%)	7 (19%)
p-value	0.45	
Modified ACR 70 (%)		
Number of responders	9 (11%)	0
p-value	0.04	

There were no statistically significant differences in the ACR 20, ACR 50, and ACR 70 responses at Day 360 between the abatacept + etanercept group compared to the placebo + etanercept group (Table 64).

Table 64. ACR 20, ACR 50, and ACR 70 Responders at Day 360

	Abatacept 2 mg/kg + Etanercept (n=85)	Placebo + Etanercept (n36)
Modified ACR 20 (%)		
Number of responders	41 (48%)	11(31%)
p-value	0. 07	
Modified ACR 50 (%)		
Number of responders	24 (28%)	6(17%)
p-value	0.18	
Modified ACR 70 (%)		
Number of responders	8 (9%)	2 (6%)
p-value	0.48	

Review of the remaining major secondary analyses regarding signs and symptoms generally failed to demonstrate statistically significant or clinically meaningful differences among the abatacept-treated subjects as compared to the placebo-treated subjects (data not shown). These analyses included the proportion of subjects achieving a major clinical response and the individual components of the ACR criteria. Additionally, although the absolute change in the HAQ score had a p value <0.05 for the difference between the treatment arms, the proportion of subjects achieving >0.3u improvement was similar at 6 months in the abatacept group (34%) compared to the placebo group at day 180 (22%; p=0.19) and at 1 year (35% vs. 28%, respectively; p=0.42).

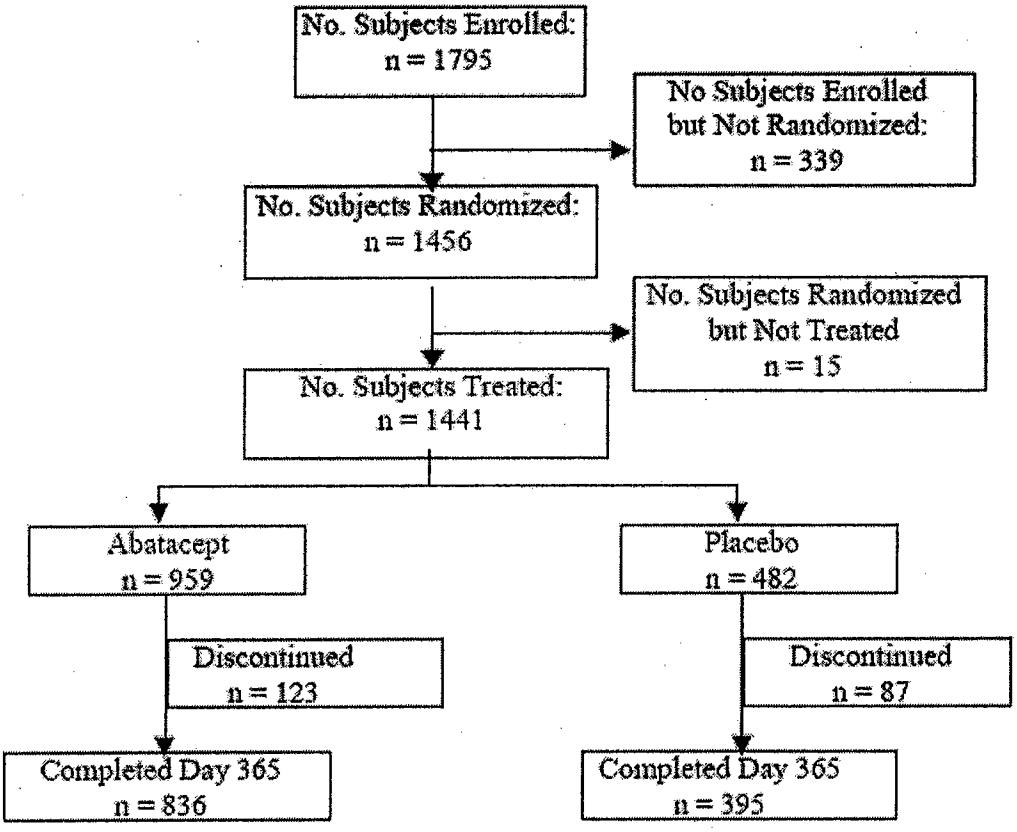
Since study IM101101 is not a pivotal trial for the assessment of the clinical efficacy of abatacept, and given the results of the trial, further analyses that were conducted will not be presented or discussed in this review. Overall, study IM101101 did not provide significant evidence of clinical efficacy 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.

6.1.4.5 Study IM101031

6.1.4.5.1 Study Disposition for 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 10).

Figure 10. 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.

12 subjects from the abatacept 2 mg/kg + etanercept arm:

- 8 subjects missed ≥2 consecutive doses of and continued beyond the last missed dose
- 4 subjects had a n average subject global assessment of disease activity <20 mm at screening and Day 1

5 subjects from the placebo + etanercept arm

- 4 subjects missed ≥2 consecutive doses of and continued beyond the last missed dose
- 1 subjects met <4 of the 7 ACR criteria for the classification of RA

These violations were unlikely to affect the conclusions of the study and were included in all analyses. Unblinding of a single subject occurred following subject's withdrawal of consent of Day 197. This subject was included in all data summaries and listings.

Site 151 enrolled 19 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 65). 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 65. 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%)
AE	51 (5%)	19 (4%)
LOE	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 66). 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 66). 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 66. 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
AE	42 (5%)	17 (4%)	9 (9%)	2 (3%)
LOE	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%).

6.1.4.5.2 Study Demographics for IM101031

The baseline characteristics were generally similar across both treatment arms of the study and are shown in Table 67. The majority of subjects were white and female, with a mean age of ~52 years, and a mean weight of 72 kg.

Table 67. 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 68 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 68. 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 69. 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 69. 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 70. 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%)

6.1.4.5.3 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 71). 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 71. 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 72 shows the mean change from baseline in HAQ scores during the double-blind period by DMARD used.

Table 72. 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

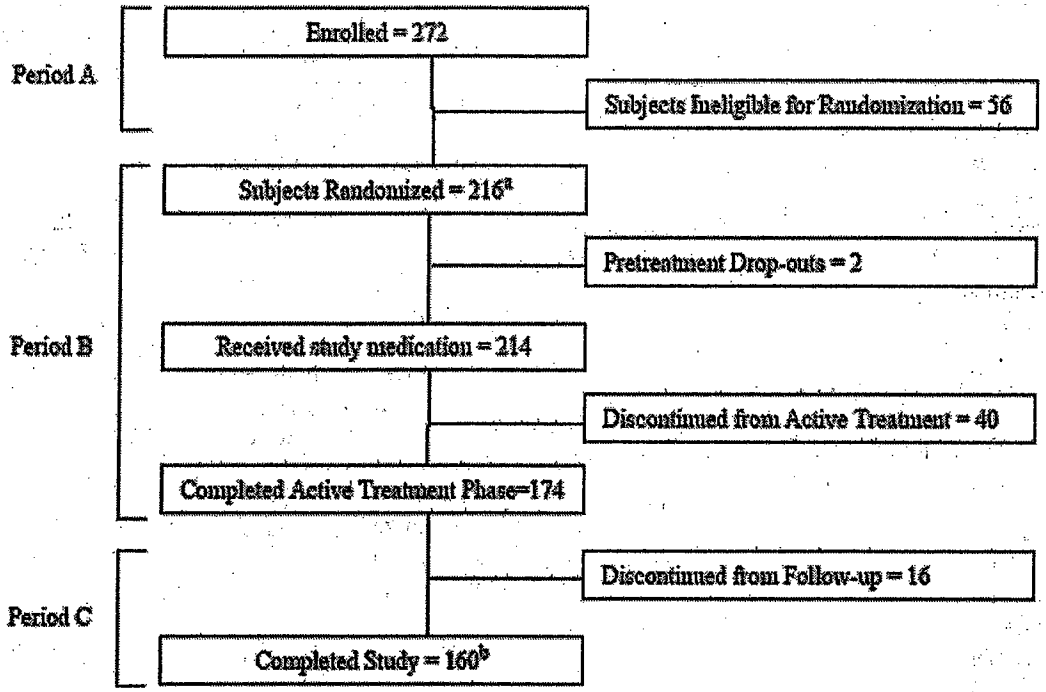
6.1.4.6 Study IM103002

6.1.4.6.1 Study Conduct of IM103002

A total of 272 subjects were enrolled with 214 subjects being randomized to receive abatacept, BMS-224818 (a closely related molecule to abatacept with similar mechanism of action), or placebo. The most frequent reasons for not being randomized were subjects failing to meet inclusion and/or exclusion criteria (Figure 11). The 121 subjects were randomized as follows:

- Abatacept (90 subjects)
  - 0.5 mg/kg: 26 subjects
  - 2 mg/kg: 32 subjects
  - 10 mg/kg: 32 subjects
- BMS224818 (92 subjects)
  - 0.5 mg/kg: 32 subjects
  - 2 mg/kg: 29 subjects
  - 10 mg/kg: 31 subjects
- Placebo (32 subjects)

Figure 11. Subject Disposition for Study IM103002



Study drug was administered by intravenous infusion on Days 1, 15, 29, and 57:
A total of 184 of 214 subjects (86%) received all 4 doses of study drug and 202 of 214 subjects (94%) received at least 3 doses. The number of missed infusions was distributed evenly among the 3 arms.

Table 73 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%) or BMS-224818 (9%). Loss of efficacy, noted as worsening RA, was the most common reason for discontinuation in all treatment arms but to the greatest degree in the placebo arm (10%).

Table 73. Subject Discontinuations During the Active Treatment Phase

	Placebo	Abatacept			BMS-224818		
	(n=32)	0.5 mg/kg (n=26)	2 mg/kg (n=32)	10 mg/kg (n=32)	0.5 mg/kg (n=32)	2 mg/kg (n=29)	10 mg/kg (n=31)
Total Discontinued	12	8	8	4	2	2	4
Death	0	0	0	0	0	0	0
AE	0	2	2	0	0	0	1
LOE	10	5	4	3	1	1	2
Lost to Follow-Up	1	0	0	1	0	1	0
Withdrawal of Consent	1	1	0	0	0	0	0
Other	0	0	2	0	1	0	1

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.

6.1.4.6.2 Study Demographics for IM103002

The baseline characteristics were generally similar across all treatment arms of the study and are shown in Table 74. The majority of subjects were white and female, with a mean age of ~48 years, and a mean weight of 71 kg.

Table 74. Baseline Demographics

	Placebo	Abatacept			BMS-224818		
	(n=32)	0.5 mg/kg (n=26)	2 mg/kg (n=32)	10 mg/kg (n=32)	0.5 mg/kg (n=32)	2 mg/kg (n=29)	10 mg/kg (n=31)
Age (years, mean ± SD)	48 ± 12	47 ± 12	46 ± 13	52 ± 12	49 ± 9	51 ± 11	46 ± 10
Weight (kg, mean)	73	71	73	70	70	69	72
Gender (female %)	81%	85%	72%	69%	72%	69%	77%
Race (%)							
White	94%	88%	94%	94%	91%	86%	87%
Black	6%	0	0	3%	3%	10%	6%
Other	0%	12%	6%	3%	6%	3%	6%

The baseline disease characteristics of the study subjects are shown in Table 75. 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 75. Baseline Disease Characteristics

	Placebo	Abatacept			BMS-224818		
	(n=32)	0.5 mg/kg (n=26)	2 mg/kg (n=32)	10 mg/kg (n=32)	0.5 mg/kg (n=32)	2 mg/kg (n=29)	10 mg/kg (n=31)
Duration of RA (years, mean ± SD)	3.2 ± 2.0	4.2 ± 2.0	3.3 ± 1.7	3.4 ± 2.1	3.7 ± 2.0	3.1 ± 1.8	3.0 ± 2.2
Swollen joints (mean ± SD)	24 ± 10	19 ± 6	27 ± 11	23 ± 13	18 ± 8	23 ± 9	20 ± 9
Tender joints (mean ± SD)	32 ± 15	32 ± 15	32 ± 15	29 ± 15	26 ± 12	31 ± 13	31 ± 13
Morning Stiffness (min)	157	212	145	150	161	160	148
CRP (mg/dL)	5.7	2.6	4.8	3.4	2.8	4.8	3.7

6.1.4.6.3 Analysis of Primary Endpoint

6.1.4.6.3.1 Improvement of Signs and Symptoms

The primary endpoint was the proportion of subjects achieving an ACR 20 at Day 85. As shown in Table 76, 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 76. ACR 20 Response on Day 85

	Placebo	Abatacept			BMS-224818		
	(n=32)	0.5 mg/kg (n=26)	2 mg/kg (n=32)	10 mg/kg (n=32)	0.5 mg/kg (n=32)	2 mg/kg (n=29)	10 mg/kg (n=31)
ACR 20 Responders N (%)	10 (31%)	6 (23%)	14 (44%)	17 (53%)	11 (34%)	13 (45%)	19 (61%)
95% CI	NA	-31, 15	-11, 26	-2, 46	-20, 26	-10, 38	7, 54

6.1.4.6.4 Analysis of Secondary Endpoints

6.1.4.6.4.1 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 77. 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 77. ACR 50 and ACR 70 Responders at Day 85

	Placebo	Abatacept			BMS-224818		
	(n=32)	0.5 mg/kg (n=26)	2 mg/kg (n=32)	10 mg/kg (n=32)	0.5 mg/kg (n=32)	2 mg/kg (n=29)	10 mg/kg (n=31)
ACR 50 Responders N (%)	2 (6%)	0	6 (19%)	5 (16%)	3 (9%)	3 (10%)	19 (61%)
95% CI	NA	-15, 2	-3, 28	-6, 25	-10, 16	-10, 18	-8, 21
ACR 70 Responders N (%)	0	0	4 (13%)	2 (6%)	2 (6%)	1 (3%)	1 (3%)
95% CI	NA	0	1, 24	-2, 15	-2, 15	-3, 10	-3, 9

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 (Table XXX shows the ACR 20 response at Day 169). 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.

6.1.5 Clinical Microbiology

This section does not apply to this review as abatacept has no anti-microbial activity.

6.1.6 Efficacy Conclusions

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

6.1.6.1 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 support the claim that abatacept therapy reduces the signs and symptoms of RA in subjects who have failed DMARDs and/or a TNF blocker. Furthermore, the data support the use of abatacept as monotherapy. Study IM101029 was conducted in subjects with persistent RA disease activity despite treatment with a TNF-blocker, and thus, the demonstration of the clinical efficacy of abatacept therapy to decrease the signs symptoms of RA in this patient population supports its use in patients who have had an inadequate clinical response to TNF-blocking drugs.

6.1.6.2 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 indicate 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 and the effect appears to be maintained at 2 years.

6.1.6.3 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.

7 INTEGRATED REVIEW OF SAFETY

7.1 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) and BMS-224818 (a molecular entity closely related to abatacept) monotherapy (n=92) 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=258 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 78). 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 78. 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.

7.1.1 Deaths

There were a total of 23 deaths reported during the RA trials evaluating abatacept; 15 subjects died during the double-blind periods (Table 79) and 8 subjects died during the open-label periods. 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 79. Subject Deaths During Double-Blind Periods of RA Studies

Subject Number (age/gender)	Onset Day	Cause of Death
Abatacept (n=1955)		
IM101029-102-3 (67/M)	30	CHF s/p 5-vessel CABG and valve replacement
IM101031-21-9 (58/F)	17	Found Dead at Home. Autopsy: hypertensive heart disease
IM101031-99-18 (56/F)	294	MI undiagnosed in ER Autopsy: ischemic cardiomyopathy
IM101031-118-21 (49/M)	262	Found Dead at Home Autopsy: Grade III CAD, myocardial hypertrophy
IM101031-150-10 (77/F)	101	Found Dead at Home Cause of death unknown
IM101031-197-6 (49/M)	306	Cardiac Arrest in subject with DM-type I s/p 3rd-degree burns
IM101100-28-2 (61/F)	259	Cardiac Arrest s/p MI and CABG and complicated post-op course
IM101100-35-2 (83/M)	332	Lung CA
IM101102-136-5 (53/M)	346	Bronchopulmonary Aspergillosis
PLACEBO (n=989)		
IM101031-38-3 (60/F)	195	Found Dead at Home Cause of death unknown
IM101031-78-30 (58/F)	376	Myocardial Infarction
IM101031-108-16 (61/F)	321	PCP, HIV
IM101031-109-36 (36/M)	364	CVA
IM101100-24-6 (55/F)	231	Endometrial CA
IM101102-96-11 (77/M)	342	Pneumonia Sepsis

Narratives for the 9 abatacept-treated subjects are as follows:

- Subject IM101029-102-3 was a 67-year-old male with history of hypertension, CVA with residual left sided weakness, bradycardia with pacemaker implantation, and smoking history who received 1 infusion of abatacept 500 mg on study Day 1 and died of CHF, pneumonia and procedure-related infection following CABG. On Study Day 30 he developed dyspnea and was admitted to the hospital for CHF and treated with nitroglycerin, metoprolol, clopidogrel, heparin, and furosemide. He underwent a 5-vessel CABG with valve replacement and was discharged for rehab on Day 49. He was later re-admitted to the hospital for CHF, pneumonia, and vein donor site infection and died on study Day 104.

