CLINICAL REVIEW

Application Type	sBLA
Submission Number	125118/45
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Reviewer Name	Keith M. Hull, MD, PhD KMH 2-25-08
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Through	Bob Rappaport, MD Division Director DAARP
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Established Name	ORENCIA®
Trade Name	Abatacept
Therapeutic Class	Fusion Protein
Applicant	Bristol-Myer-Squibb
Priority Designation	S
Formulation	intravenous infusion
Dosing Regimen	10 mg/kg Week 0, 2, 4, then Q4 weeks
Indication	moderate to severe polyarticular juvenile idiopathic arthritis
Intended Population	moderate to severe polyarticular juvenile idiopathic arthritis

1. EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

I recommend approving this efficacy supplement with revisions to the proposed package insert.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Study IM101-033 was a multicenter, double-blind, randomized withdrawal study evaluating the safety and efficacy of abatacept in patients with juvenile idiopathic arthritis or juvenile rheumatoid arthritis (JIA/JRA). The study design consisted of 3 phases or periods: Period A was a 4-month, open-label lead-in phase; Period B was a 6-month, double-blind, randomized, withdrawal phase; and Period C is an ongoing, 5-year follow-up, open-label extension phase. The study enrolled patients between 6 and 17 years of age who were diagnosed with polyarticular JIA/JRA and who had had an inadequate response to previous DMARD therapy, including methotrexate (MTX) and/or biologic therapy (e.g., TNF antagonists or anakinra). Throughout the study, abatacept was administered as an intravenous (IV) infusion at a dose of 10 mg/kg. The primary efficacy endpoint of the study was the time to JIA/JRA disease flare in the double-blind phase (Period B) defined as the number of days between the first double-blind dose of study drug and the study day that disease flare was confirmed. Time to disease flare during Period B was compared between abatacept-treated and placebo-treated patients using a log-rank test, with a significance level of 0.05 (2-sided). Kaplan-Meier curves were used to represent the distribution of time to disease flare over the course of the study for all patients who received study drug during Period B. In addition, a Cox proportional-hazards model with treatment as the only covariate was used to estimate the hazard ratio of disease flare between treatment arms.

1.3.2 Efficacy

Analysis of the primary and secondary endpoints of Study IM101033 provides statistically strong and consistent evidence for the efficacy of abatacept in treating the signs and symptoms of patients with JIA/JRA in patients who have had an inadequate response to one or more DMARDs.

During the lead-in phase (Period A), 123 out of 190 (65%) patients treated with open-label abatacept achieved an ACR Pediatric 30 response rate (Table 7). An improvement was seen in each of the individual components that comprise the ACR Pediatric response score, demonstrating that the clinical effect was not due to a single component driving the composite score. Subset analyses also demonstrated that abatacept was clinically effective in patients regardless of

whether they had previously had an inadequate response to a biologic agent (Table 8). A total of 76% of "biologic-therapy naïve" patients demonstrated an ACR Pediatric 30 response, which is comparable to the etanercept JRA study. Additionally, 39% of patients who had previously failed biologic therapy, a population generally considered to have more refractory disease, responded to abatacept therapy, thus providing an additional therapeutic option for this subset of patients. Also, the data during Period A demonstrated that abatacept was clinically effective regardless of whether the patient was receiving concomitant MTX, although the data suggest that there is a small advantage for patients using concomitant MTX.

At the end of the 6-month randomized, double-blind, withdrawal phase (Period B), 53% of placebo-treated patients had experienced a disease flare compared to only 20% of abatacept-treated patients (Table 17). Subset analysis demonstrated that only 25% of the abatacept-treated patients who had previously had an inadequate response to biologic therapy experienced a disease flare, which was comparable to the "biologic-therapy naïve" abatacept-treated patients that experienced a disease flare (19%). These data suggest that abatacept therapy is effective in patients who have previously had an inadequate response to other biologic DMARDs. Abatacept was also clinically effective regardless of whether patients were receiving concomitant MTX, although similar to the results seen in Period A, the data suggest that there is a somewhat higher response for patients using concomitant MTX.

Efficacy data collected during Period C demonstrated that the proportion of patients achieving ACR Pediatric 30/50/70 responses was maintained out to Day C169 supporting the conclusion that abatacept's treatment effect was durable (Figure 5 and Table 25).

Overall, these data provide substantial evidence that abatacept is effective for reducing the signs and symptoms of moderately to severely active polyarticular-course JIA/JRA in patients who have had an inadequate response to one or more DMARDs.

1.3.3 Safety

A total of 190 patients were exposed to abatacept in all study periods. In general, the types and frequencies of adverse events (AE) reported in Study IM101033 were similar to those seen in the abatacept trials for adult RA. No new safety signal was observed. During Period B, adverse events (AE) were more frequent in abatacept-treated patients compared to placebo-treated patients (62% vs. 55%, respectively). Infections were more frequent in patients treated with abatacept (45%) than placebo (44%) and included influenza (8% vs. 7%), bacteriuria (7% vs. 0), nasopharyngitis (7% vs. 5%), and gastroenteritis (5% vs. 2%). The next most frequently reported AEs were gastrointestinal disorders (17% vs. 15%), respiratory disorders (10% vs. 5%), nervous system disorders (5%

vs. 3%), musculoskeletal disorders (5% vs. 3%), renal/urinary disorders (5% vs. 2%), and vascular disorders (5% vs. 2%). There were no deaths reported during the study. A case of acute lymphoblastic lymphoma (ALL) reported early during Period A (after four doses) was the only malignancy reported; this case may have been a misdiagnosis of JIA/JRA as JIA/JRA has many overlapping features with ALL in children. A total of 6 SAE were reported in Period A and 9 SAE were reported in Period C. There were no SAE reported for abatacept-treated patients during Period B.

2. INTRODUCTION AND BACKGROUND

Juvenile rheumatoid arthritis (JRA) and juvenile idiopathic arthritis (JIA) are terms commonly used to describe the clinical presentation of persistent arthritis (≥6 weeks in duration) of unknown etiology that affects children less than 16 years of age. JIA/JRA is the most commonly diagnosed rheumatic disease in children with an incidence rate in the US of 2-20/100,000 children and a prevalence of 16-150/100,000 children. The majority of patients present with symptoms by 5 years of age but rarely before 6 months of age. Females are affected approximately twice as frequently as males but the ratio varies depending on the disease subtype. In the US, the prevalence of the disease has been reported to occur equally in black and white patients but more commonly among Native Americans. JIA/JRA leads to significant functional and emotional disability and, contrary to the widely held belief that children "outgrow" JIA/JRA, long-term studies have demonstrated that about 50% of children continue to suffer from persistent inflammation and disability as adults.

The classification for JRA was developed by the American College of Rheumatology (ACR) and comprises three separate categories: pauciarticular, polyarticular, and systemic disease. Alternatively, the International League of Associations for Rheumatology (ILAR) has categorized 7 distinct subsets of JIA based on clinical and laboratory features: systemic onset, oligoarthritis, polyarthritis rheumatoid factor negative (RF-), polyarthritis rheumatoid factor positive (RF+), psoriatic arthritis, enthesitis-related arthritis, and undifferentiated arthritis.

Although the terms JRA and JIA describe the same patient population, the use of the particular nomenclature has become controversial. The term JRA is used almost exclusively in the US, but many clinicians feel that the limited subcategorization of JRA makes the correlation of research worldwide difficult. Moreover, the use of the pauciarticular and polyarticular subtypes reflects the onset of disease, which is felt to be less relevant than the course of the disease. Consequently, the JIA classification is gaining widespread acceptance. In light of the fact that the present study was conducted in North America as well as South America and Europe, the sponsor allowed either set of criteria to be used to include patients, consequently, the term JIA/JRA will be used throughout this review.

The etiology of JIA/JRA is unknown but the disease is characterized by chronic inflammation of the synovium. Studies of JIA/JRA synovium reveal B-cell, T-cell, and macrophage infiltration and expansion which subsequently release proinflammatory cytokines and promote synovial proliferation. The resulting thickened pannus causes joint destruction. In addition to the articular manifestations, children with JIA/JRA also commonly present with constitutional symptoms such as anorexia, weight loss, and growth failure.

Abatacept is a recombinant, soluble fusion protein consisting of the extracellular domain of human CTLA-4 and the hinge CH2-CH3 regions of the Fc domain of human IgG1, which has been modified to prevent complement fixation and antibody dependent cellular cytotoxicity. CTLA-4 is an endogenous competitive inhibitor of co-stimulation, binding B7-1 and B7-2 ligands with higher affinity than CD28, preventing the co-stimulatory signal. The interaction between CD28 and the B7-1/B7-2 ligands is required to obtain full T cell activation. Abatacept, being a CTLA-4 fusion protein, also binds the ligands B7-1 and B7-2 on antigen presenting cells and thereby inhibits their binding to the T cell co-stimulatory receptor CD28 on T cells. Thus, by antagonizing this interaction, abatacept inhibits T cell activation as well as the activation of other inflammatory effector cells, e.g., macrophages, B cells, and synoviocytes.

In December of 2005, intravenous (IV) abatacept was approved by the Agency for the treatment of reducing the signs and symptoms, inducing major clinical response, improving physical function, and slowing the progression of structural damage, in adult patients with moderately to severely active RA who have had an inadequate response to one or more DMARDs, such as MTX or TNF-antagonists. In February 2007 the Agency approved a sBLA that modified the structural damage claim to state that abatacept *inhibited* the progression of structural damage, based on longer-term data showing ≥75% inhibition in radiographic scores.