- Subject IM101031-21-9 was a 58-year-old female weighing 104 kg, who was treated with 2 doses of abatacept 1000 mg and was found dead at home. Subject had a history of hypertension, edema, hypercholesterolemia, hypothyroidism, smoking, asthma, bronchitis, and shortness of breath. Concomitant medications included leflunomide, estropipate, levothyroxine, dextroamphetamine, furosemide, ranitidine, enalapril, lovastatin, and HCTZ. Two days following her last abatacept infusion the subject was found unresponsive at home. An autopsy was not performed but the cause of death on the death certificate was noted as hypertensive heart disease.

- Subject IM101031-99-18 was a 56-year-old white female who had received 12 infusions of abatacept who died of ischemic cardiomyopathy . She had a history of hypertension and was being treated with atenolol and chlorthalidone, as well as MTX, prednisone, and meloxicam. On study Day 294, 13 days after her last infusion, she presented to the emergency room with vomiting and gastric pain of several hours duration. Diagnostic evaluation did not include laboratories or an EKG. The subject died later that day and autopsy revealed the cause of death to be ischemic cardiomyopathy as a result of coronary artery disease.

- Subject IM101031-118-21 was a 49-year-old white male weighing 71 kg who received 11 infusions of abatacept 750 mg. He had no significant past medical history. During the course of the study he developed 2 episodes of hypertension that were treated with enalapril and amiloride/HCTZ. Additional concomitant medications included MTX, prednisone, folate, and ibuprofen. On study Day 262, 7 days following last abatacept infusion, he developed severe heart failure and was found dead at home on study Day 265. Autopsy revealed that he died on study Day 262 but due to putrefaction an exact cause of death could not be ascribed; however, autopsy noted Grade III coronary artery disease with focal stenoses, and myocardial hypertrophy.

- Subject IM101031-150-10 was a 77-year-old white female weighing 46 kg who had received 5 infusions of abatacept 500 mg who died of unknown causes. Previous medical history included Sjogren's syndrome, hypertension, systolic ejection murmur, gastritis, anemia, and remote tobacco use. Subject experienced 3 episodes of worsening of her hypertension during the study with the last episode occurring on study Day 27 and was ongoing at the time of her death. Her medications included MTX, folate, diclofenac, and enalapril. On study Day 101, 16 days after the last infusion, the subject was found dead at home. The cause of death is unknown.

- Subject IM101031-197-6 was a 49-year-old Asian male weighing 99 kg who had received 12 infusions of abatacept 750 mg who had a work related injury and died of cardiac arrest. Past medical history was significant for insulin-diabetes mellitus, diabetic retinopathy, and former alcohol abuse. On study Day 38 subject experienced uncontrolled diabetes mellitus. On study Day 93 he experienced myocardial ischemia secondary to coronary artery disease. On study Day 306, 24 days after his last abatacept infusion, the subject developed 3rd-degree burns over 36% of his body due to a work-related accident. Treatment during his subsequent hospitalization included aggressive fluid resuscitation and analgesics. On study Day 310 his serum creatinine rose to 1.7-2.3 mg/dL. On study Day 312 he went into cardiac arrest and could not be resuscitated and subsequently died.

- Subject IM101100-28-2 was a 61-year-old white female weighing 105 kg who had received 10 infusions of abatacept 2 mg/kg who died of complications of CABG. Subject had a history of diastolic hypertension. On study Day 259, 16 days after the last infusion of abatacept, the subject developed myocardial ischemia and an angiogram revealed 100% occlusion of the right coronary artery and 80% occlusion of the proximal circumflex artery. On study Day 262 she underwent a CABG due to ischemic coronary heart disease and unstable angina. Subject had a complicated post-operative course including renal failure and left ventricular failure requiring a balloon pump. Subject returned to surgery. On study Day 273 subject died due to cardiac arrest.

- Subject IM101100-35-2 was a 83-year-old white male weighing 69 kg who had received 13 infusions of abatacept 10 mg/kg who died of lung cancer. Past medical history included emphysema due to previous smoking (discontinued 1991). On study Day 332, 1 day after last infusion, subject had a chest radiograph revealing a density that was later confirmed to be lung cancer. Diagnostic evaluation revealed metastases and the subject refused further invasive procedures for further diagnosis and refused treatment. Subject died approximately 13 months after last infusion of abatacept.

- Subject IM101102-136-5 was a 53-year-old white male who had received 14 infusions of abatacept 750 mg/kg who died of Pseudomonas aeruginosa septicemia. Previous medical history was significant for TB (pulmonary and extra-pulmonary) with residual scarring of the lungs. On study Day 313, 4 days after the most recent infusion, he developed a bronchopneumonia with atelactasis that was subsequently found to be due to aspergillosis. Subject died on study Day 372 while in the ICU due to Pseudomonas aeruginosa septicemia.

Eight abatacept-treated subjects died during the open-label periods of the RA studies (Table 80).

Table 80. Subject Deaths During the Open-Label Periods of RA Studies

Subject Number (age/gender)	Onset Day	Cause of Death
IM101031-58-11 (61/M)	429	Myocardial Infarction Subject with history of 2 angioplasties/stents
IM101031-109-38 (36/M)	365	Aortic Dissection
IM101031-176-2 (78/F)	505	Pancytopenia Sepsis (?)
IM101029-124-10 (70/F)	232	Cholangiocarcinoma
IM101101-14-2 (61/F)	1115	B-cell Lymphoma
IM101100-21-1 (83/M)	538	Lung adenocarcinoma
IM101100-41-8 (65/M)	1051	MTX-induced pulmonary fibrosis & Pulmonary Emboli
IM101100-76-4 (65/M)	649	Cardiopulmonary failure

Narratives for the 8 abatacept-treated subjects are as follows:

- Subject IM101031-58-11 was a 61-year-old white male weighing 93 kg who had received 16 infusions of abatacept 750 mg who died of cardiac arrest. Significant prior medical history included 4 myocardial infarctions, 2 coronary angioplasties with stent placement, and idiopathic thrombocytopenic purpura. On study Day 429, 36 days after the last infusion of abatacept, the subject experienced a cardiac arrest and died.

- Subject IM101100-21-1 was a 61-year-old white female weighing 86 kg who had received 17 infusions of abatacept 10 mg/kg who died of lung cancer. Past medical history was significant for a history of smoking. On study Day 470, 18 days after the last infusion of abatacept, the subject developed a pleural effusion. Diagnostic evaluation ultimately diagnosed a pulmonary adenocarcinoma from which the subject died on study Day 538.

- Subject IM101100-41-8 was a 65-year-old white male weighing 78 kg who had received 36 infusions of abatacept 10 mg/kg who developed MTX-induced pulmonary fibrosis and pulmonary emboli and died. Past medical history was significant for Raynaud's disease. On study Day 1051, 34 days after the last infusion of abatacept, the subject developed severe dyspnea and subsequently died on study Day 1063. Diagnostic evaluation conducted on study Day 1051 revealed MTX-induced pulmonary fibrosis and 2 pulmonary emboli. Further investigations are ongoing.

- Subject IM101100-76-4 was a 84-year-old white female weighing 86 kg who had received 23 infusions of abatacept 10 mg/kg who was found cyanotic at home and died. Past medical history was significant for peripheral edema. During the course of treatment the subject developed 3 episodes of mild rales at the bilateral bases of his lungs with the most recent event occurring at the time of his death. On study Day 649, 18 days after the last infusion of abatacept, the subject was found cyanotic on the floor of his home and brought to an emergency room by ambulance. The subject was intubated due to cardiopulmonary failure but developed asystole and was pronounced dead.

- Subject IM101101-14-2 was a 61-year-old white female weighing 71 kg who had received 38 infusions of abatacept 2 mg/kg who died of a B-cell lymphoma. On study Day 1086 subject was found to have hepatosplenomegaly that was later found to be due to a diffuse large B-cell lymphoma. After a complicated medical course the subject died on study Day 1115.

- Subject IM101029-124-10 was a 70-year-old white female weighing 59 kg who had received 6 infusions of abatacept 500 kg who died of a cholangiocarcinoma. Significant medical history included pancreatic insufficiency, right carotid endarterectomy, COPD, chronic anemia, and previous smoking. Subject was hospitalized on study Day 157 due to gastroesophagitis. Evaluation revealed thrush, hilar adenopathy, and mildly elevated CEA and CA19-9. Endoscopy revealed a defect in the duodenum and common bile duct dilation with biliary sludge. Subject ultimately received a retrograde cholecystopancratogram on study Day 198 which revealed cholangiocarcinoma. Subject was discharged to home hospice and died on study Day 232.

- Subject IM101031-109-38 as a 36-year-old white male weighing 84 kg who had received 14 infusions of abatacept who had a cardiac arrest and died. Subject had no significant past medical history. On study Day 360, 23 days after last infusion of abatacept, subjected presented to the emergency room with chest pain. EKG did not demonstrate ishcemic changes and vital signs were normal and subject was discharged to home. On study Day 364 subject returned to the emergency room with headache, vomiting and progressive sensory loss. One hour after admission the subject developed cardiac arrest, was resuscitated but died on study Day 365.

- Subject IM101031-176-2 was a 78-year-old white female weighing 65 kg who had received 16 infusions of abatacept who died of unknown causes. On study Day 450 subject was discontinued from the study due to several dermatologic complaints: nasal ulcer, a symmetric erythema on the face and arm, and pruritis. On study Day 499, 69 days after the last infusion of abatacept, subject was admitted to the hospital for increasing shortness of breath. On study Day 500 she was found to be pancytopenic. Concomitant medications included MTX, prednisone, celecoxib, acetaminophen/codeine, azithromycin, labetalol, zalepon, levothyroxine, and alendronate. On study Day 504 subject developed fever, dyspnea, and tachycardia and died the following day. Cause of death is currently unknown.

In summary, 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.

7.1.2 Other 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 81). 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 81. Most Frequently Reported (>1%) SAE in the Double-Blind Periods

System Organ Class Preferred term	Abatacept (n=1955)	Placebo (n=989)
Total Subjects with SAE	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).

7.1.2.1 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 82).

Table 82. Serious Infections in Double-Blind Periods where abatacept-treated subjects > Placebo-treated subjects and total subjects > 2

Serious Infection Preferred term	Abatacept (n=1955)	Placebo (n=989)
Total Subjects with SAE	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 82, 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 83. 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 83. 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)

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 84, 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 84. Infections of Special Interest during Double Blind Period where abatacept-treated subjects SAEs> Placebo and > 2 subjects

Infection Preferred term	Abatacept (n=1955)	Placebo (n=989)
Total Subjects with AE	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 was determined to be HIV-positive, 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 85.

Table 85. 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	
AE	%	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.

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.

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.

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.

7.1.2.2 All Infections

Table 86 shows that a higher proportion of abatacept-treated subjects (54%) developed infections compared to placebo-treated subjects (48%).

Table 86. Most Frequently reported infections in double-blind study periods

Infection Preferred Term	Abatacept (n=1955)	Placebo (n=989)
Total Subjects with AE	1051 (54%)	478 (48%)
URI	248 (13%)	119 (12%)
Nasopharyngitis	225 (12%)	90 (9%)
Sinusitis	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 (Table 87).

Table 87. Serious Infections during the Open-label Period Occurring in ≥2 subjects

Serious Infection Preferred term	Abatacept (n=2285)
Total Subjects with SAE	27 (1%)
Arthritis bacterial	3 (0.1%)
Pneumonia	3 (0.1%)
Diverticulitis	2 (<0.1%)
E. coli sepsis	2 (<0.1%)

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 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 88. 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 88. 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%)
AE	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%)

7.1.3.2 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%; Table 89). Infections were the most common reason for study discontinuation and were reported by similar proportions (1%) of subjects in both treatment groups. Except for back pain that occurred in 0.3% of placebo subjects, no specific AEs led to discontinuation in >0.2% of subjects. The majority of AEs that led to study discontinuation were only reported by 1 subject for each AE. Those AEs that led to discontinuation in >0.2% of subjects in the abatacept group were: pneumonia, localized infection, dizziness, CHF, asthenia, rash, cough, and leukopenia.

Table 89. AEs leading to discontinuation in ≥2 subjects during double-blind periods*

SOC Preferred Term	Abatacept n=1955	Placebo n=989
Total Subjects with AE	107 (6%)	39 (4%)
Infections	24 (1%)	10 (1%)
Pneumonia	4 (0.2%)	1 (0.1%)
Localized infection	3 (0.2%)	0
Bronchitis	2 (0.1%)	2 (0.2%)
Sepsis	1 (<0.1%)	2 (0.2%)
Nervous System Disorders	14 (0.7%)	4(0.4%)
Cardiac Disorders	13 (0.7%)	2 (0.2%)
CHF	3 (0.2%)	1 (0.1%)
CAD	4 (0.2%)	0
Myocardial Ischemia	2 (0.1%)	1 (0.1%)
General Disorders	10 (0.5%)	6 (0.6%)
Skin & Subcutaneous Tissue Disorders	10 (0.5%)	4 (0.4%)
Neoplasms	10 (0.5%)	3 (0.3%)
Lung CA	2 (0.1%)	0
Endometrial CA	0	2 (0.2%)
Respiratory Disorders	10 (0.5%)	3 (0.3%)
Investigations	7 (0.4%)	2 (0.2%)
Blood and Lymphatic System Disorders	7 (0.4%)	0
Vascular Disorders	6 (0.3%)	1 (0.1%)
M-S System Disorders	5 (0.3%)	6 (0.6%)
Immune System Disorders	3 (0.2%)	1 (0.1%)
Psychiatric Disorders	3 (0.2%)	1 (0.1%)

*more than 1 SOC preferred terms may have been reported per subject

A higher proportion of abatacept-treated subjects discontinued study drug compared to placebo-treated subjects due to blood and lymphatic disorders (0.4% vs. 0%), nervous system disorders (0.7% vs. 0.4%, respectively) and cardiac disorders (0.7% vs. 0.3%, respectively).

Review of the respective cases for nervous system disorders demonstrated a total of 14 AE that led to study discontinuation in abatacept-treated subjects and comprised: 3 subjects with dizziness, 2 subjects with headache, 2 subjects with transient ischemic attack, and 1 subject each reporting CVA, carotid artery stenosis, hypoaesthesia, mononeuropathy multiplex, paraesthesia, reflex sympathetic dystrphopy, or tremor. Seven of the 14 subjects had an AE reported as a SAE. A total of 4 subjects from the placebo group reported a nervous system disorder AE leading to discontinuation and comprised 1 subject each reporting headache, transient ischemic attack, CVA, and a diabetic neuropathy. The proportion of subjects experiencing the most severe nervous system AE (namely, transient ischemic attack and CVA) was the same between abatacept-treated subjects and placebo-treated subjects (0.1% of the respective groups). Thus, although a higher number of nervous system AE events resulting in study discontinuation occurred in the abatacept-treated subjects, most of the AE were not of a life-threatening nature

and those AE that were life-threatening occurred at the same frequency between treatment arms. Additionally, the overall reported nervous system disorder AEs were reported in similar frequencies between the 2 groups.

Review of the cases for cardiac disorders demonstrated a total of 13 AE (10 of which were reported as a SAE) that led to study discontinuation in abatacept-treated subjects and were comprised of 1 or more of the following reported system organ class (SOC) preferred terms: (note: >1 preferred term may have been reported for an individual subject) 3 subjects with congestive heart failure, 4 subjects with coronary artery disease (2 subjects with reported coronary artery disease, 1 subject with coronary artery occlusion, and 1 subject with coronary artery atherosclerosis), 2 subjects with myocardial ischemia (1 subjects with reported myocardial ischemia and 1 subject with angina pectoris) and 1 subject each reporting atrial fibrillation, cardiac arrest, hypertensive heart disease, mitral valve prolapse, palpitations, pericarditis, tachycardia, and paroxysmal tachycardia. A total of 2 subjects from the placebo group reported a cardiac disorder AE leading to discontinuation and comprised 1 report of atrial fibrillation, unstable angina, and cardiac failure. Although there was a higher reported percentage of abatacept-treated subjects who discontinued from the study due to cardiac disorders, review of the reported AEs suggests that the most serious AEs (cardiac failure and myocardial ischemia) occurred in proportions similar to placebo-treated subjects. The one exception was with coronary artery disease of which there were 4 reported cases in the abatacept group but none in the placebo group. This may be accounted for by duplication of reported preferred terms and chance alone given the small number of subjects. Thus, although a higher number of cardiac disorder AE events resulting in study discontinuation occurred in the abatacept-treated subjects, most of the AE were not of a life-threatening nature and those AE that were life-threatening occurred at a similar frequency between treatment arms. Additionally, the overall reported cardiac disorder AEs were reported in similar frequencies between the 2 groups. It should also be noted that for purposes of clarity, this review reports AEs with similar underlying pathophysiological processes that have been pooled, e.g., "coronary artery disease" included reports of coronary artery disease as well as coronary artery atherosclerosis and coronary artery occlusion. Consequently, numbers in this review may not directly correspond to the sponsor's reported numbers.