The purpose of Study IM101033 was to evaluate the safety and efficacy of abatacept (ORENCIA) in children with active JRA or JIA despite treatment with methotrexate (MTX) and/or a biologic agent (adalimumab, etanercept, infliximab, anakinra).

4. DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

This review is based on the data obtained from Study IM101033 conducted by the sponsor, Bristol-Myers-Squibb Company.

4.3 Review Strategy

The efficacy and safety assessment of abatacept in patients with JIA/JRA is based on the patients enrolled in Study IM101033. This trial was a multicenter, double-blind, randomized withdrawal study consisting of 3 phases or periods: Period A was a 4-month, open-label lead-in phase; Period B was a 6-month, double-blind, randomized, withdrawal phase; and Period C is the ongoing, 5-year follow-up, open-label extension phase. Baseline demographics and disease activity suggest that the study enrolled patients representative of those seen in clinical practice with JIA/JRA, including a proportion of patients who were on concomitant background DMARD therapy e.g., MTX, corticosteroids, and NSAIDs as well as a subset of patients who had had an inadequate response to biologic therapy, e.g., a TNF antagonist or anakinra. Consequently, as designed, this study allows for a reasonable analysis of the efficacy and safety of abatacept as it will likely be used in clinical practice.

Both Period A and Period B results were considered important for the analysis of efficacy of abatacept in patients with JIA/JRA. The results of Period A (proportion of patients achieving an ACR Pediatric 30 response at the conclusion of Period A) were used to estimate the magnitude of the treatment effect of abatacept in the JIA/JRA patient population, although these results were not controlled. Responders (patients with at least ACR pediatric 30 response at the conclusion of Period A) were then enrolled in Period B, which was designed to provide controlled evidence of efficacy, by comparing time to flare in patients who were randomized to continue abatacept versus patients who were randomized to withdraw from abatacept. Efficacy analyses during Period C were used to evaluate the durability of abatacept's effect.

For reasons of clarity, this review will be organized in chronological order of the study periods.

4.4 Data Quality and Integrity

In general, the data quality and integrity of the study were good. The amount of missing data was small and did not interfere with reaching conclusions regarding efficacy or safety. The study was conducted in accordance with Good Clinical Practice as defined by the International Conference on Harmonization and in accordance with the ethical principles underlying European Union Directive 2001/20/EC and the United States Code of Federal Regulations, Title 21, Part 50. There were two minor protocol amendments accepted by the Division since the filing of the original protocol in September 2003. The first protocol amendment included changes to the inclusion and exclusion criteria to ensure that only patients who had failed at least one DMARD were enrolled in the study. Additional changes primarily involved clarification of protocol procedures. The second protocol amendment lengthened the duration of the infusion of study medication from 30 minutes to 60 minutes at the request of French pediatricians. This amendment only affected French study sites.

The study was conducted in accordance with the ethical principles in the Declaration of Helsinki and the protocol, amendments and patient informed consent received approval by the local Institutional Review Board/Independent Ethics Committee prior to initiation of study at the site. All patients freely provided written informed consent.

All study personnel involved in the conduct of the study were qualified. The determination of a patient's status as either a "responder/non-responder" or as having a "flare" was made at centrally located coordinating centers based on CRF faxed by the study site. The coordinating centers communicated the patients' status back to the appropriate study site as soon as possible. ESR assessments were performed locally and the results were faxed simultaneously with the other core variable data to the coordinating centers to determine the patient's clinical status. Representatives of the sponsor monitored the study, including periodic visits to all study sites, and assessment of data quality and study integrity. Additionally, the study was internally audited by the Regulatory Compliance Department of BMS. Data were recorded at each site on standard CRFs provided by the sponsor. Data reported on the CRF were derived from source documents and were required to be consistent with the source documents. The present study was overseen by a Data Monitoring Board.

4.4.1 Protocol Violations

A total of 8 patients (2 abatacept-treated patients and 6 placebo-treated patients) had protocol deviations during the double-blind phase (Period B) of the study (Table 1). These protocol deviations did not adversely affect the ability to interpret the results of the study. The three patients with inadequate washout of DMARDs and the two patients who received intra-articular injection were in the placebo group; these violations would have been expected to increase responses in the placebo group and therefore would not bias the results in favor of abatacept. The two patients who were enrolled with fewer joints with limited motion were in the abatacept group; these patients might be expected to have less activity and therefore less likely to meet criteria for ACR pediatric 30 response. Thus overall, the number of protocol deviations was small, and the majority of the deviations would be expected to bias results against abatacept, if at all.