Given the disproportionate number of abatacept-treated subjects who developed blood and lymphatic disorders (7 compared to none in the placebo arm) a more detailed review of the individual cases was conducted:

- IM101031-119-14 is a 54-year-old female with RA whose concomitant medications included sulfasalazine, diclofenac, and prednisolone who developed leukopenia leading to study discontinuation. The subject's baseline WBC was 3.0 x 10^9/L. Prior to her first infusion of abatacept her laboratories revealed a WBC of 2.1 x 10^9/L, and prior to her 2nd dose of abatacept her WBC was 2.5 x 10^9/L at which time sulfasalazine was discontinued. Following the 2nd infusion her WBC was 2.8 x 10^9/L and subject was discontinued from study.

- IM101031-122-1 is a 67-year-old male with RA, diabetes mellitus type 2, hypertension, and sicca symptoms receiving MTX, prednisone, and indomethacin. His baseline WBC

was 6.6 x 10^9/L. On study Day 41 he developed fever, aphthous stomatitis, and 3 days later was reported to have leukopenia despite a normal WBC of 5.4 x 10^9/L and was discontinued from the study after receiving 3 infusions of abatacept.

- IM101100-28-5 is a 51-year-old female with RA and history of iron-deficiency anemia who was taking MTX. Baseline WBC was 3.9 x 10^9/L and on study Day 148 she was noted to have a SAE of leukopenia with a WBC 3.3 x 10^9/L with a low ANC of 1.5 x 10^9/L. MTX was discontinued and she received 2 doses of leucovorin. She was discontinued from the study on Day 183 (received a total of 8 doses of abatacept) at which time her WBC was 3.0 x 10^9/L and ANC of 1.4 x 10^9/L. On Day 275 her WBC recovered and was reported as 5.4 x 10^9/L.

- IM101100-25-10 is a 58-year-old male with RA receiving MTX, prednisone and indomethacin. On the day of his first abatacept infusion his WBC was 8.9 x 10^9/L with an absolute lymphocyte count of 0.5 x 10^9/L. On study Day 268 he was noted to have an absolute lymphocyte count of 0.5 x 10^9/L and was discontinued from study after having received a total of 10 infusions of abatacept. Lymphocytopenia resolved after Day 376.

- IM101031-77-2 is a 67-year-old female with RA and a medical history of received a blood transfusion for anemia in 2002. Concomitant medications included MTX, sulfasalazine, and diclofenac. During the 12th infusion of abatacept she experienced gastritis, fatigue, dizziness, and palpitations for which she was hospitalize and found to have severe anemia with Hgb 5.5 g/dL (baseline Hgb 8.2 g/dL). She received a blood transfusion with resolution of the anemia. Twenty-seven days after the blood infusion she developed moderate dizziness and generalized pallor, with a Hgb of 7.5 g/dL. She was readmitted to the hospital for endoscopy (results not known) and an additional blood transfusion. She was discontinued from the study on Day 311.

- IM101031-117-9 is a 53-year-old female with RA and a medical history of erythrocyte macrocytosis since 2001 and depression for which she was receiving lithium. Concomitant medications included MTX, celecoxib, etanercept, and prednisone. Her baseline WBC was 6.2 x 10^9/L. On study Day 71 she had a normal WBC, Hgb, and platelet count. Between study Day 76 and Day 83 she experienced a short febrile illness and presented with bleeding from multiple sources (gums, nose, and vagina). Results of a CBC revealed pancytopenia with a WBC of 700 cells/μl, Hgb 4.3 g/dL, and platelet count of 11,000 cells /μl. Subsequent bone marrow aspirate revealed a hypocellular marrow with a morphology compatible with a partial recovery phase from toxic marrow damage. She was treated with supportive therapy and antibiotics. Subjects was discontinued from study after receiving a total of 3 infusions of abatacept.

- IM101102-89-1 is a 64-year-old female with RA who underwent a left hip arthroplasty in May 2002 and development of a thrombosis and pseudoaneurysm of the left femoral artery. Her past medical history was significant for Sjogren's syndrome, post-phlebitits syndrome (2002), chronic venous insufficiency (1980), varicose veins with surgical removal bilaterally (1980), prosthesis right hip (1999), mitral insufficiency, atrial

fibrillation, hypertension, hypothyroidism, and osteoporosis. Concomitant medications included methotrexate, folate, prednisone, alendronate, atenolol, captopril, amlodipine, and acetaminophen. On study Day 30, the subject experienced mild ecchymosis over a venipuncture site. On study Day 35, the subject was noted to have areas of ecchymoses on her legs with periorbital hemorrhages around the left eye that the investigator noted to be symptoms of DIC. Subject was hospitalized on study Day 39 with interruption of study drug, and a platelet count of 164,000/L (baseline was 403,000/L), and a partial thromboplastin time (PTT) of 41.6 seconds. Subject was treated with unspecified anticoagulants on study Day 48. On study Day 52, 23 days after the 3rd infusion of abatacept, she experienced moderate worsening of her post-phlebitis syndrome as evidenced by small ecchymoses appearing on both legs. Laboratories revealed fibrinogen of 1.3 g/L, prothrombin time (PT) of 12.7 minutes, and a PTT of 31.4 seconds. On study Day 62, 33 days after the last infusion the subject was found to have a pseudoaneurysm in the left femoral artery with a severe thrombosis that was subsequently treated with stent placement and subsequent resolution of symptoms.

Each of these cases is complicated by concomitant medications and/or medical conditions that may have contributed to the AE. The change in WBC from baseline for all 3 subjects (IM101031-119-14, IM101031-122-1, IM101100-28-5) who discontinued the study due to leukopenia was relatively small and the 1 subject with absolute lymphopenia (IM101100-25-10) had the diagnosis at the time of enrollment (prior to receiving abatacept) and tolerated all doses of abatacept without further decrease of lymphocytes. This subject was apparently discontinued from the study after recognition of the lymphopenia on subsequent laboratory assessment. Subject IM101031-77-2 who discontinued due to anemia had a history of anemia prior to the present case and her entry Hgb suggests a mild chronic anemia. The case of DIC (IM101102-89-1) is difficult to interpret, as it appears that the subject may have been misdiagnosed with DIC in light of an unrecognized thrombosis, which can give a similar laboratory profile to DIC. In summary, although the majority of the 7 cases of blood and lymphatic disorders could be attributed to other factors it is difficult to eliminate a contributing role of abatacept.

During the open-label period approximately 2% of subjects were reported to have discontinued study enrollment due to an AE. There were no AEs that resulted in discontinuation of more than 2 subjects. The most common AE by SOC was neoplasms (0.4%) and infection (0.3%).

7.1.3.3 Other significant adverse events

There were 8 abatacept-treated subjects who discontinued study infusions due to a hepatic-related AE (see section 7.1.7 for details), 6 abatacept-treated subjects and 1 placebo-treated subject who discontinued study infusions due to the development of autoimmune symptoms and disorders (see section 7.1.5 for details), and 2 abatacept-treated subjects who developed an anaphylactic/anaphylactoid reaction following abatacept infusion and were discontinued from the study.

7.1.4 Other Search Strategies

No additional algorithms were specifically constructed to assess a particular toxicity. However, as noted above, an increased incidence of lymphomas and mammary tumors were identified during preclinical investigations. 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 preneoplastic 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. There were 2/1956 (0.1%) abatacept-treated subjects who developed breast cancer compared to 2/989 placebo-treated subjects (0.2%) indicating that the evidence to date does not suggest that abatacept increases the risk of breast cancer. Additionally, the available data do not demonstrate an increased risk of lymphoma in RA patients treated with abatacept. Details of the incidence of breast cancer and lymphomas are discussed in detail in Section 7.1.11.

7.1.5 Common Adverse Events

7.1.5.1 Eliciting Averse Event Data in the Development Program

In BMS clinical trials, an AE was defined as any new untoward medical occurrence or worsening of a pre-existing medical condition in a subject administered study drug. An AE could be any unfavorable or unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product. Investigators documented the AEs on the AE page of the CRF base on information volunteered by the subject and those elicited by general questioning and examination at each visit regardless of relationship to study drug. The information included: the event, onset and resolution dates, intensity, treatment required and information about resolution/outcome. Subjects who prematurely discontinued from the study had any AEs and concomitant medications recorded 28, 56, and 85 days after the last dose of study medication. Laboratory findings that the investigator felt was clinically relevant were to be recorded as AEs. Subjects received safety assessments at Days 1, 15, 29 then at least every 28 days thereafter for the duration of the study.

AEs that occurred more than once in the same subject in a given study period (double-blind or open-label period) were counted only once in each study period. Within each study period, the AE that was counted was the event that occurred first, unless the intensity of the AE increased, in which case the AE with the most severe intensity was counted. AE summaries were based on the rates that represented the number of subjects experiencing AEs divided by the total number of subjects infused with at least 1 dose of study medication. AEs from the time of first dose until 2 months after the last dose of study medication were included in the frequency tabulations. All

AEs in the open-label period were counted; AEs that occurred more than once during the open period in the same subject were counted only once. If the event increased in intensity, the most severe event was counted. If a subject had an event in the double-blind period that continued in the open-label period, this event was counted in the double-blind period and the open-label period.

A separate CRF page was used for the collection of SAE information. AEs were classified as serious if they met any of the following criteria:

- results in death
- any life-threatening event (defined as an event in which the subject or subject was at risk of death at the time of the event)
- any event that required inpatient hospitalization or causes prolongation of existing hospitalization
- any event that resulted in persistent or significant disability/incapacity
- a new diagnosis of cancer
- any congenital anomaly/birth defect
- any other important medical event that may have jeopardized the subject or may require intervention (e.g., medical, surgical) to prevent one of the other serious outcomes listed in the definition above (BMS also considered the occurrences of pregnancy or overdose, regardless of adverse outcome, as events which must be reported)

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

All AEs for the 5 core RA studies were coded and grouped into Preferred Terms by System Organ Class (SOC), using the Medical Dictionary for Regulatory Activities (MedDRA). AE terms for study IM103002 were coded using an International Classification of Diseases (ICD) dictionary and were not re-coded using MedDRA.
The sponsor's categorization of events and preferred terms using the above methods is acceptable.

7.1.5.3 Incidence of common adverse events

Section 7.1.5.4 discusses in detail the incidence of common AEs of the major clinical RA trials as well as presenting common AE tables.

7.1.5.4 Common adverse event tables

During the double-blind periods 89% of abatacept-treated subjects reported an AE compared to 85% of placebo-treated subjects (Table 90). 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 90. 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 AE	1736 (89%)	840 (85%)
Infections	1051 (54%)	478 (48%)
URI	248 (13%)	119 (12%)
Nasopharyngitis	225 (12%)	90 (9%)
Sinusitis	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 Acute	28 (1%)	10 (1%)
Ear Infection	23 (1%)	8 (1%)
Fungal Infection	22 (1%)	11 (1%)
Cellulitis	21 (1%)	9 (1%)
Gastrointestinal Disorders	750 (38%)	351 (36%)
Nausea	224 (12%)	105 (11%)
Diarrhea	189 (10%)	105 (11%)
Dyspepsia	126 (6%)	42 (4%)
Vomiting	94 (5%)	48 (5%)
Abdominal Pain	74 (4%)	30 (3%)
Abdominal Pain Upper	73 (4%)	37 (4%)
Mouth Ulceration	50 (3%)	14 (1%)
Constipation	41 (2%)	22 (2%)
Aphthous Stomatitis	30 (2%)	4 (<1%)
Gastritis	27 (1%)	18 (2%)
Toothache	24 (1%)	9 (1%)
Stomatitis	22 (1%)	8 (1%)
Gastroesophageal Reflux Disease	21 (1%)	12 (1%)
Abdominal Tenderness	20 (1%)	5 (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%)
Hypoaesthesia	28 (1%)	10 (1%)
Migraine	25 (1%)	14 (1%)
Sciatica	21 (1%)	2 (<1%)
Dysgeusia	14 (1%)	8 (1%)
Musculoskeletal and CT Disorders	589 (30%)	304 (31%)
RA	157 (8%)	87 (9%)
Back Pain	144 (7%)	58 (6%)

Arthralgia	77 (4%)	34 (3%)
Pain in Extremity	60 (3%)	19 (2%)
Myalgia	45 (2%)	24 (2%)
Bursitis	29 (2%)	16 (2%)
Neck Pain	29 (2%)	15 (2%)
Muscle Cramp	24 (1%)	15 (2%)
Respiratory, Thoracic & Mediastinal Disorders	443 (22%)	192 (19%)
Cough	162 (8%)	71 (7%)
Pharyngolaryngeal Pain	67 (3%)	45 (5%)
Dyspnea	55 (3%)	26 (3%)
Sinus Congestion	28 (1%)	10 (1%)
Nasal Congestion	27 (1%)	7 (1%)
Rhinitis Allergic	22 (1%)	9 (1%)
Asthma	19 (1%)	9 (1%)
Epistaxis	19 (1%)	6 (1%)
Skin and Subcutaneous Tissue Disorders	443 (22%)	179 (18%)
Rash	85 (4%)	32 (3%)
Pruritus	41 (2%)	20 (2%)
Alopecia	34 (2%)	16 (2%)
Erythema	25 (1%)	7 (1%)
Eczema	24 (1%)	6 (1%)
Skin Lesion	23 (1%)	14 (1%)
Hyperhidrosis	23 (1%)	7 (1%)
Ecchymosis	21 (1%)	8 (1%)
Urticaria	19 (1%)	9 (1%)
General Disorders & Administration Site Conditions	430 (22%)	240 (24%)
Fatigue	126 (6%)	68 (7%)
Edema Peripheral	65 (3%)	47 (5%)
Pyrexia	60 (3%)	30 (3%)
Asthenia	58 (3%)	24 (2%)
Chest Pain	48 (3%)	22 (2%)
Rigors	24 (1%)	17 (2%)
Influenza-like Illness	22 (1%)	5 (1%)
Pain	20 (1%)	11 (1%)
Injury, Poisoning and Procedural Complications	295 (15%)	119 (12%)
Fall	48 (3%)	22 (2%)
Contusion	38 (2%)	16 (2%)
Investigations	265 (14%)	126 (13%)
Blood Pressure Increased	54 (3%)	13 (1%)
Alanine Aminotransferase Increased	38 (2%)	15 (2%)
Weight Increased	33 (2%)	7 (1%)
Aspartate Aminotransferase Increased	30 (2%)	11 (1%)
Vascular Disorders	252 (13%)	93 (9%)
Hypertension	129 (7%)	43 (4%)
Flushing	28 (1%)	6 (1%)
Hot Flush	27 (1%)	6 (1%)
Hypotension	21 (1%)	10 (1%)
Psychiatric Disorders	189 (10%)	98 (10%)

Insomnia	69 (4%)	29 (3%)
Depression	64 (3%)	33 (3%)
Anxiety	42 (2%)	17 (2%)
Eye Disorders	181 (9%)	82 (8%)
Conjunctivitis	36 (2%)	17 (2%)
Keratoconjunctivitis Sicca	31 (2%)	10 (1%)
Vision Blurred	12 (1%)	9 (1%)
Cardiac Disorders	115 (6%)	58 (6%)
Palpitations	32 (2%)	16 (2%)
Tachycardia	25 (1%)	7 (1%)
Blood and Lymphatic System Disorders	90 (5%)	58 (6%)
Anemia	30 (2%)	29 (3%)
Leukopenia	22 (1%)	7 (1%)
Ear and Labyrinth Disorders	74 (4%)	38 (4%)
Vertigo	27 (1%)	15 (2%)
Renal and Urinary Disorders	86 (4%)	38 (4%)
Dysuria	23 (1%)	12 (1%)
Immune System Disorders	57 (3%)	26 (3%)
Seasonal Allergy	20 (1%)	3 (<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.

During the open-label periods RA was the only AE reported at a frequency ≥5%. 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 from the open-label periods of the Phase II studies, where it was reported in >30% of subjects over a 2-year follow-up period. Other less frequently reported AEs (reported in ≥3% of subjects) included upper respiratory tract infection (4%), nasopharyngitis (4%), headache (4%), and bronchitis (3%).