Table 1. Protocol Deviations for Study IM101033

	Abatacept (N=60)	Placebo (N=62)
Pre-Treatment		
Inadequate washout of DMARDS other than MTX	0	3
Age <6 years or >17 years	0	1
Joints with LOM<2	2	0
On Treatment		
Received intra-articular injection during Period A or B	0	2
Increased in steroid dose during Period A	1	1
Change in MTX dose during Period A	1	0

Adapted from Sponsor's Submission, Document Control Number 930016107, Table 4.3

4.4.2 Unblinding

There were 2 cases of unblinding during Period B. The first case involved a patient who developed varicella and encephalitis several days after receiving a single dose of study drug (placebo). The case was unblinded and reported as a SAE while the investigator remained blinded to the treatment arm for this patient. The second case of unblinding occurred at study site 068 when an administrative assistant mistakenly provided a confirmation fax from the IVRS system to the principle investigator. The investigator did not analyze the documents and was not involved in safety or efficacy assessment of the patients. These instances of unblinding did not lead to biasing of the study and did not adversely affect the ability to interpret the results of the study.

6. INTEGRATED REVIEW OF EFFICACY

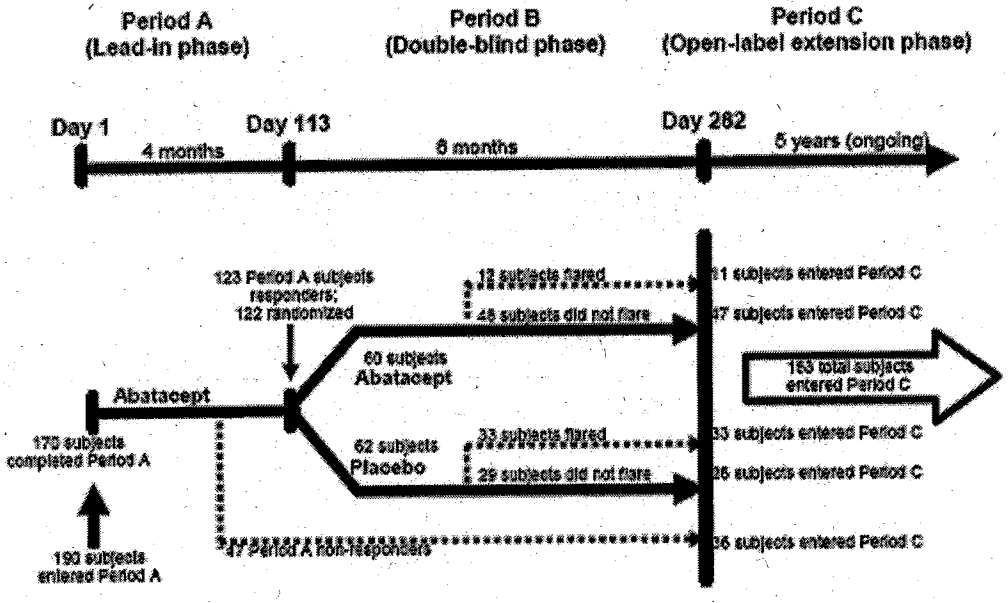
6.1 Indication

The sponsor proposes expanding the indication for abatacept to include the improvement of signs and symptoms of patients with JIA/JRA who have had an inadequate response to MTX or other DMARD therapy.

6.1.3 Study Design

Due to ethical considerations in conducting a clinical study involving children, Study IM101033 was designed as a randomized withdrawal trial such that no symptomatic child was left untreated for a prolonged period of time. The study was conducted at 45 sites worldwide with 10 sites in the US, 21 sites in Europe (Austria, France, Germany, Italy, Portugal, Spain, and Switzerland), and 14 sites in South America (Brazil, Mexico, and Peru). The overall trial had three separate periods (Figure 1).

Figure 1. Study Design Overview



Adapted from Sponsor's Submission, Document Control Number 930019981, Figure 1.3.6

Period A was a lead-in phase in which all patients were treated with open-labeled abatacept for 4 months, after which time patients were assessed as either responders or non-responders as defined by a ≥30% improvement in ≥3 of the 6 JIA core set variables and ≥30% worsening in ≤1 of the 6 JIA core set variables. The ACR Pediatric components (JIA core set variables) are as follows:

- Number of active joints
- Number of joints with limited range of motion
- Physician global assessment of disease severity
- Parent global assessment of overall well being
- CHAQ
- ESR

Period B randomized those patients classified as responders at the end of Period A in a double-blind manner to receive either abatacept or placebo. Patients were treated for 6 months or until they experienced a disease flare defined as follows:

- ≥30% worsening in ≥3 of the 6 JIA core set variables
- ≥30% improvement in ≤1 of the 6 JIA core set variables
- ≥2 cm of worsening of the Physician or Parent Global Assessment was necessary if used as 1 of the 3 JIA core set variables used to define flare
- worsening in ≥2 joints if the number of active joints or joints with limitation of motion was necessary if used as 1 of the 3 JIA core set variables used to define flare

Period C is designed as a 5 year follow-up treatment phase with open-label abatacept for patients who had participated in early phases of the study. These patients included those who completed Period A without an adequate response, patients who completed Period B without experiencing a flare and patients who discontinued from Period B due to a flare.