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

7.1.5.5 Identifying common and drug-related adverse events

Adverse events that occurred in greater frequency than 1% of the abatacept group is shown in Section 7.1.5.4 in Table 90. 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 which are discussed in detail in Sections 7.1.2.1 and 7.1.2.2.

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.

7.1.5.6 Additional analyses and explorations

7.1.5.6.1 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 anytime 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 91). The frequencies of all AEs and discontinuation due to AEs were also higher in abatacept-treated subjects (Table 91). There were no reported deaths.

Table 91. 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%)
SAEs	40 (20%)	12 (9%)	226 (13%)	110 (13%)
Discontinuations	9 (4%)	3 (2%)	44 (3%)	13 (2%)
Related SAEs	11 (5%)	3 (2%)	47 (3%)	14 (2%)
AEs	192 (94%)	113 (84%)	1544 (88%)	727 (85%)
Discontinuations	19 (9%)	6 (5%)	88 (5%)	33 (4%)
Related AEs	124 (61%)	67 (50%)	889 (51%)	389 (46%)

As shown in Table 92, 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.

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Table 92. 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 (N=204)	Placebo (N=134)	Abatacept (N=1751)	Placebo (N=855)
Total with AEs	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 93 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 93. 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 SAEs	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 94, 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 94. 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 SAEs	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 95). 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 95. 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 (12)	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 extremely 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 (Table 96).

Table 96. Overview of AEs in Subjects Receiving Biologic RA Therapy During the Open-Label Periods

	Number (%) of Subjects Open-Label Period
	Abatacept (n=196)
Deaths	1 (<1%)
SAEs	31 (16%)
Discontinuations (SAEs)	5 (3%)
Related SAEs	4 (2%)
AEs	121 (62%)
Discons (AEs)	10 (5%)
Related AEs	69 (35%)
RA	24 (12%)
Headache	15 (8%)
Upper Respiratory Tract Infection	27 (14%)
Nausea	13 (7%)
Sinusitis	20 (10%)
Fatigue	15 (8%)
Diarrhea	14 (7%)
Dizziness	9 (5%)
Cough	12 (6%)
Nasopharyngitis	14 (7%)

A greater proportion of subjects administered abatacept + biologic RA developed infections (64%) compared to placebo + biologic RA therapy (43%) and subjects receiving abatacept + non-biologic RA therapy (53%). The overall incidence rate of serious infections (per 100 person-years) was higher in the abatacept + biologic RA therapy group compared to placebo + biologic RA therapy group (5.3 events vs. 2.2 events, respectively). This higher rate of serious infections was consistent with the finding that a higher number of subjects receiving concomitant biologic RA therapy discontinued due to infections compared to placebo-treated subjects (3.4% vs. 1.5%).

Closer analyses of study IM101031 were performed to better understand the incidence of SAEs and serious infections. 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 97). The overall frequency of SAEs was almost 2-fold higher in abatacept + biologic DMARD treated subjects compared with placebo treated subjects (Table 97). 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 were small (1-2 subjects), making it difficult to draw meaningful conclusions of risk within these subgroups.

Table 97. 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 97). 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. 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 98).

Table 98. 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
Hydroxychloquine/ 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.

7.1.5.6.2 Abatacept Monotherapy

Additional analyses were performed for abatacept monotherapy. Study design and efficacy results for study IM103002 is outlined in Section 6.1.4.1. This section discusses only analysis of

the safety of abatacept monotherapy. A total of 272 subjects were enrolled, of whom 216 were randomized to receive study drug. A total of 90 subjects received abatacept (0.5 mg/kg, n= 26; 2 mg/kg, n=32, 10 mg/kg, n=32); 92 subjects received BMS-224818 (a closely related molecule with similar mechanism of action; 0.5 mg/kg, n= 32; 2 mg/kg, n=29, 10 mg/kg, n=31); and 32 subjects received placebo. Of the original 216 subjects randomized, 174 (81%) subjects, completed the active treatment period through Day 85, and 160 subjects, or 75% of 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%) or BMS-224818 (9%). Four subjects from the abatacept group and 1 subject from the BMS-224818 group discontinued due to AEs. There were 518 AEs reported by 173/214 subjects during the treatment period and a total of 774 AEs reported during the study. Arthritis was the most frequently reported AE during the treatment period with 37%, 22%, and 21% of subjects in the placebo, BMS-224818, and abatacept subjects, respectively. A total of 117 peri-infusional AEs occurred with similar frequency among those who received placebo (31%), abatacept (29%), or BMS-224818 (34%). During the treatment period, 4% of subjects treated with active drug experienced SAEs compared with 12% of subjects in the placebo arm. No deaths were reported. Review of the safety of abatacept monotherapy did not identify additional safety concerns.

7.1.5.6.3 Autoimmune Symptoms and Disorders

Lastly, 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.

7.1.5.6.3.1 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.

7.1.6 Less Common Adverse Events

7.1.6.1 Vasculitis

Ten (0.5%) abatacept-treated subjects and 3 (0.3%) placebo-treated subjects had vasculitis or vasculitis-related AE, all of which were limited to cutaneous involvement without systemic symptoms. One of the 10 abatacept-treated subjects had a SAE of leukocytoclastic vasculitis that required discontinuation of abatacept. Four of the 10 abatacept-treated subjects were receiving an additional background biologic RA treatment.

7.1.6.2 Sicca Symptoms

Sicca-related AEs for abatacept- and placebo-treated subjects included keratoconjunctivitis sicca (1.6% vs. 1%), Sjogren's syndrome (0.2% vs. 0.3%), and sicca syndrome (<0.1% vs. 0.1%). All AE of sicca symptoms were of mild to moderate severity except for 1 abatacept-treated subject who developed severe keratoconjunctivitis sicca.

7.1.6.3 Systemic Lupus Erythematous-like Symptoms

There were 2 reports of SLE-like AE both in subjects receiving abatacept. IM101031-173-6 is a 38-year-old female with reported SLE-like syndrome on study Day 174 that did not result in interruption of study therapy or discontinuation from study. Subject was on concomitant adalimumab therapy, a TNF blocker reported to cause ANA seroconversion and lupus-like syndrome. IM101031-77-12 is a 27-year-old female with reported SLE on study Day 8 that led to discontinuation from the study on Day 15. Investigator and sponsor suggest that signs and symptoms of SLE were present on screening physical exam prior to study entry.

7.1.6.4 Anti-Nuclear Antibody (ANA) and Anti-Double Stranded DNA (anti-DNA)

Fewer abatacept-treated subjects became ANA-positive compared to placebo-treated subjects at 6 months (4% vs. 6%) and 12 months (10% vs. 11%). Additionally, fewer abatacept-treated subjects became anti-dsDNA-positive compared to placebo-treated subjects at 6 months (1% vs. 2%) and 12 months (3% vs. 5%).

7.1.6.5 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.

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

Blood and/or urine samples were obtained prior to infusion at all visits (screening, Days 1, 15, 29 then every 28 days thereafter and 18 days after last study infusion) and the following laboratory results obtained:

Blood Chemistry:
Sodium
Creatinine

Potassium
Blood urea nitrogen (BUN)
Chloride
Total bilirubin
Total Protein
Albumin
Alanine aminotransferase (ALT)
Albumin Aspartate aminotransferase (AST)
Calcium
Gamma-glutamyltransferase (GGT)
Phosphorus
Alkaline phosphatase
Uric Acid
Glucose

Hematology:
Hemoglobin
Hematocrit
Total WBC count, including differential
Platelet count
RBC

Urinalysis:
pH
Protein
Glucose
Blood
Microscopic examination of the urine sediment if blood, protein or glucose are positive on the dipstick.

Pharmacodynamic (PD) tests:
RF
CRP
ESR (processed locally)
Soluble IL2-R
Inflammatory cytokines
Quantitative Immunoglobulins, (IgG, IgA, IgM)

Autoimmune Serology:
Anti-nuclear Antibody (ANA)
Anti-double stranded DNA

Serum samples for determination of immunogenicity were obtained at visit Days 1, 29, 85, 169 (and if appropriate study Days 281 and 365) as well as 28 days after the last dose of study medication. Subjects who complete the study had a serum sample collected 28 and 56 days after the last visit. Subjects who did not complete the study had a serum sample collected 28, 56 and

85 days after the last dose of study medication. Samples were collected just prior to the start of the IV infusion.

A chest x-ray, mammogram (female subjects only) and ECG at the screening visit were required if not performed within 6 months of study entry or if documentation was not on file. Additionally, a hepatitis screen was performed at baseline.

To identify subjects with latent tuberculosis (TB), all subjects underwent a PPD test if not performed within 6 months of study entry or if documentation of testing within 6 months was not on file. PPD skin test was performed in accordance to published guidelines that provided recommendations for PPD testing and interpretation in subjects with rheumatoid arthritis who are being considered for treatment with biologic agents, subjects who are immunosuppressed, and subjects with a prior history of BCG vaccinations.

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

Analyses for drug-control comparison of laboratory values were performed on the pooled data from the 5 major RA studies outlined in Section 7.1.

7.1.7.3 Standard analyses and explorations of laboratory data

Analyses focus on clinical chemistry and hematology laboratory values

7.1.7.3.1 Analyses focused on measures of central tendency

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.

7.1.7.3.2 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 a small proportion of subjects in both the abatacept and placebo arms met the marked abnormality criteria in hematological laboratories. At 12 months there was 1 abatacept-treated subject with a Hgb < 7.5 mmol/L. At 6 months there was 1 abatacept-treated subject with a platelet count < 100 x 10^9/L, and at 12 months there were 4 abatacept-treated subjects with platelet counts < 100 x 10^9/L. No subject had a platelet count < 80 x 10^9/L. Of subjects with normal baseline values, at 6 months there were 2 abatacept-treated subjects with WBC <2.0 x 10^9/L and 14 abatacept-treated subjects with elevations >15 x 10^9/L compared with 10 placebo-treated subjects. At 12 months there were 8 abatacept-treated subjects and 8 placebo-treated subjects with elevations in WBC >15 x 10^9/L. Overall, there were no clinically remarkable differences between the abatacept and placebo groups meeting the marked abnormality criteria.
During the open-label period 1.2% of abatacept-treated subjects on non-biologic and biologic DMARDS had an Hgb value below the normal range. Approximately 1% of subjects had a low leukocyte count, while 3.6% of subjects had an elevated leukocyte count, and 0.2% of subjects had a low platelet count. These changes were not considered clinically significant.

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.

7.1.7.3.3 Marked outliers and dropouts for laboratory abnormalities

Additional analyses were performed to assess AE of hepatic origin. Overall there were few SAE reports suggestive of hepatobiliary disease with similar proportions of SAE reported by subjects in the abatacept (0.4%) and placebo (0.3%) groups, which led to study discontinuation in 8 abatacept-treated subjects and 2 placebo-treated subjects respectively, largely due to elevated transaminasemias (Table 99). The majority of subjects had only 1 liver enzyme reported as abnormal. All events that led to discontinuation during the double-blind period were non-serious.

Table 99. Hepatic-Related AEs that led to discontinuation in the double-blind periods

	Number (%) of Subjects	
Preferred Term	Abatacept (n=1955)	Placebo (n=989)
Subjects that discontinued	8 (0.4%)	1 (0.1%)
Elevated ALT	1 (<0.1%)	1 (0.1%)
Elevated AST	0	1 (0.1%)
Elevated Alk Phos	1 (<0.1%)	0
Elevated Bilirubin	1 (<0.1%)	0
Cholelithiasis	1 (<0.1%)	0
Elevated GGT	2 (0.1%0	0
Elevated hepatic enzyme	1 (<0.1%)	0
Hepatitis	1 (<0.1%)	0
Abnormal LFT test	1 (<0.1%)	0
Elevated transaminases	1 (<0.1%)	0

Assessment of the AEs, SAEs, and laboratory abnormalities do not suggest an increased safety signal regarding hepatotoxicity in the overall RA study population; however, given that 8 abatacept-treated subjects discontinued study drug due to a hepatoxic-related AE should be noted in the package insert.

7.1.7.4 Additional analyses and explorations

Further analyses of the most common AEs suggestive of hepatobiliary disease reported by > 1% of subjects in the abatacept than placebo groups were increased ALT (1.9% vs. 1.5%) and increased AST (1.5% vs 1.1%; Table 100). The majority of ALT and AST enzyme elevations was mild in intensity and rarely resulted in study discontinuation. The majority of these subjects were on a background of MTX or leflunomide both of which are known to be associated with hepatic enzyme elevations and abnormal liver function tests.

Table 100. Most Common Hepatic-Related AEs Reported During Double-Blind Period

	Number (%) of Subjects	
Preferred Term	Abatacept (n=1955)	Placebo (n=989)
Investigations		
Elevated ALT	38 (2%)	15 (1.5%)
Elevated AST	30 (1.5%)	11 (1%)
Elevated hepatic enzymes	17 (1%)	9 (1%)
Elevated GGT	17 (1%)	6 (<1%)
Abnormal LFT test	11 (<1%)	6 (<1%)
Elevated transaminases	7 (<1%)	3 (<1%)
Elevated alkaline phosphatase	4 (<1%)	5 (<1%)
Palpable liver	2 (<1%)	0
Hepatobiliary Disorders		
Cholelithiasis	16 (1%)	7 (1%)
Biliary Colic	2 (<1%)	2 (<1%)
Hepatomegaly	2 (<1%)	1 (<1%)
Biliary Dilitation	2 (<1%)	0
Hepatic Steatosis	1 (<1%)	1 (<1%)
Hepatitis	1 (<1%)	1 (<1%)
Cholecystitis	2 (<1%)	0
Hepatic Cyst	1 (<1%)	0
Hepatotoxicity	1 (<1%)	0
Cholestasis	1 (<1%)	1 (<1%)
Cytolytic Hepatitis	0	1 (<1%)
Abnormal Hepatic Function	0	1 (<1%)
Hepatic Necrosis	0	1 (<1%)
Toxic Hepatitis	0	1 (<1%)

The few AEs of hepatobiliary disease that were reported as related to study drug were predominantly liver function abnormalities for the abatacept group.

Comparisons for ALT at 6 months and 12 months showed a similar proportion of abatacept- and placebo-treated subjects with elevations 3X to ≤ 5X ULN (<0.1% vs. 0.3% at 6 months; 0.1% vs. 0.2% at 12 months). For elevations > 5X ULN there were only 2 abatacept-treated subjects (0.1%) at 6 months and 1 placebo-treated subject (0.2%) at 12 months. Comparisons for AST at 6 and 12 months demonstrated 1 abatacept-treated subject with elevations 3X to ≤ 5X ULN, and for elevations > 5X ULN there was 1 abatacept-treated subject (< 0.1%) and 1 placebo-treated subject (0.2%) at 12 months. These changes were only observed for subjects on a background of non-biologic RA therapy, such as MTX or leflunomide.

Overall, AEs suggestive of hepatobiliary disease were infrequently reported by abatacept-treated subject and were reported by a similar proportion of placebo-treated subjects.

7.1.7.5 Special assessments

Special assessment of hepatobiliary disease can be found in Sections 7.1.7.3 and 7.1.7.4.

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

All of the RA trials included measurements of vital signs (blood pressure, heart rate, temperature) at screening and at all study drug infusion visits (study Days 1, 15, 29 then every 28 days thereafter) just prior to the start of each infusion and 60 minutes after the end of the infusion.

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

Analyses for drug-control comparison of vital signs were performed on the pooled data from the 5 major RA studies outlined in Section 7.1.

7.1.8.3 Standard analyses and explorations of vital signs data

The proportion of subjects who were outliers for blood pressure and heart rate at 6 and 12 months were balanced between treatment groups (data not shown). The proportion of subjects who were outliers for blood pressure and heart rate at 6 and 12 months were balanced between treatment groups. A discussion of subjects with hypertension can be found in Section 7.1.5.4. Overall, the proportion of subjects with blood pressure > 140/90 was similar for both treatment groups.

7.1.9 Electrocardiograms (ECGs)

7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

Preclinical in vivo assessments demonstrated that abatacept did not have any direct or indirect cardiovascular liabilities. Additionally, there are no data to indicate that molecules of the molecular weight (i.e., approximately 100kD) of abatacept are able to access the cardiac ion channels and alter ion currents or channel selectivity, as can be expected to occur with a variety of small molecular drugs. Consequently, no dedicated studies were carried out to evaluate specifically for QT prolongation or other cardiovascular effects in humans. However, ECGs were obtained at baseline and at the end of the double-blind period (or early termination) for all subjects in the 5 core RA studies.

7.1.9.2 Selection of studies and analyses for overall drug-control comparisons

Analyses for drug-control comparison of ECGs were performed on the pooled data from the 5 major RA studies outlined in Section 7.1.

7.1.9.3 Standard analyses and explorations of ECG data

In the double-blind portion of the RA studies there were similar proportions of subjects with abnormal ECGs in the abatacept- (22%) and placebo-treated (20%) subjects. The most common abnormalities were sinus bradycardia, left axis deviation, and sinus tachycardia. Overall there were no clinically significant safety signals or trends identified.

7.1.10 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.

7.1.11 Human Carcinogenicity

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

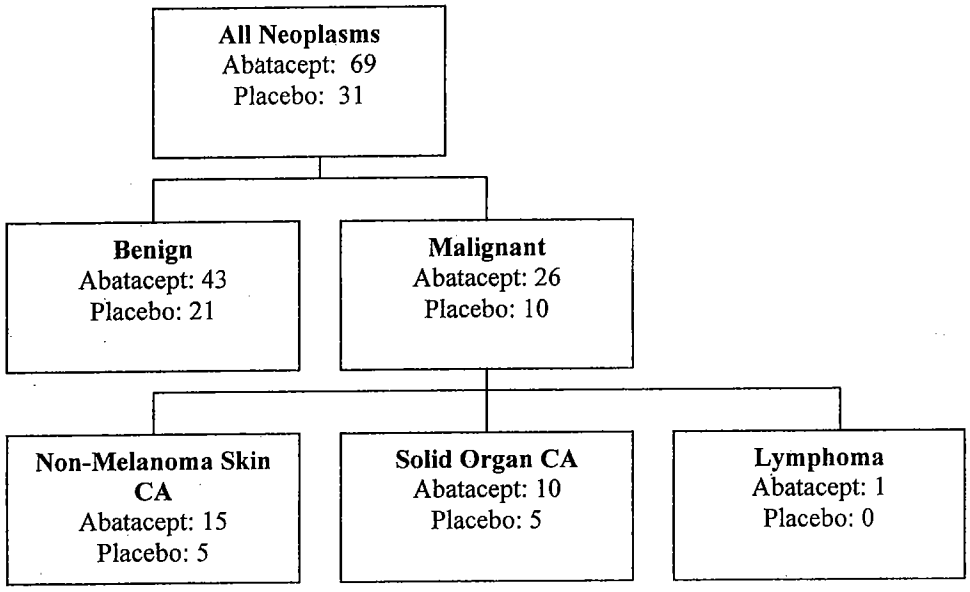
that some immunosuppressives may increase the risk of lymphoma (e.g., MTX, azathioprine, and TNF blockers).

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.

7.1.11.1 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 12). 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 12. 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 101). 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 101. 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
IM101100-255 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

7.1.11.2 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.

7.1.11.3 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

Table 102, 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 (

Table 102).

Table 102. 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 103 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

Table 103). 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 103. 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 104.

Table 104. 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 105.

Table 105. 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.

7.1.11.4 Lung Cancers

There were a total of 8 lung cancers reported in abatacept-treated subjects and none in the placebo-treated subjects. Given the disproportionate number of subjects who developed lung cancer a more detailed review of the individual cases were conducted:

Double-Blind Period

- Subject IM101031-203-10 was a 69-year-old white female non-smoker with RA who received 3 infusions of abatacept 500mg prior to diagnosis of lung cancer on Day 29 of the study. Subject had a normal chest X-Ray at baseline and was asymptomatic but underwent a repeat chest X-ray at her physician's request in which an abnormality was identified. She subsequently underwent biopsy and right pulmonary middle lobectomy with negative regional lymph nodes. She did not require radiation or chemotherapy and the malignancy was considered resolved. Concomitant medications included MTX, azathioprine, and hydroxychloroquine.

- Subject IM101031-161-5 was a 68-year-old white male active smoker (50+ pack-year history) with RA who presented with pulmonary symptoms and hemoptysis by study Day 52 but this resolved then presented again on study Day 100, 15 days after the 5th abatacept infusion, at which time the subject was diagnosed with non-small cell lung cancer. Baseline chest X-ray was consistent with COPD but no evidence of malignancy. Subject under went left pneumonectomy and the event was considered resolved and no adjuvant treatment was administered. Concomitant medications included azathioprine, sulfasalazine, prednisone, celecoxib, diazepam, acetaminophen, and oxycodone/acetaminophen. Staging of the tumor, the temporal relationship of the clinical presentation, and subject's smoking history suggests the tumor was pre-existent to the administration of abatacept.

- Subject IM101031-97-25 was a 72-year-old white female active smoker (80 pack-year history) with RA diagnosed with squamous cell lung CA after 13 infusions of abatacept. Subject presented with thoracic pain on study Day 275 and on Day 320 was found to have a pulmonary apical mass. A retrospective review of the subject's previous chest X-rays 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. During subsequent cancer staging a left renal mass was observed and biopsy revealed a primary renal cell carcinoma. Given the results of the baseline chest X-ray it would appear that the subject had pre-existent lung cancer prior to study enrollment. It is difficult to ascertain what role, if any, abatacept may have played in the simultaneous occurrence of the renal cell carcinoma.

- Subject IM101100-35-2 was an 83-year-old white male with a history of cigarette smoking but discontinued for 10 years, and benign prostate hypertrophy or cancer. On study Day 332, after 13 infusions of abatacept, a routine chest X-ray revealed a vague density on the right lobe that was found to be malignant and the family refused treatment. Baseline chest X-ray was without masses or nodules.

In 3 of the 4 cases of lung cancer there was a substantial smoking history, a well-known risk factor for lung cancer. Malignancy was present in 1 of the cases (subject IM101031-97-25) prior to treatment with abatacept and there is strong evidence to suggest pre-existing malignancy in another case (Subject IM101031-161-5) as well.

Open-Label Period

- Subject IM101031-71-6 was a 62-year-old white female former smoker with a 96 pack-year history who was randomized to the abatacept arm (750 mg) during the double-blind portion of the study and received 2 infusions in the open-label period, On study Day 404 she underwent bronchoscopy with biopsy of the left upper lung lobe which revealed small cell carcinoma of the lung. Concomitant RA therapy included MTX, prednisone, sulfasalazine, hydroxychloroquine, and leflunomide. She had received etanercept, anakinra and valdecoxib in the past. Subject died on study Day 554.

- Subject IM101100-21-1 was a 61-year-old white female with a smoking history of 10 pack years who was diagnosed with adenocarcinoma of the lung during the open-label period of IM101100. Her pre-treatment chest X-ray was interpreted as abnormal with signs of interstitial fibrosis that were felt to be not clinically significant. During the double-blind portion of the study she had received 10 mg/kg abatacept and received 4 infusions of abatacept in the open-label period before undergoing femoral bypass surgery on Day 427 for severe arterial insufficiency of the lower extremities. On study Day 470 she presented with severe pleural effusions and ultimately diagnosed with adenocarcinoma with pleural metastasis. Subject died on study Day 538.

- Subject IM101102-14-5 was a 71-year-old white female active smoker with a 68 pack-year history who was diagnosed with lung cancer on Day 397. She had received 13 infusions of abatacept during the double-blind period and 1 infusion during the open-label portion of the study. A retrospective review of the pre-treatment chest X-ray revealed an apical dorsal consolidation of the left superior lobe of the lung measuring 5.2 x 2.6 cm.

- Subject IM101102-98-12 was a 63-year-old white male active smoker with a 44 pack-year history who was diagnosed with lung cancer during the open-label portion of the study. On study Day 415 the subject underwent a CT for persistent cough and dyspnea and was found to have a mass in the posterior segment of the left lower lobe. Biopsy revealed a well-differentiated adenocarcinoma versus bronchiole-alveolar carcinoma. A retrospective review of the pre-treatment chest X-ray revealed bibasilar reticular nodular changes in the subhilar region of the lungs.

In each of the 4 cases subjects had a substantial smoking history. There appears to be strong evidence that at least 1 of the cases (subject IM101102-14-5) had a pre-existing tumor prior to treatment with abatacept based on pre-treatment chest X-ray.

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 106).

Table 106. 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 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

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.

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]

entire abatacept population to a comparable RA cohort (Table 107). These analyses demonstrate the expected number of lung cancers in the abatacept group would range from 3.6 to 10 (data not shown).

Table 107. 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.
- 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

7.1.11.5 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 and is summarized here:

IM101101-34-5 is a 42-year-old, white, female, weighing 66 kg with RA who enrolled in study IM101101, which evaluated abatacept 2 mg/kg +/- etanercept. The subject initiated treatment with abatacept + etanercept on 16-MAY-2001 for a total of 7 infusions of abatacept and discontinued study participation on study Day 176 (07-NOV-2001) due to lack of efficacy. At the time of discontinuation, the subject was receiving the following medications: etanercept, prednisone, risidronate sodium, alprazolam, sertraline hydrochloride, lansoprazole, and nizatidine. The subject's screening mammogram, performed on study Day -61 [ ], was reported to be normal. An annual mammogram, performed on study Day 324 [ ], was reported by the investigator to be abnormal and clinically relevant. On study Day 392 [ ] a breast biopsy was performed and the subject was diagnosed with ductal breast carcinoma. It was later reported that the subject subsequently developed ductal breast carcinoma in the contralateral breast.

It is difficult to attribute the above 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.

7.1.11.6 Lymphomas

During the double-blind period 1 subject developed lymphoma compared to none in the placebo group. A narrative for subject IM101102-39-9 follows:

IM101102-39-9 is an 81-year-old, female, weighing 81 kg receiving treatment with abatacept (750 mg) + methotrexate for a total of 10 infusions prior to the event. Significant prior medical history included hypothyroidism and bladder cancer (1992) who developed a large B-cell lymphoma. Concomitant medications also included levothyroxine. On study Day 241 [ ] 7 days after the last infusion, the subject underwent CT scan of the neck and chest that confirmed the presence of a 4.5 cm mass at midline that appeared to originate from the isthmus of the thyroid. Right and left lobes of the thyroid were enlarged and the mass was causing

airway obstruction and left vocal cord paralysis. There was no evidence of parapharyngeal, cervical, or supraclavicular lymphadenopathy. A biopsy of the mass, taken on study Day 248 [ ] was inconclusive. The subject was admitted to the hospital on study Day 254 [ ] for subtotal thyroidectomy and frozen section biopsy. Pathologic diagnosis found the subject to have diffuse large B-cell lymphoma and Hashimoto's thyroiditis. The subject was treated with surgery and chemotherapy in response to the event. Study medication was discontinued as a result of this event and the subject discontinued the study on study Day 275 [ ]

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. A narrative follows:

IM101101-14-2 is a 61-year-old female with a history of alcohol use, pancreatitis and depression who was diagnosed with a diffuse B-cell lymphoma in the open-label period of IM101101. During the double-blind period she was randomized to 2 mg/kg of abatacept. She received 25 infusions of abatacept in the open-label period while continuing to receive etanercept. On study Day 1086, hepatosplenomegaly was reported. Liver biopsy on study Day 1099 revealed Stage 4 diffuse large B-cell lymphoma with metastases to the spleen, bone marrow, lungs and central nervous system. Multi-system organ failure ensued and she died in hospice on study Day 1115.

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.

7.1.11.7 Most Frequently Observed Malignancies

Table 108 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

[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.

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.

Table 108. 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

7.1.12 Special Safety Studies

7.1.12.1 Co-Morbid Conditions

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 109): diabetes mellitus (n=96), asthma (n=83), COPD (N=54), and CHF (N=18).

[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 109. 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)
SAEs	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)
AEs	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)

7.1.12.1.1 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.

7.1.12.1.2 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.

7.1.12.1.3 Asthma and CHF

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

7.1.12.2 Comparison of AE with Abatacept 10 mg/kg vs. Tiered-Dosing

The sponsor intends on marketing abatacept using a tiered-dose regimen whereby patients will receive approximately 10 mg/kg. This dosing 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, 2 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 (Phase II) was compared with that for abatacept tiered-dose that approximated 10 mg/kg used in the similarly designed study IM 101102 (Phase III). 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 110 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 in 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 110. 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 111 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. Although, abatacept-treated subjects weighing >110 kg had an approximately 6-fold greater frequency of SAE than placebo-treated subjects, the sample size is very small and it is difficult to draw firm conclusions from the data.

Table 111. 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 112 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 112. 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 113 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 113. 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 summary, although there is dose variation for subjects at the extremes of the weight intervals for the proposed abatacept tiered-dose regimen, AE, SAE, serious infections, and serious neoplasms do not seem to occur at a higher or lower frequency based on the variations of abatacept dose.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

Study IM103002 was a randomized, double-blind, placebo-controlled, parallel, multiple-dose study with the primary objective to assess the relative safety and efficacy of abatacept monotherapy and BMS-224818 (molecularly similar to abatacept) monotherapy in subjects with RA. The study also specifically collected data to assess the potential for RA subjects to develop RA flares upon discontinuation of abatacept and BMS-224818.

A total of 216 subjects were randomized to 1 of 8 dosing groups, of which 214 received treatment: abatacept at 0.5 mg/kg (N=26), 2 mg/kg (N=32) or 10 mg/kg (N=32); BMS-224818 at 0.5 mg/kg (N=32), 2 mg/kg (N=29) or 10 mg/kg (N=31); or placebo for abatacept or for BMS-224818 (N=32). Study medication was administered by IV infusion over 1 hour on Days 1, 15, 29, and 57.

During the double-blind period (Days 1-85), worsening RA/flare was reported as a SAE in 0% of abatacept-treated subjects compared with 9.4% of placebo-treated subjects. During the follow-up period (Days 86-169), serious reports of worsening RA/flare were reported by 5.6% of abatacept-treated subjects compared with 3.1% of placebo-treated subjects.

Thus, there does not appear to be an increase in the risk of RA flare in subjects previously treated with abatacept compared with those previously treated with placebo based on the safety data from study IM101031.

There was no evidence of abuse potential in any of the RA clinical studies reviewed.

7.1.14 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. Subject IM101031-159-5 had a history of 2 previous spontaneous abortions; subject IM101031-109-26 had a history of a previous unsuccessful pregnancy, and subject IM101102-19-6 had no prior history of pregnancy. Subject IM101102-141-11 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.

Although there are no adequate and well-controlled studies in pregnant women, animal studies have demonstrated rare adverse events in rodent offspring. Given the theoretical concern of T-cell co-stimulatory inhibition and possible development of autoimmunity during the neonatal period, it would be appropriate for abatacept to be considered a pregnancy category C.

7.1.15 Assessment of Effect on Growth

Abatacept has not been studied in the pediatric population to date but future studies are planned by the sponsor in juvenile idiopathic arthritis where the effect on growth will be assessed.

7.1.16 Overdose Experience

Doses of abatacept up to 50 mg/kg were administered to subjects with psoriasis on Days 1, 3, 16, and 29 without apparent toxic effect. There were no incidences of overdosing of abatacept in the RA studies. However, since abatacept was administered as a tiered-dose based on subjects weight there were minor variations in the actual dose received based on a mg/kg basis. 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. Weight-based analysis is discussed in Section 7.1.12.

7.1.17 Postmarketing Experience

Abatacept is not approved for use for any indication anywhere in the world. Consequently, there is no postmarketing experience with abatacept.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

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 114). 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) with a mean duration of exposure of 12 months. Approximately 58% of subjects were exposed to 10 mg/kg of abatacept for >12 months.

Table 114. 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 of 2670 subjects (98%) receiving the recommended dose of abatacept for a mean of 12 months representing 2621 person years of exposure.

7.2.1.1 Study type and design/patient enumeration

Section 4 describes the overall clinical development of abatacept for RA.

7.2.1.2 Demographics

The baseline characteristics of the safety database are shown in Table 115. There were no baseline imbalances between study arms with the majority of subjects being white and female, mean age of 52 years, and mean weight of 74 kg. The study population is representative of subjects with RA in the US.

Table 115. Baseline Demographic of Abatacept Safety Database

	Abatacept (n=1955)	Placebo (n=989)
Age (years, mean ± SD)	53±12	52±12
Weight (kg, mean ± SD)	74 ± 19	74 ±19
Gender (female)	1543 (79%)	788 (80%)
Race		
White	1716 (88%)	864 (87%)
Black	76 (4%)	41 (4%)
American Indian	3 (<1%)	1 (<1%)
Asian	18 (4%)	10 (5%)
Other	23 (5%)	11 (5%)
Geographical Region		
North America	891 (46%)	444 (45%)
South America	451 (23%)	234 (24%)
Europe	483 (25%)	243 (25%)
ROW	130 (7%)	68 (7%)

The baseline disease characteristics of the study subjects are shown in

Table 116.
Despite an average dose of MTX 16 mg/week, subjects still demonstrated active RA as demonstrated by the number of swollen joints (~21), tender joints (~31), and elevated CRP (~2.6 mg/dL). The mean duration of RA was approximately 10 years. There were no imbalances between arms.