6.1.3.1 Major Inclusion Criteria

- Diagnosis of JRA or JIA as follows:
  - JRA (ACR criteria): pauciarticular, polyarticular, or systemic disease onset and polyarticular course
  - JIA (ILAR criteria): extended oligoarticular, polyarticular (RF(+)), polyarticular (RF(-)), or systemic with a polyarticular course
- History of ≥5 joints with active arthritis and currently active articular disease defined as follows:
  - ≥ 2 active joints whereby "active" was defined as swelling but if swelling was not present then limited range of motion accompanied by pain and/or tenderness
  - ≥ 2 joints with limited range of motion at screening and at Visit Day 1
  - The same joint could separately meet the definition of a active joint and a joint with limited range of motion
- An inadequate therapeutic response or intolerance to ≥1 DMARD
- Males and Females between 6 to 17 years of age
- Achieved washout and drug stabilization criteria as follows:
  - Patients receiving MTX (10 to 30/mg/m2/week; maximum dose of 40 mg/week) remained at a stable dose and route of administration for 4 weeks prior to the first dose of study medication and throughout Periods A and B. Patients receiving MTX received either folinic acid or folic acid at recommended doses
  - Patients who did not receive background MTX ≥ 4 weeks prior to the planned first dose of study medication were enrolled, but did not initiate MTX treatment during Periods A and B
  - A minimum of a 4-week washout period of any DMARD other than MTX, thalidomide, or biologic therapy (i.e., etanercept and anakinra) prior to the first dose of study medication
  - A 60 day washout of infliximab [Remicade®] and adalimumab [Humira®] prior to first dose of study medication
  - Patients treated with leflunomide had to complete the recommended prescribed course of cholestyramine washout prior to receiving study medication or have been off the medication for a period of 2 years prior to study start
  - Oral corticosteroid treatment was reduced and stabilized to the equivalent of ≤10 mg/day (or 0.2 mg/kg/day) for 4 weeks prior to the first dose of study medication
  - NSAIDs were required to be at a stable dose for 4 weeks prior to the first dose of study medication

6.1.3.2 Major Exclusion Criteria

- Women who were pregnant or breastfeeding
- Women of child bearing potential who were unwilling or unable to use an acceptable method of contraception to avoid pregnancy
- Males who were unwilling or unable to use an adequate method of contraception
- Had systemic onset JRA or systemic JIA with any of the following manifestations within 6 months prior to enrollment:
    - intermittent fever due to JRA/JIA
    - rheumatoid rash
    - hepatosplenomegaly
    - pleuritis
    - pericarditis
    - macrophage activation syndrome
- Patients with active uveitis
- Patients with other rheumatic disease or major chronic infectious/inflammatory/immunologic disease (eg inflammatory bowel disease
- Evidence of infection at screening or history of frequent acute or chronic infections within 3 months prior to the first dose of study medication
- History of live vaccines within 3 months of the first dose of study medication
- Active vasculitis of a major organ system
- Symptoms of severe, progressive, or uncontrolled renal, hepatic, hematological, gastrointestinal, pulmonary, cardiac, neurological, or concomitant medical conditions that place the patient at an unacceptable risk for participation in this study
- History of cancer within the previous 5 years
- History of any serious bacterial infection unless previously treated and resolved with antibiotics
- History of opportunistic infections, including, cytomeglovirus, *Pneumocystis carinii*, aspergillosis, TB, or atypical mycobacterium
- All patients were evaluated with a PPD test. Patients who were PPD(+) at screening were not eligible unless they initiated therapy for latent TB
- Patients with Herpes zoster that had resolved <2 months prior to enrollment
- HBV, HCV, HIV (+)
- Had any of the following clinical laboratory values:
    - Hemoglobin (Hgb) < 9.0 g/dL
    - White blood cell count (WBC) < 2000/mm3 (2 x 10^9/L)
    - Platelet count < 150,000/mm3 (150 x 10^9/L)
    - Serum creatinine > 1.5x upper limit of normal (ULN)
    - Serum ALT or AST> 2.0x upper ULN
    - Intra-articular/systemic corticosteroids ≤4 weeks prior to enrollment
- Had received MTX doses > 30mg /m2/week or > 40 mg/week

The dose of abatacept in all phases of the study was 10 mg/kg (maximum dose of 1000 mg) by IV infusion. During Period A, all patients received abatacept infusions on Visit Days 1, 15, and 29 then every 4 weeks for the remainder of Period A. During Period B, patients received an IV infusion of either abatacept or placebo every 4 weeks depending on their designated treatment arm. Patients entering Period C received abatacept infusions every 4 weeks. All infusions were administered in a fixed volume of 100 mL D5W or NS at a constant rate over 30 minutes with the exception of patients treated in France, where patients received the infusion over 60 minutes.