Table 116. Baseline Disease Characteristics of the Abatacept Safety Database

	Abatacept + MTX (n=433)	Placebo + MTX (n=219)
Duration of RA (years, mean ± SD)		
Median	8	7
Mean ± SD	10 ± 9	10 ± 9
≤2 years	407 (21%)	200 (20%)
>2-≤5 years	367 (19%)	203 (21%)
>5-≤10 years	424 (22%)	223 (23%)
> 10 years	756 (39%)	360 (36%)
Swollen joints (mean ± SD)	21 ± 9	22 ± 9
Tender joints (mean ± SD)	31 ± 13	32 ± 13
Physical Function (HAQ)	1.7	1.7
CRP	2.6	2.6

7.2.1.3 Extent of exposure (dose/duration)

The majority of RA trials for abatacept were conducted using ~10 mg/kg with subjects completing the double-blind periods and continuing into open-label periods resulting in 1586 subjects having safety data collected at the proposed licensed dose of abatacept for greater than 12 months at the time of the submission.

As noted above in Section 7.2.1.1, 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. 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) with a mean duration of exposure of 12 months. Approximately 58% of subjects were exposed to 10 mg/kg of abatacept for >12 months.

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.

Additional analyses were conducted regarding the comparison of AEs with abatacept 10 mg/kg and abatacept tiered-dose regimen since abatacept was administered as a tiered-dose based on a subject's baseling weight (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, there were minor variations in the actual dose received based on a mg/kg basis. 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. Weight-based analysis of safety is discussed in Section 7.1.12.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

There is no postmarketing experience with abatacept. The sponsor did not submit any secondary source data and consequently this review does not consider any secondary clinical data sources.

7.2.3 Adequacy of Overall Clinical Experience

This application and review rely primarily on the 5 major RA studies (IM101100, IM101101, IM101102, IM101029, and IM101031) and study IM103002 for evidence of the efficacy and

safety of abatacept. These 6 studies provide placebo-controlled experience with abatacept in 2760 subjects with RA and provide a sufficiently large primary database in this disease. The number of subjects in the abatacept RA studies exceeds the minimum size of the safety database recommended in the ICH EIA document for products intended for long-term treatment of non-life-threatening diseases. The assessment of safety in this review is based on a median of 14 months of exposure to abatacept, which is adequate to make an initial safety assessment.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

Pre-clinical testing in mice revealed an increased incidence of mammary tumors and lymphomas, which were later confirmed to be due to re-activation of the murine retroviruses (MMTV and MLV, respectively) as a result of abatacept-induce immunosuppression. The remainder of the pre-clinical testing was unremarkable. For a complete review of pre-clinical animal pharmacology/toxicology refer to the review by Dr. Hanan Ghantous.

7.2.5 Adequacy of Routine Clinical Testing

The methods and timing of acquisition of vital signs, ECG, laboratory, immunogenicity, and AEs data in all of the RA clinical trials were adequate to assess the safety of abatacept and are described in section 7.1.7 (lab findings), 7.1.8 (vital signs, etc..)

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

The metabolic, clearance, and drug-interaction appears adequate and is discussed in Dr. Anil Rajpal's Clinical Pharmacology review.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

Abatacept is a is a fully human, recombinant, soluble fusion protein consisting of the extracellular domain of human CTLA-4 and a fragment of the Fc domain of human IgG1 that acts to inhibit T-cell activation. Consequently, anticipated AEs for abatacept include infections, malignancies, infusion reactions, and immunogenicity. Discussion of these events as they occurred in the RA clinical trials can be found in sections 7.1.2.1, 7.1.11, 7.3.2 and 7.1.10.

This reviewer recommends further study of abatacept regarding the following safety issues:

- The effect of abatacept on pregnancy outcomes including the postnatal health status of the children.
- The effect of abatacept in the pediatric population with juvenile idiopathic arthritis.

- The effect of abatacept of neoantigen immunization and on recall antigen responses. Since abatacept is an immunosuppressant, it may interfere with the ability to generate a beneficial response to a vaccine.

See Section 9 for postmarketing commitments.

7.2.8 Assessment of Quality and Completeness of Data

The data provided for the safety review is of very high quality and included 5 major RA clinical trials that were multicenter, randomized, double-blind, and placebo-controlled. The studies included subjects on concomitant background RA therapy, biologic and non-biologic, as well as enrolling a representative target RA population and subjects with co-morbidities.

7.2.9 Additional Submissions, Including Safety Update

7.2.9.1 4-Month Safety Update

The original application was submitted on 12/20/2004. A 4-month safety update report was submitted on 5/9/05 for the 5 major RA trials (IM101100, IM101101, IM101102, IM101029, and IM101031).

7.2.9.1.1 Subject Disposition

Small numbers of subjects discontinued abatacept during the 4-month incremental period: 1.4% in IM101100; 0% in IM101101; 3.5% in IM101102; and 4.6% in IM101031. Approximately 17% of subjects in study IM101029 discontinued mostly due to lack of efficacy (11%), the majority of which were non-responders during the double-blind period.

7.2.9.1.2 Deaths

The sponsor reported a total of 8 deaths during the 4-month period, however, 5 of the 8 deaths have already been accounted for in this review. Consequently, there were 3 deaths during the 4-month period:
Subject IM101031-102-18 was a victim of homicide
Subject IM101031-1-4-14 was a 42-year-old female with history of aortic and mitral valve insufficiency who developed severe decompensated CHF and underwent valve replacement surgery but died several days post-operatively due to suture dehiscence
Subject IM101102-81-1 was a 65-year-old female with medical history of hypertension who died of myocardial ischemia

7.2.9.1.3 Serious Adverse Events

A total of 17 subjects experienced a SAE during the 4-month period of studies IM101100 and IM101101.

- 7 SAE due to musculoskeletal and connective tissue disorders (generally related to underlying RA)
- 3 SAE due to infections (viremia, otitis externa, and pneumonia)
- 2 SAE due to nervous system disorders (both CVAs)
- 2 SAE due to surgical and medical procedures (surgical sterilization and CABG)
- 2 SAE due to general disorders (hernia and chest pain.

There were no unusual SAEs reported during this period for these studies.

Table 117 shows the incidence rates of SAE of clinical interest reported by abatacept-treated subjects in all Phase III studies. The rates of these SAEs were comparable between the double-blind and open-label periods of the studies.

Table 117. Incidence Rates of SAEs of Clincal Interest Reported by Abatacept-Treated Subjects in the Phase III RA Studies

	Number (incidence rate/100 person-years)		
	IM101102	IM101029	IM101031
Total person-years of exposure	OL/DB OL=398/DB=410	OL/DB OL=293/DB=115	OL/DB OL=794/DB=899
Total SAEs	57 (19)/67 (20)	67 (30)/67 (37)	105 (17)/126 (20)
Musculoskeletal	21 (5)/22 (5)	30 (10)/6 (5)	25 (3)/31 (3)
Infections	15 (4)/17 (4)	12 (4)/6 (5)	23 (3)/28 (3)
Serious Neoplasms	6 (1.5)/5 (1.2)	6 (2)/4 (3.5)	7 (1)/17 (2)

OL=open-label period; DB=double-blind period

During the 4-month incremental period, the first 2 cases of polyneuropathy were reported as SAEs. One subject received abatacept in the double-blind period of study IM101102 and the other subject received placebo in the double-blind period of study IM101031. Two non-serious cases were reported during the double-blind period of study IM101031 (1 subject from each treatment arm). There were 3 cases of disseminated Herpes infection (2 cases of shingles and 1 case of Herpes zoster) in 3 subjects who had reported a non-serious Herpes infection in the double-blind period.

7.2.9.1.4 Malignancies

There were 4 malignancies reported during the 4-month incremental period.
Breast cancer. Subject IM101029-88-9 is a 38 year-old female with a normal mammogram at study baseline. She received a total of 15 doses of abatacept 750 mg and was found to have an abnormal finding on her annual mammogram. Fine-needle biopsy revealed low to moderate

grade ductal carcinoma with staging $T_{IS}N_0M_0$. She was discontinued from the study and is undergoing radiation and chemotherapy.

Endometrial cancer. Subject IM101102-145-9 is a 44 year-old female who received a total of 22 infusions with abatacept 750 mg. The subject underwent an endometrial biopsy due to vaginal bleeding and was found to have adenocarcinoma of the endometium. Subject was discontinued from study and underwent hysterectomy and will follow with an oncologist for follow-up therapy if necessary.

Lymphoma. Subject IM101102-136-15 is a 46 year-old male on concomitant MTX who received 14 placebo infusions during the double-blind portion of the study and 8 abatacept 750 mg infusions during the open-label period. Subjects were evaluated for inguinal lymphadenopathy and a subsequent fine-needle biopsy confirmed the diagnosis of non-Hodgkin's lymphoma (high-grade, large cell type). Subject was discontinued from study and will have chemotherapy initiated.

Malignant melanoma in situ. Subject IM101031-177-12 is a 70-year old male who received 16 doses of abatacept 750 mg. Subject had a lesion removed that was found to be malignant melanoma. The subject was discontinued from the study. The case is ongoing and subject is being referred for further evaluation by a dermatologist.

The incidence rate of neoplasms and malignancies by 6-month intervals is shown in Table 118. Although there is limited exposure beyond 2 years, there does not appear to be a trend in the incidence of neoplasms or malignancies with continued abatacept exposure. The low number of subjects and total person-years of exposure for each 6-month interval declined with few events resulting in fluctuating incidence rates.

Table 118. Incidence Rates by 6 Month Intervals for Neoplasms

	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
Neoplasms (Benign & Malignant)	44 (3.45) (2.5, 4.6)	43 (4.20) (3.0, 5.7)	33 (4.19) (2.9, 5.9)	11 (2.77) (1.4, 5.0)	7 (6.04) (2.4, 12.4)	7 (3.61) (1.5, 7.4)
Total Malignancies	15 (1.17) (0.7, 1.9)	17 (1.65) (1.0, 2.7)	11 (1.39) (0.7, 2.5)	3 (0.75) (0.2, 2.2)	3 (2.57) (0.5, 7.5)	3 (1.52) (0.3, 4.5)
Total Malignancies excluding NMSC	6 (0.47) (0.2, 1.0)	8 (0.78) (0.3, 1.5)	7 (0.88) (0.4, 1.8)	1 (0.25) (0.01,1.4)	2 (1.71) (0.2, 6.2)	2 (1.01) (0.1, 3.6)

7.2.9.1.5 Discontinuations Due to Adverse Events

Discontinuations by Study:
IM101100: 1 subject (<1%) due to possible pregnancy
IM101101: 0 subjects
IM101102: 11 subjects (2%) most commonly due to neoplasms (0.7%)
IM101029: 12 subjects (4%) most commonly due to neoplasms (1.6%)
IM101031: 18 subjects (2%) most commonly due to infection (0.3%)

7.2.9.1.6 Pregnancies

1 subject who had received 7 infusions of abatacept withdrew from the study to become pregnant. Subject is currently pregnant without incident. Another subject reported a possible pregnancy and was discontinued from the study but was later found to not be pregnant.

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7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

Important AEs that are likely to be treatment-related include infections and infusion reactions.

7.3.1 Infections

The incidence of upper respiratory infections, nasopharyngitis, urinary tract infections, influenza, rhinitis, Herpes simplex, and pneumonia were increased in subjects who received abatacept. These infections presented in a typical manner and followed a typical clinical course.

7.3.2 Infusion Reactions

Infusion reactions that occurred within 1 hour after study drug infusion were more common in the abatacept group compared to the placebo group. The most commonly reported events were of mild to moderated intensity and included dizziness, headache, and hypertension. A larger proportion of abatacept-treated subjects also experienced infusion reactions within 24 hours after the start of the infusion compared to placebo-treated subjects. 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, dizziness, nausea, hypertension, flushing, and arthralgia.

There was 1 case of anaphylactic/anaphylactoid reaction in the double-blind period and 1 case in the open-label period. 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.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

This safety review pooled data from the 5 major RA clinical trials (IM101100, IM101101, IM101102, IM101029, and IM101031) and the individual study IM103002 evaluating abatacept monotherapy.

7.4.1.1 Pooled data vs. individual study data

This safety review used pooled data from studies IM101100, IM101101, IM101102, IM101029, and IM10031. Study IM103002 was reviewed individually.

7.4.1.2 Combining data

This review combines studies by simple combination of numerators and denominators and does not employ other pooling procedures.

7.4.2 Explorations for Predictive Factors

7.4.2.1 Explorations for dose dependency for adverse findings

The sponsor intends on marketing abatacept using a tiered-dose regimen whereby patients will receive approximately 10 mg/kg. This dosing was used in Phase III trials where 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, 2 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 (Phase II) was compared with that for abatacept tiered-dose that approximated 10 mg/kg used in the similarly designed study IM 101102 (Phase III). 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 119 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 in 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 119. 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 120 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. Although, abatacept-treated subjects weighing >110 kg had an approximately 6-fold greater frequency of SAE than placebo-treated subjects, the sample size is very small and it is difficult to draw firm conclusions from the data.

Table 120. 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 121shows 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 121. 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 122 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 122. 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 summary, although there is dose variation for subjects at the extremes of the weight intervals for the proposed abatacept tiered-dose regimen, AE, SAE, serious infections, and serious neoplasms do not seem to occur at a higher or lower frequency, respectively, based on the variations of abatacept dose.

7.4.2.2 Explorations for time dependency for adverse findings

Infusion reactions, by definition, occurred close to the time of abatacept administration. Additionally, 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 85. 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.

7.4.2.3 Explorations for drug-demographic interactions

Approximately 85% of subjects in both treatment arms were younger than 65 years of age. A similar frequency of AEs occurred in abatacept- and placebo-treated subjects <65 years-old and subjects ≥65 years-old (Table 123). A greater proportion of subjects ≥65 years-old reported cough, hypertension, and peripheral edema compared with both abatacept- and placebo-treated subjects < 65 years-old (data not shown).

In contrast, SAEs occurred at a greater frequency in abatacept-treated subjects ≥65 years of age but not for subjects <65 years-old (Table 123).

Table 123. AEs and SAEs during Double-Blind Periods based on Age, Sex, Race, and Weight

	AEs		SAEs	
	Abatacept	Placebo	Abatacept	Placebo
Total Subjects	1736 (89%)	840 (85%)	266 (14%)	122 (12%)
Age (years)				
<65	1447 (89%)	710 (84%)	188 (12%)	98 (12%)
≥65	289 (90%)	139 (88%)	78 (24%)	24 (16%)
Sex				
Male	351 (85%)	166 (83%)	64 (16%)	27 (13%)
Female	1385 (90%)	674 (86%)	202 (13%)	95 (12%)
Race				
White	1515 (88%)	725 (84%)	245 (14%)	102 (12%)
Black	70 (92%)	39 (95%)	5 (7%)	5 (12%)
Other	151 (93%)	76 (91%)	16 (10%)	15 (18%)
Weight (kg)				
<60	434 (89%)	193 (85%)	65 (13%)	27 (12%)
60-100	1133 (88%)	564 (85%)	175 (14%)	83 (13%)
>100	168 (92%)	82 (85%)	26 (14%)	12 (12%)

Table 124, shows the frequency of SAEs were higher in both abatacept- and placebo-treated subjects ≥ 65 years of age. The most common SAEs in subjects < 65 years of age were reported in similar frequencies in the abatacept and placebo groups. The frequency of bronchitis, dyspnea, chest pain and fall (each reported in < 1% of abatacept-treated subjects) were higher with abatacept-treated subjects compared with placebo-treated subjects ≥ 65 years-old. The SAEs observed in subjects ≥ 65 years-old are commonly reported by older subjects. Additionally, although the frequency of several individual SAEs was higher in abatacept- compared with

placebo-treated subjects, the data are limited by the relatively small number of subjects reporting individual SAEs.

Although there was an overall increase in the number of SAEs in abatacept-treated subjects ≥65 years-old, there was no single event that disproportionately accounted solely for the increased incidence rate.

Table 124. Selected SAEs during Double-Blind Period by Age (≥2 subjects in any abatacept group)

	Age <65		Age ≥ 65	
	Abatacept (n=1632)	Placebo (n=841)	Abatacept (n=323)	Placebo (n=148)
Total SAEs	188 (12%)	98 (12%)	78 (24%)	24 (16%)
RA	32 (2%)	17 (2%)	5 (1%)	2 (1%)
Chest Pain	8 (<1%)	4 (<1%)	3 (<1%)	0
Pneumonia	5 (<1%)	3 (<1%)	4 (1%)	2 (1%)
Cholelithiasis	4 (<1%)	2 (<1%)	1 (<1%)	1 (<1%)
Abdominal Pain	3 (<1%)	1 (<1%)	1 (<1%)	0
Cellulitis	3 (<1%)	2 (<1%)	2 (<1%)	0
TIA	3 (<1%)	0	0	1 (<1%)
UTI	3 (<1%)	1 (<1%)	1 (<1%)	0
Anemia	2 (<1%)	2 (<1%)	1 (<1%)	0
CVA	2 (<1%)	1 (<1%)	1 (<1%)	0
COPD Exacerbation	2 (<1%)	0	1 (<1%)	0
DVT	2 (<1%)	0	1 (<1%)	1 (<1%)
Pleural Effusion	2 (<1%)	1 (<1%)	1 (<1%)	0
Acute Pyelonephritis	2 (<1%)	0	1 (<1%)	0
Bronchitis	1(<1%)	0	3 (1%)	0
CHF	0	3 (<1%)	4 (1%)	2 (1%)
Dyspnea	0	3 (<1%)	3 (1%)	0
Fall	0	2 (<1%)	3 (1%)	0
Angina	0	1 (<1%)	2 (<1%)	1 (<1%)
CAD	0	0	2 (<1%)	0
Lung Neoplasms	0	0	2 (<1%)	0
MI	0	2 (<1%)	2 (<1%)	0

Sex

Approximately 79% (n=2331 of 2944 total subjects) of all subjects in the RA studies were female. A similar frequency of AEs occurred in abatacept- and placebo-treated male subjects (75% vs. 83%, respectively) and female subjects (81% and 86%, respectively). SAEs also occurred at similar frequencies between abatacept- and placebo-treated male subjects (16% vs. 14%, respectively) and female subjects (13% and 12%, respectively). There were no medically significant AEs that would limit the use of abatacept in older patients.

Race

Approximately 88% (n=2580 of 2944 total subjects) of all subjects in the RA studies were White, and thus interpretation of the data for the incidence of AEs and SAEs of Black n=(117 of 2944 total subjects) and "Other" (n=147 of 2944 total subjects) subjects must be interpreted with caution given the small number of subjects. In general, the pattern of AEs and differences between treatments appears to be consistent in all racial subgroups with the proportion of White, Black, and "Other" abatacept-treated subjects reporting AEs (88%, 92%, and 93%, respectively) compared to placebo-treated subjects (84%, 95%, and 91%, respectively). There were no AEs of particular concern in any racial subgroup. SAEs also occurred at similar rates between White subjects receiving abatacept compared to placebo (14% vs. 12%, respectively). Black and "Other" subjects had a lower frequency of SAEs who received abatacept (7% vs. 10%, respectively) compared to those who received placebo (12% vs. 18%, respectively). These data should be interpreted cautiously in light of the small number of subjects in each group. There were no medically significant AEs that would limit the use of abatacept in older patients

Weight

Review of AEs and SAEs by subject weight is discussed in Section 8.1.3.

7.4.2.4 Explorations for drug-disease interactions

The study population consisted almost entirely of subjects with established RA (mean 9 years) on background RA therapy who met the 1987 ACR diagnostic criteria for RA. Additional exploratory safety analyses for a drug-disease interaction are unlikely to reliable and are not warranted.

7.4.2.5 Explorations for drug-drug interactions

Subjects treated with abatacept and concomitant biologic RA therapy reported an increase in overall infections compared to subjects receiving placebo and a biologic RA therapy (64% vs. 43%, respectively), as well as serious infections (4.4% vs. 1.5%, respectively). Section 7.1.5.6 discusses the safety and efficacy, respectively, of the combination of abatacept and concomitant biologic RA therapy. Overall, the combination of abatacept and concomitant biologic RA therapies, especially TNF-blockers, appears to increase the incidence of AEs, SAEs, and infections. Efficacy data of the combination therapy with the proposed dose of abatacept 10 mg/kg is limited. Thus, the combination of abatacept with other biologic DMARDs is associated with an increased safety signal and unproven efficacy.

7.4.3 Causality Determination

AEs that are most clearly associated with abatacept administration include infections and infusion reactions.
Infections: although the increase in incidence of infections associated with abatacept administration is small, an increase in risk of infection is expected based on abatacept's mechanism of action. The increased risk of infection is consistent across studies.

Infusion reactions: the incidence of infusion reactions is higher in abatacept-treated subjects,which is not unexpected since abatacept is an exogenous foreign protein.

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8 ADDITIONAL CLINICAL ISSUES

8.1 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. As discussed below in Sections 8.1.1 and 8.1.2, these 2 studies clearly demonstrate that the abatacept 10 mg/kg dose is clinically superior to the 2 mg/kg and 0.5 mg/kg doses.

8.1.1 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 125 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 125. 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 with 8% and 6% of the of the abatacept 10 mg/kg and 2 mg/kg subjects, respectively, achieving the endpoint compared to 1% of placebo-treated subjects. Additionally, a greater proportion of subjects in the 10 mg/kg group and 2 mg/kg group achieved an improvement in physical function as assessed by an improvement in baseline HAQ score ≥0.3u at Day 360 compared to the placebo group (38%, 30%, and 20%, respectively).

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 higher incidence of AEs.

8.1.2 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), the molecularly related drug BMS-224818 (0.5 mg/kg, 2 mg/kg or 10 mg/kg), or placebo infusions at Days 1, 15, 29, and Day 57. Table 126 shows the dose-response relationship of abatacept, and BMS-224818 as assessed by the proportion of subjects achieving an ACR 20, ACR 50, and ACR 70 at Day 85.

Table 126. Study IM103002: Number of Subjects Achieving an ACR 20 Response on Day 85

	Placebo	Abatacept			BMS-224818		
	(n=32)	0.5 mg/kg (n=26)	2 mg/kg (n=32)	10 mg/kg (n=32)	0.5 mg/kg (n=32)	2 mg/kg (n=29)	10 mg/kg (n=31)
ACR 20 Responders N (%)	10 (31%)	6 (23%)	14 (44%)	17 (53%)	11 (34%)	13 (45%)	19 (61%)
ACR 50 Responders N (%)	2 (6%)	0	6 (19%)	5 (16%)	3 (9%)	3 (10%)	19 (61%)
ACR 70 Responders N (%)	0	0	4 (13%)	2 (6%)	2 (6%)	1 (3%)	1 (3%)

Details of the efficacy of study IM103002 are discussed in Section 6.1.4.6, 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. BMS-224818, which is a closely related molecule to abatacept with the same mechanism of action, also demonstrated a similar dose-response relationship with similar efficacy. Safety review of study IM103002 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.

8.1.3 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. Safety analyses have been discussed in Section 7.1.12.2. To summarize, although there is dose variation for subjects at the extremes of the weight intervals for the proposed abatacept tiered-dose regimen, AE, SAE, serious infections, and serious neoplasms do not seem to occur at different incidence rates based on the variations of abatacept dose.

ACR 20 responses and clinically meaningful HAQ responses (≥0.3u improvement from baseline) for abatacept-treated subjects in studies IM101102 and IM101029 were higher than those for placebo-treated subjects in all of the weight categories (data not shown). The HAQ responses in study IM101031 were also consistently higher for abatacept-treated subjects than for placebo-treated subjects (data not shown).

There does not appear to be a relationship between ACR 20 response or HAQ response and weight (by 10 kg intervals). This lack of relationship is further supported by the lack of a relationship between efficacy and weight in the dosing subgroups around the tiered-dose cut-points of 60 kg and 100 kg.

8.1.4 Dosing Regimen Summary

In summary, abatacept 10 mg/kg was the highest dose tested in subjects with RA, and was clearly more effective than either the 0.5 mg/kg or 2 mg/kg doses. Although abatacept 10 mg/kg proved to be the most effective of the doses tested, it is not known whether higher doses would have been more efficacious and perhaps further improves clinical outcomes, in particular, induction of a greater degree of inhibition of structural damage. Analyses of the abatacept tiered-dosing regimen based on the subject's weight compared to 10 mg/kg dosing did not demonstrate safety or efficacy concerns despite dose variation at the extremes of weight intervals. Furthermore, review of the safety database did not identify any special population that would require alteration of the proposed dosing regimen. In conclusion, the sponsor's proposed dosing regimen appears adequate.

8.2 Drug-Drug Interactions

Subjects treated with abatacept and concomitant biologic RA therapy reported a higher rate of overall infections compared to subjects receiving placebo and a biologic RA therapy (64% vs. 43%, respectively), as well as serious infections (4.4% vs. 1.5%, respectively). Section 7.1.5.6 discuss the safety and efficacy, respectively, of the combination of abatacept and concomitant biologic RA therapy. Overall, the combination of abatacept and concomitant biologic RA therapies, especially TNF-blockers, appears to increase the incidence of AEs, SAEs, and infections. Efficacy data of the combination therapy with the proposed dose of abatacept 10 mg/kg is limited. Thus, the combination of abatacept with other biologic DMARDs is associated with an increased safety signal and unproven efficacy.

8.3 Special Populations

The study population for the RA trials was primarily White females with a median age of 53 years. Thus, exploratory safety analyses for drug-demographic interactions based on race and/or gender are unlikely to be useful. Important co-morbidities (Diabetes Mellitus, COPD, Asthma, and CHF) that might be expected to impact the safety of abatacept. Subjects with hepatic or renal insufficiency were excluded from the clinical trials and consequently there is inadequate data to recommend dosing in these patients. The limited experience with pregnant or lactating subjects are discussed in Section 7.1.14.

8.4 Pediatrics

During an End-of-Phase II meeting with the sponsor on March 25, 2003, the agency agreed that a pediatric program would be initiated with the Phase III program, but that the study data would not need to be included in the initial marketing application. The sponsor has submitted a pediatric study (IM101033) that was reviewed and subsequently revised. In a Pre-BLA meeting with the agency on October 12, 2004, the agency agreed that a request for deferral was appropriate for this program based on this information.

8.5 Advisory Committee Meeting

This review will be discussed at an advisory committee meeting that has been scheduled for September 6, 2005.

8.6 Literature Review

This submission contains data on all studies that have been conducted with abatacept in patients with RA. Therefore the literature does not contain additional pertinent information.

8.7 Postmarketing Risk Management Plan

The clinical development plan for abatacept did not identify safety risks that would warrant a formal risk management plan. Therefore none was submitted. A pharmacovigilance plan and postmarketing commitments can be found in Section 9.3.3.

8.8 Other Relevant Materials

Review of this application included consultations from the Office of Drug Safety (ODS) and the Division of Drug Marketing, Advertising, and Communications (DDMAC).

9 OVERALL ASSESSMENT

9.1 Conclusions

1. Abatacept is effective (see Section 6) 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 a large effect size substantiated across 3 adequate and well controlled studies and additional Phase 2 trials. Abatacept was associated with the improvement of signs and symptoms of RA, including a greater proportion of subjects achieving a major clinical response, inhibition of structural damage, and improvement of physical function. Each of the submitted studies was adequately large, multicenter, randomized, double-blind, and placebo-controlled and provides statistically persuasive evidence of benefit. The consistency of abatacept's effects across multiple endpoints and multiple subgroups, combined with statistically robust results, provides convincing evidence of efficacy.

2. In view of the efficacy demonstrated, abatacept has an acceptable safety profile (see Section 7) 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 2760 subjects who were exposed to abatacept for a median of 14 months.

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

4. At the present time, the use of abatacept with concomitant biologic RA therapy (i.e., etanercept, infliximab, adalimumab, anakinra) should not be recommended due to increased 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.

9.2 Recommendation on Regulatory Action

This clinical reviewer recommends approval of abatacept for improving signs and symptoms, slowing progression of structural damage, and improvement of physical function in patients with moderately to severely active RA who have had an inadequate response to one or more DMARDs, including TNF blocking agents.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

No special risk management actions are recommended.

9.3.2 Required Phase 4 Commitments

None.

9.3.3 Other Phase 4 Requests

This reviewer recommends that the sponsor commit to following the approximately 2000 subjects currently enrolled in the open-label extension portion of the studies discussed in this review for at least 5 years on abatacept treatment. The sponsor should also commit to completing 2 additional studies the sposor has indicated they plan to conduct:

- Protocol IM101045A is designed as a nested case-control study to assess the risk of hospitalization due to infection (all hospitalized infections, hospitalized pneumonia, and all opportunistic infections) among patients with RA treated with abatacept in comparison to other DMARDs within a large cohort of individuals with commercial health insurance.

- Protocol IM101045B is designed as a cohort study to assess the risk of malignancies and infection in patients with RA treated with abatacept in comparison to other DMARDs within 2 existing registries containing patients with rheumatoid arthritis.

This reviewer also recommends the sponsor commit to:

3. Collecting and analyzing data on the incidence rate of lung cancer in smokers and non-smokers of RA subjects treated with abatacept.

4. Conducting a pregnancy registry, with concurrent controls, for women who become pregnant while exposed to abatacept to identify the pregnancy outcome and postnatal health status of the children.

For CMC postmarketing commitments, see the review of this application by Dr. Joy Williams. For toxicology postmarketing commitments, see the non-clinical toxicology review of this application by Dr. Hanan Ghantous.

9.4 Labeling Review

The first labeling review meeting was held July 18, 2005 and at the time of this review are in discussions with the sponsor regarding the final draft of the label. The Division of Medication Errors and Technical Support (DMETS) has reviewed the trade name and deemed the name Orencia to be acceptable. A Patient package Insert has been proposed and has been reviewed by DDMAC.

9.5 Comments to Applicant

None.

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04/21/05

DIAGNOSTIC IMAGING REVIEW

Application Type	**BLA**
Submission Number	**STN 125118/0**
Submission Code	**N/A**
Letter Date	**November 15, 2004**
Stamp Date	**April 4, 2005 (RPM)**
PDUFA Goal Date	**September 30, 2005**
Reviewer Names	**H. W. Ju, MD** **Barbara Stinson, DO**
Review Completion Date	**August 30, 2005**
Through	**Patricia Keegan, MD** **Director, DTBOP** **Jeffrey Siegel, MD** **Team Leader**
Established Name	**ORENCIA™ (abatacept)**
Therapeutic Class	**CTLA4Ig humanized recombinant fusion protein**
Applicant	**Bristol-Myers-Squibb**
Priority Designation	**P**
Formulation	**Injectable**
Dose Regimen	**10 mg/kg IV**
Indication	**Moderate to severe RA**
Intended Population	**Moderate to severe RA**

TABLE OF CONTENTS

1. EXECUTIVE SUMMARY

1.1 Recommendation on Approval

Recommend approving the BLA with the proposed label

8 ADDITIONAL CLINICAL ISSUES

8.1 Reason for Consult

This consultation is requested to perform an analysis of the imaging dataset (Joint Radiographs) submitted to the BLA. This review is to perform a quality check on the images submitted for completeness and an image review of 171 subjects identified by the clinical and imaging reviewers.

8.1.1 Clinical Study

Protocol IM101102 was a phase 3, multi-center, randomized, double-blind placebo controlled study to evaluate the efficacy and safety of abatacept (BMS-188667) in combination with methotrexate (MTX) vs MTX alone in subjects with active rheumatoid arthritis (RA) and inadequate response to MTX. Subjects for this study were randomized 2:1 to receive abatacept or placebo on a background of MTX (minimum of 15 mg/wk) for at least 3 months and at a stable dose for 28 days prior to Day 1. The following parameters were used as the primary endpoints to compare the clinical efficacy of abatacept plus MTX versus placebo plus MTX in subjects with active RA currently receiving MTX: (i) symptomatic relief as measured by ACR 20 response following 6 months of treatment (Day 169), (ii) physical function as measured by the disability index of the HAQ at 12 months (Day 365), and (iii) structural damage as assessed by erosion score using a Genant modified Sharp method at 12 months (Day 365). In addition, Genant-modified Sharp joint space narrowing (JSN) and total scores were evaluated as secondary endpoints. This report will focus on the radiographic endpoints of the study.

8.1.2 Description of Scoring System

The primary radiological end point was structural damage as assessed by the change from baseline in erosion score using the Genant modified Sharp method at 12 months (Day 365). In addition, structural damage as assessed by radiographic evaluation using Genant-modified Sharp Joint Space Narrowing (JSN) and total scores were evaluated as secondary endpoints. The Erosion scores and Joint Space Narrowing Scores for each reader were calculated and the mean score derived. The final Total Sharp Score (TSS) was defined as the sum of the Erosion and JSN scores. If the subject's radiograph had been adjudicated, only the adjudicator's score was used.

The readers used a Genant-modified Sharp method to score the joints of both hands and feet. The original Sharp method scored 27 joints of each hand-wrist for erosion and joint space narrowing (JSN). In 1985, the Sharp method was revised to score 17 joints of each hand-wrist for erosion and 18 joints for joint space narrowing. In 1989, van der Heijde added the 5 metatarsophalangeal (MTP) joints and the first PIP of the forefoot. This method was modified by Genant in this protocol using the Genant-modified Sharp scoring system. The Genant-modified Sharp Scoring method evaluated 14 joints of each hand-wrist and 6 joints of each forefoot for erosions and 13 joints of each hand-wrist and 6 joints of each forefoot for joint space narrowing. The original Sharp score for erosions was on a scale from 0 to 5. The Genant-modified Sharp score for erosion in this protocol was on a scale of 0 to 3.5 with a 0.5 interval. The original Sharp score for JSN was on a scale from 0 to 4. The Genant-modified Sharp score for JSN in this protocol has been modified to 0 to 4 with a 0.5 interval.