All patients and clinical assessors were blinded to treatment assignment during Period B. Patients receiving MTX were required to maintain a stable dose for at least 4 weeks prior to the first dose of study drug. Patients not receiving concomitant MTX could be enrolled in the study but were not allowed to initiate MTX treatment within 4 weeks prior to enrollment or during the study. Other DMARDs were not permitted and were required to be discontinued prior to the first dose of study drug. Stable doses of corticosteroids (≤10 mg prednisone QD or equivalent) and NSAIDs were permitted. Analgesics not containing acetylsalicylic acid were permitted but not within 12 hours prior to joint assessments. Intra-articular injections were not permitted within 4 weeks before the enrollment visit, during Period A or Period B. Prohibited therapies also included cyclophosphamide, azathioprine, mycophenolate mofetil, thalidomide, D-penicillamine, cyclosporine (and other calcineurin inhibitors), biologic response modifiers (e.g., TNF antagonists, IL-1 antagonists), immunoadsorption columns, and leflunomide.

All efficacy analyses were based on the Intent-to-treat (ITT) population with the exception of the responder analysis performed at the end of Period A. The primary efficacy endpoint of the study was the time to JIA/JRA disease flare in the double-blind phase (Period B) defined as the number of days between the first double-blind dose of study drug and the study day that disease flare was confirmed. Time to disease flare during Period B was compared between abatacept-treated and placebo-treated patients using a log-rank test, with a significance level of 0.05 (2-sided). Kaplan-Meier curves were used to represent the distribution of time to disease flare over the course of the study for all patients who received study drug during Period B. In addition, a Cox proportional-hazards model with treatment as the only covariate was used to estimate the hazard ratio of disease flare between treatment arms.

Major secondary endpoints included analysis of the proportion of patients with disease flare from the first double-blind dose of medication to Visit Day 169 during Period B using a 2-sided continuity corrected Chi-square test at the 5% significance level. Additional analyses included changes from baseline for each of the JIA individual core-response variables during Period B, analysis of change in ACR Pediatric 30, 50, and 70 from baseline through the four month visit of

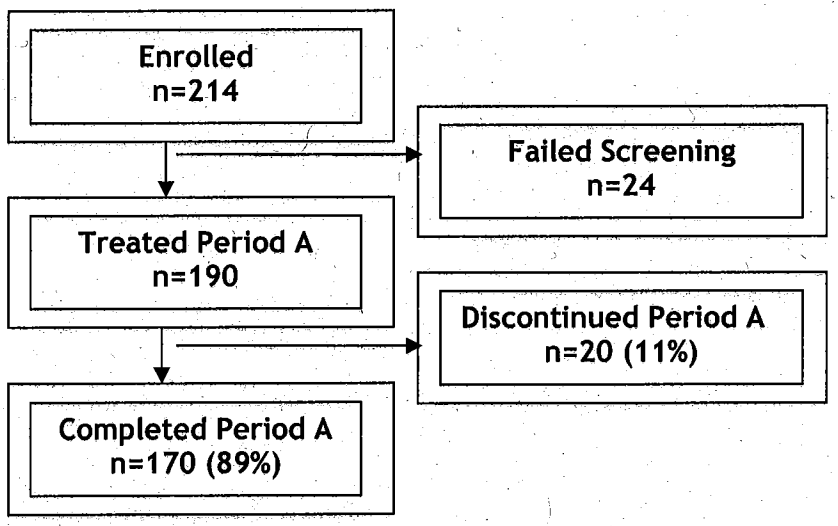
Period A, physical function (CHAQ), and quality of life assessments. These analyses used last observation carried forward data sets. Patients who had only baseline values were excluded.

6.1.4 Efficacy Findings-Period A

6.1.4.1 Study Conduct-Period A

Study IM101033 enrolled 214 patients and treated 190 patients for the lead-in phase, Period A (Figure 2).

Figure 2. Patient Disposition-Period A



Of the 190 patients treated, 170 (89%) completed Period A and 20 (11%) patients discontinued. The most common reason for patient discontinuation was lack of efficacy (Table 2).