The sponsor states that the Genant modification improves sensitivity by increasing the range of grading (8-point scale for erosion, 9-point scale for JSN) and improves simplicity and reproducibility by excluding locations with radiographic superimposition and complicated geometry.

8.1.3 Independent Reader Procedure

The independent review of radiographs for Protocol IM101102 was conducted by [ ] an independent Contract Research Organization. The clinical trial sites followed a standardized imaging manual developed by [ ] and forwarded the images to [ ] for data processing and preparation for the independent readings. The independent radiologists performing evaluations for Protocol IM 1012 were trained at a training session conducted by [ ] The objectives of the independent imaging review were:

- To evaluate the radiographic changes due to abatacept in combination with MTX vs MTX alone in subjects with active rheumatoid arthritis and inadequate response to MTX
- To evaluate the damage to joints using serial radiographic of the hands and feet
- To assess the extent of damaged with separate scores for erosions and joint space narrowing using a modified Genant-modified Sharp method, and the Total Scores.

The protocol specified that each patient was to have radiographic examinations of the both hands and feet at baseline and one year from baseline, and at early termination from the study detailed in the procedure manual. For patient with early termination, radiographs were to be taken at the date of early termination, and the subject would return at Day 365 for a follow up radiographic exam. Repeat exams were to be taken within 1 week of the scheduled visit. [ ] had prospectively established criteria on how plain film radiographs and digital image radiographs could be received and processed for incorporation into an electronic database from the clinical trial sites. [ ] provided quality control for all the radiographs obtained at each local site. The radiographs used

for the analysis performed by the independent readers were the baseline and 1 year radiographs X-rays for each patient.

Two radiologists not affiliated with BMS made the assessment of RA and its progression. The radiologists participated in training and validation sessions to ensure consistency in scoring. The radiologists used [ ] proprietary image scoring system,[ ] which has been customized for the evaluation of RA. Using [ ] the digital images of the hands/wrists and feet were presented to the radiologist on 2 high resolution monitors and a computerized score sheet incorporating the Genant-modified Sharp scoring system.

[ ] and BMS developed a Data Transfer Specification to define the content and format for the data transfer file. [ ] created a transfer file in a SAS data set containing all current information and sent this file to BMS. BMS loaded the file into the study database.

An image set was all the time points for a single image (right-hand overview and strips of PIP, MCP, and wrist, left hand overview and strips of PIP, MCP, and wrist, right forefoot, and left forefoot) for a patient. The [ ] system evaluates the images in a side-by-side comparison that is blinded to sequence and allows for discerning the subtle progression and/or regression of the joints without bias. Two radiologists evaluated radiographs of all subjects independently. The radiologists independently viewed and scored the images from the baseline and Year 1 visits if available. In addition, available early termination visit radiographs were assessed. The images from all visits for a subject were displayed to the radiologists in random time order with blinding of the chronological sequence. The radiographic readers were required to log on the [ ] system using a secure ID and password (which constitutes their electronic signature) to conduct the readings. Scores for the reading could be entered into the system under their user ID only. The readers could not access the other reader's scores, as the system would only display the images that were to be read for each specific reader.

Consistency checks are checks of the scores assigned by the radiologists that are inconsistent or unusual, and might be the results of an error. Flagged cases were defined according to the following criteria:

- 10% of subjects with the largest discrepancy in the change in total score between the two radiologists.
- 5% of subjects with the largest changes in total score from baseline for each reader.

The flagged cases were reviewed and adjudicated by a third independent blinded radiologist. For analysis, the average of the 2 readers' scores was used unless the

subject's radiograph had been adjudicated, in which case only the adjudicator's score was used. There was a total of 81 adjudicated cases.

The agreement between readers was assessed by the intra-class correlation coefficients (ICC) and the Pearson correlation coefficients for total score, erosion score, and JSN score. The intra-class coefficients (ICC) were all grater than 0.85, and the Pearson Correlation coefficients were greater than 0.93 for total scores, erosion scores, and JSN scores at each time points. All coefficients exceeded the acceptable threshold of 0.70.

8.14 Financial Disclosure

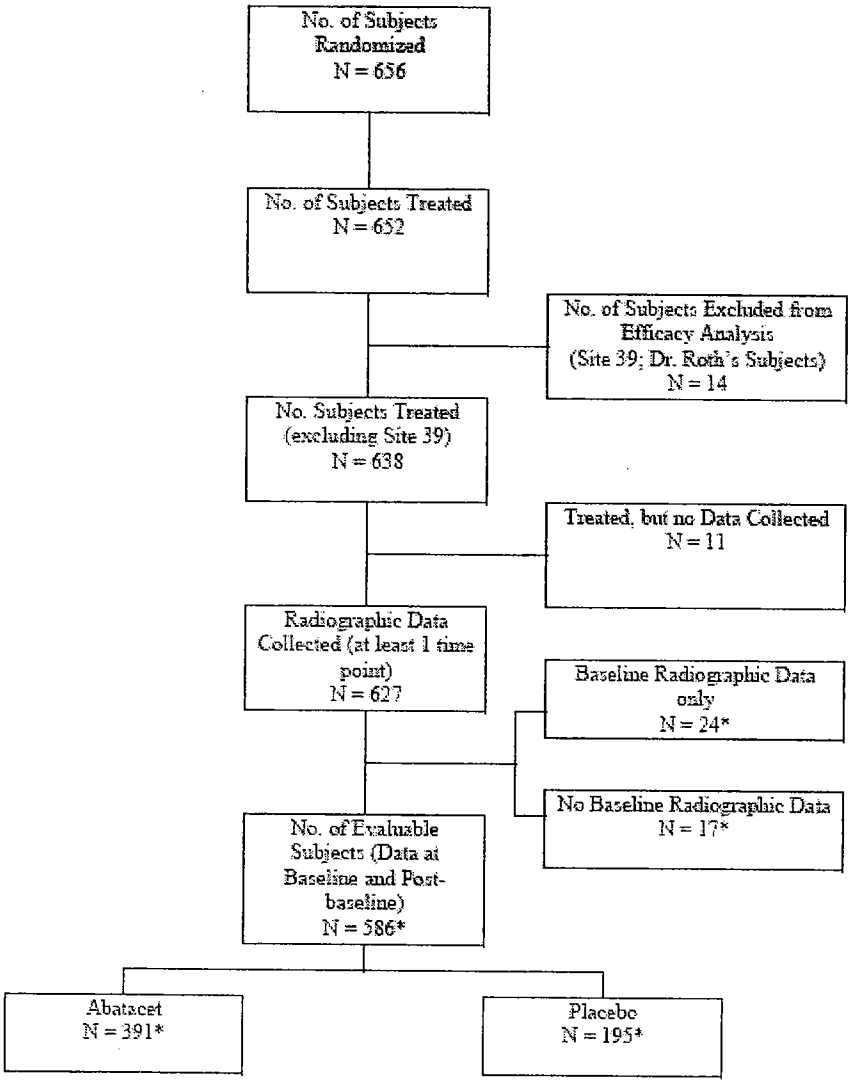
The sponsor provided financial disclosures of radiologists who had performed the independent reader assessment for the study. The financial disclosure forms for each blinded reader have been submitted with no apparent conflict of interest.

8.2 Description of the Material Provided for Review.

The sponsor has submitted a 1 Year Image Database for protocol IM101102. The image database contains a hard drive that contains digitized radiographs for patients enrolled in this protocol.

Six hundred fifty six (656) subjects enrolled into the 1 year study of Protocol IM101102. Of these 656 subjects, 652 subjects were treated. Of these 652 subjects, 14 subjects (site 39) were excluded from efficacy analysis. Site 39 was excluded due to multiple data auditing problems (incomplete CRF's, availability of source documents, etc.). In the remaining 638 subjects, patients were excluded for the following reasons: 11 subjects due to incomplete data collection, 41 subjects due to missing baseline (n=17) or missing follow-up data (n=24). The final dataset consisted of 586 subjects that were included in this primary radiographic analysis. This data set comprised radiographs obtained at baseline and post-baseline (either on Day 365 [572 subjects] or on day of discontinuation prior to Day 365 [14 subjects]). Of these 586 subjects, 391 subjects received abatacept and 195 subjects received placebo. The Radiographic Analysis Flow Chart shown below shows the dataset breakdown.

Radiographic Analysis Flowchart



The Imaging Database was successfully loaded by the [ ](CRO) representative on November 10, 2004.

8.3 Consultant's Review of Radiographic Dataset

On February 23, 2005, a formal training session was organized by Anthony J. Calandra, Ph.D., Director, Global Regulatory Strategy of Bristol-Myers Squibb (BMS). [ ] conducted the training. Dr.[ ] is a consultant to BMS regarding protocol development and study conduct and served as the adjudicator for the

independent review. This information was discussed and previously known to the clinical review team.

Drs. Ju, Stinson, and Martynec from FDA were the participants in the sponsor's training session.

The reviewer was able to open the full imaging dataset consisting of all images from the 586 subjects. The data set for each of the 586 subjects from baseline to year 1 was complete.

Keith Hull, M.D., clinical reviewer, requested review of the following images for subjects based on the following criteria.

- Placebo: Subjects with large x-ray progression from baseline; i.e. comparing with the baseline values, the patients are getting worse
- Abatacept: Subjects with small x-ray progression (even 0)

In consultation with Kyung Y. Lee, PhD, FDA statistician, the following images were selected.

- Placebo group: Change from baseline erosion score greater than 5.7 (95th percentile) or change from baseline joint space narrowing score greater than 7.7 (95th percentile) or change from baseline total score greater than 12.5 (95th percentile) - 7 subjects
- Abatacept group: Change from baseline erosion, JSN, and Total score were equal to 0 – 22 subjects

PLACEBO GROUP	ABATACEPT GROUP
# 017-002	# 019-004
# 017-002 (or)	# 026-002
# 027-007	# 053-005
# 027-007 (or)	# 072-004
# 105-003	# 073-006
# 105-003 (or)	# 084-013
# 116-034	# 088-004
# 116-034 (or)	# 090-011
# 117-023	# 096-008
# 117-023 (or)	# 099-010
# 143-003	# 100-013
# 143-003 (or)	# 102-005
# 148-039	# 117-007
# 148-039 (or)	# 134-004
	# 141-006
	# 143-018
	# 144-001
	# 145-038
	# 148-003
	# 163-004
	# 164-012
	# 175-009

At the request of Dr. Hull, the following 34 subjects with adjudication were randomly chosen and reviewed.

PATIENT	PATIENT	PATIENT	PATIENT
# 003-005	# 027-007	# 075-005	# 155-001
# 004-002	# 036-009	# 076-001	# 161-005
# 004-011	# 046-011	# 140-001	# 162-001
# 009-001	# 058-001	# 143-015	# 164-001
# 011-001	# 058-006	# 145-008	# 164-021
# 016-001	# 072-002	# 147-002	# 165-004
# 017-002	# 073-003	# 147-012	# 165-007
# 018-002	# 073-005	# 148-039	# 175-001
		# 154-006	# 177-010

The reviewers (Drs. Ju and Stinson) were able to validate the reading score of the independent readers for all of the subjects for whom review was requested.

Radiographs from an additional 108 subjects were also reviewed. The subject radiographs for the review were chosen randomly by the reviewers. At least one set of radiographs from 79 of the 111 participating sites participating in the one year follow-up was reviewed. The radiographs that were reviewed for the 108 subjects are listed below.

PATIENT	PATIENT	PATIENT	PATIENT
# 003-001	# 084-005	# 130-001	# 160-003
# 004-002	# 084-006	# 130-003	# 164-004
# 006-003	# 096-009	# 134-002	# 165-005
# 010-001	# 098-020	# 134-004	# 167-001
# 013-003	# 099-019	# 135-001	# 168-003
# 014-005	# 102-003	# 135-003	# 171-002
# 029-001	# 102-007	# 135-017	# 172-001
# 029-002	# 102-009	# 136-009	# 173-005
# 035-001	# 116-004	# 138-015	# 175-003
# 036-001	# 116-005	# 140-002	# 175-008
# 036-002	# 117-003	# 140-013	# 175-012
# 042-003	# 117-005	# 141-004	# 175-016
# 043-004	# 117-008	# 141-014	# 175-019
# 046-002	# 117-012	# 142-006	# 177-003
# 046-010	# 118-002	# 142-023	# 177-005
# 048-001	# 118-008	# 143-008	# 178-002
# 050-002	# 118-013	# 144-004	# 178-008
# 053-006	# 120-001	# 145-029	# 178-010
# 055-002	# 120-006	# 146-003	# 178-013
# 057-002	# 122-003	# 147-002	# 178-014
# 058-003	# 127-004	# 147-009	# 178-017
# 060-001	# 127-008	# 148-021	# 179-003
# 061-003	# 127-015	# 149-003	# 181-001
# 062-002	# 128-006	# 153-006	# 183-006
# 063-002	# 129-002	# 154-007	# 183-008
# 080-001	# 129-003	# 155-002	# 189-001
# 082-007	# 129-005	# 155-009	# 189-002

In assessing inter-reader variability, only minor differences in scoring interpretation was noted. The reviewer was able to validate the reading score of the independent reader for all of the patients reviewed. The majority of scoring differences in scoring were one point between the two readers for the complete studies.

The radiographic datasets for each subject include all protocol required time points were reviewed. The following deficiencies were observed.

8.4 Deficiencies

The reviewers noted minor quality control issues as described below.

8.4.1 Minor Protocol Violations

- Artifacts
  Scratch marks: Subject # 148-001 and Subject # 148-003
  Water marks: Subject # 148-047
  Book marks: Subject # 143-004

- Technician Initials included in the Radiographs
  Subject # 105-003
  Subject # 006-003
  Site # 036 (4 subjects)
  Site # 046 (9 subjects)
- Radiographs obtained without left or right markers or inappropriate markers (including chain links and various letters)
  No markers: Site # 148 (27 subjects)
  Chain link markers: Site #117 (14 subjects) and site #118 (7 subjects)
  G and D markers: Subject #073-006 and site #120 (4 subjects) ("G" and " D" markers were used in place of right and left markers)
  I and D markers: Subject # 099-019 () ("G" and "D" markers were used in place of right and left markers)
  R and L markers on one view: Subject #082-007
  R and L markers mixed-up: Subject # 062-002
- Radiographs obtained without removing the jewelry from hand
  Ring: Subject # 105-003, Subject # 127-004, and Subject # 057-002
- Inadequate I.D. blocking
  Subject # 017-002
  Site # 046 (9 subjects)
- Failure to block out unexposed areas of film prior to digitization
  Site #117(14 subjects)
  Site #118 (7 subjects)
  Site #058 (4 subjects)
- Both hands or feet taken on one film
  Subject # 057-002 (both hands)
  Subject # 084-006 (both feet)
- Non-protocol films were used instead protocol films [ ]
  Site # 116 (23 subjects) used [ ]
  Site #146 (8 subjects) used [ ]

8.4.2 Inconsistent Reader Interpretation

The review found 1 out of 171 subjects (0.5%) had inconsistent Image interpretations among the 3 readers as described below:

- Subject # 147-002: The adjudicated scores of the left foot indicated improvement. However, the scores of the 2 readers indicated worsening of the disease. Drs. Ju and Stinson (FDA radiologists) agreed with the 2 independent readers.

8.4.3 Potion Artifacts and Appearance Artifacts

1 out of 171 (0.5%) subjects had water mark and motion artifacts in the radiographic images as described below:

- Subject #100-013: The right hand had water marks. The left foot had motion artifact

  The followings 9 out of 171 subjects (5.2%) had artifacts of a " feathery like appearance" involving the digits

- Subject #165-004, Subject #165-005 Subject #165-007, Subject # 148-039, Subject # 134-004, Subject # 118-008, Subject # 127-004, Subject # 134-004

The noted protocol violations due to the lack of CRO quality control were discussed with the sponsor

9. OVERALL ASSESSMENT

9.1 Conclusion

In conclusion, in the performance of the quality check of the 171/586 subject (29%) radiographic data sets (63 subjects identified by the clinical reviewer and an additional 108 subjects randomly selected by the reviewer) the readers were able to validate the reading score of the independent reading score for all of the patients queried. The cited minor protocol violations and artifacts including 1 case of inconsistent reading score did not affect the evaluation of the radiographic data set for efficacy.

9.2 Recommendation on Regulatory Action

The submitted radiographic database supports the approval of abatacept for the proposed indication – use 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.

REFERENCES N. A.

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