Table 2. Reasons for Discontinuation from Study-Period A

	Abatacept (N=190)
Number of Patients Enrolled	214
Patients Entering Period A	190
Patients Discontinuing Period A, n (%)	20 (11)
Death	0
Adverse event	1 (<1)
Lack of Efficacy	17 (9)
Withdrawal of consent	1 (<1)
Lost to follow-up	0
Other	1 (<1)
Patients Completing Period A, n (%)	170 (89)

Adapted from Sponsor's Submission, Document Control Number 930016107, Table 5.1

6.1.4.2 Study Demographics-Period A

As shown in Table 3, the majority of patients treated in Period A were white females with a mean age of 12 years. The study demographics suggest the patient population is similar, and therefore study results should be generalizable, to the intended U.S. patient population.

Table 3. Baseline Patient Demographic Characteristics-Period A

	Abatacept (n=190)
Characteristic	
Age (years)	
Mean ± SD	12 ± 3
Median (range in years)	13 (5-17)
Sex, n (%)	
Female	137 (72)
Race, n (%)	
White	147 (77)
Black	15 (8)
Other	28 (15)
Body weight (kg)	
Mean ± SD	42 ± 15
Geographical region, n (%)	
North America	27 (14)
South America	94 (50)
Europe	69 (36)

Adapted from Sponsor's Submission, Document Control Number 930016107, Table 5.2A

Table 4, below, shows that patients entering Period A had a high level of disease activity at baseline (16 active joints on average) despite the majority (74%) of the patients receiving treatment with MTX (mean dose 13 mg/m^2/wk). The majority of patients entered the study with polyarticular disease as defined by either the JIA or the JRA classification system.

Table 4. Baseline Patient Disease Characteristics-Period A

	Abatacept (n=190)
Duration of RA (years)	
Mean ± SD	4 ± 4
Duration of RA Disease	
≤2 years	79 (42)
>2 years to ≤5 years	42 (22)
>5 years to ≤10 years	50 (26)
>10 years	19 (10)
Active Joints	
Mean ± SD	16 ±13
Joints with LOM	
Mean ± SD	16 ± 15
CHAQ Disability Index (0-3)	
Mean ± SD	1.3 ± 0.8
Parental Global Assessment (VAS 100 mm)	
Mean ± SD	45 ± 35
Physician Global Assessment (VAS 100 mm)	
Mean ± SD	54 ± 20
JIA Disease Onset Category	
JIA Oligoarticular Persistant	3 (2)
JIA Oligoarticular Extended	27 (14)
JIA Polyarticular (RF+)	38 (20)
JIA Polyarticular (RF-)	84 (44)
JIA Systemic	37 (20)
ESR (mm/hr)	
Mean ± SD	32 ± 27
CRP (mg/dL)	
Mean ± SD	3 ± 4
RF, n (%)	
Negative	149 (78)
MTX Dose (mg/m^2/wk)	
Mean ± SD	13 ± 5

Adapted from Sponsor's Submission, Document Control Number 930016107, Table 5.2B

Concomitant Medications

The majority of patients (96%) entering Period A were on ≥1 anti-rheumatic medication (Table 5). Although patients were to have discontinued all DMARDs except MTX by the start of Period A, two patients were receiving treatment with DMARDs other than MTX (leflunomide or hydroxychloroquine).

Table 5. Concomitant Medications at the Start of Period A

	Abatacept (N=190)
Patients on Concomitant Medications, n (%)	182 (96)
Methotrexate	140 (74)
Other DMARDs	2 (1)
Hydoxychloroquine/Chloroquine	1 (<1)
Leflunomide	1 (<1)
Corticosteroids	89 (47)
NSAIDS	169 (89)
Number of DMARDS	
Mean ± SD	1 ± 0.4

Adapted from Sponsor's Submission, Document Control Number 930016107, Table 5.4

Extent of Drug Exposure and Treatment Compliance for Period A

The mean duration of exposure to abatacept during Period A was 118 days, which was determined by the number of infusions that patients received (Table 6). Overall, treatment compliance was excellent with only 6 (3%) patients having missed a single infusion and no patient missed 2 or more infusions.

Table 6. Extent of Abatacept Exposure during Period A

	Abatacept (N=190)
Days, n (%)	
30 to <60	1 (<1)
60 to <90	9 (5)
90 to <120	128 (67)
≥120	52 (27)
Mean Days ± SD	118 ±16
Median Days (Range)	112 (56, 151)

Adapted from Sponsor's Submission, Document Control Number 930016107, Table 5.5

6.1.4.3 Signs and Symptoms-Period A

A total of 123 of the 190 (65%) patients who received open-label abatacept during Period A achieved an ACR Pediatric 30 response rate (Table 7). The proportion of patients achieving an ACR Pediatric 50, 70, and 90 during Period A was 50%, 28%, and 13%, respectively (Table 7). Improvement in each of the individual components of the ACR Pediatric response criteria was observed demonstrating that no single component drove the composite score result for any of the ACR Pediatric response rates (data not shown).

Table 7. ACR Pediatric Response Rates (based on ESR)-Period A

ACR PEDIATRIC RESPONSE RATE, n (%) (95% CI for %)	Abatacept (N=190)
ACR Pediatric 30	123 (65%)
ACR Pediatric 50	94 (50%)
ACR Pediatric 70	54 (28%)
ACR Pediatric 90	24 (13%)

Adapted from Sponsor's Submission, Document Control Number 930016107, Table 5.7.1

Although it is difficult to directly compare trials, the 65% ACR Pediatric 30 response rate observed during Period A appeared to be approximately 10% lower than the response rate observed in the similarly designed etanercept JRA study. However, one major difference between the two studies was the inclusion of patients who did not receive an adequate response to a biologic agent in the present study. Consequently, we performed analyses to study the ACR Pediatric response rates in patients who had previously had an inadequate response to biologic therapy.

As shown in Table 8, a total of 57 of the 190 (30%) patients enrolled in Period A had previously been treated with a biologic compared to 133 (70%) patients who had not. Patients who had received prior treatment with a biologic therapy demonstrated ACR Pediatric 30, 50, 70, and 90 response rates of 39%, 25%, 11%, and 2%, respectively. In contrast, patients who were "biologic-therapy naïve" demonstrated ACR Pediatric 30, 50, 70, and 90 response rates of 76%, 60%, 36%, and 17%, respectively.

Table 8. ACR Pediatric Response Rates during Period A Based on Previous use of Biologic Therapy or Concomitant MTX

ACR Pediatric Response	Prior Biologics Therapy (n=57)	No Prior Biologic Therapy (n=133)
ACR Pediatric 30	22 (39%)	101 (76%)
ACR Pediatric 50	14 (25%)	80 (60%)
ACR Pediatric 70	6 (11%)	48 (36%)
ACR Pediatric 90	1 (2%)	23 (17%)

Adapted from Sponsor's Submission, Document Control Number 930016107,1.0 Supplemental Tables S.2.1.3A/B

Thus, those abatacept-treated patients who had not received previous treatment with a biologic therapy experienced a similar degree of clinical benefit as the patients in the etanercept JRA trial. Conversely, those abatacept-treated patients that had previously received biologic therapy did less well than "biologic-therapy naïve" patients. This is consistent with what has been observed in other clinical trials for adult patients with RA that enrolled patients with inadequate responses to TNF and/or IL-1 antagonists. The difference in clinical efficacy between the two groups of patients is thought to result from the fact that patients who have had an inadequate response to previous biologic therapy likely represent a more aggressive or refractory form of RA.

The overall ACR Pediatric 30, 50, 70, and 90 response rates for patients receiving concomitant MTX (69%, 51%, 28%, and 12%, respectively) was similar when compared to patients not treated with concomitant MTX (54%, 46%, 31%, and 14%, respectively; Table 9).

Table 9. ACR Pediatric Response Rates during Period A Based on Concomitant Use of MTX

ACR Pediatric Response	Concomitant MTX (n=138)	No Concomitant MTX (n=52)
ACR Pediatric 30	95 (69%)	28 (54%)
ACR Pediatric 50	70 (51%)	24 (46%)
ACR Pediatric 70	38 (28%)	16 (31%)
ACR Pediatric 90	17 (12%)	7 (14%)

Adapted from Sponsor's Submission, Document Control Number 930016107,1.0, Supplemental Tables S.2.1.4A/B

Additional analyses were performed to determine whether the clinical efficacy observed in the overall patient population was seen in each of the individual JIA subtypes. As shown in Table 10, abatacept-treated patients demonstrated similar clinical improvement in ACR Pediatric 30, 50, 70, and 90 scores in all JIA classifications. Of note, the 3 patients with oligoarticular-persistent disease were not included in subset analysis due to the small number of patients.

Table 10. ACR Pediatric Response Rates (based on ESR) for Individual JIA Classifications

ACR Pediatric Response	Oligo-Extended (n=27)	Poly (RF+) (n=38)	Poly (RF-) (n=84)	Systemic (n=37)
ACR Pediatric 30	16 (60%)	26 (68%)	54 (64%)	24 (65%)
ACR Pediatric 50	11 (41%)	24 (63%)	41 (49%)	16 (43%)
ACR Pediatric 70	9 (33%)	15 (40%)	24 (29%)	6 (16%)
ACR Pediatric 90	4 (15%)	5 (13%)	13 (16%)	2 (5%)

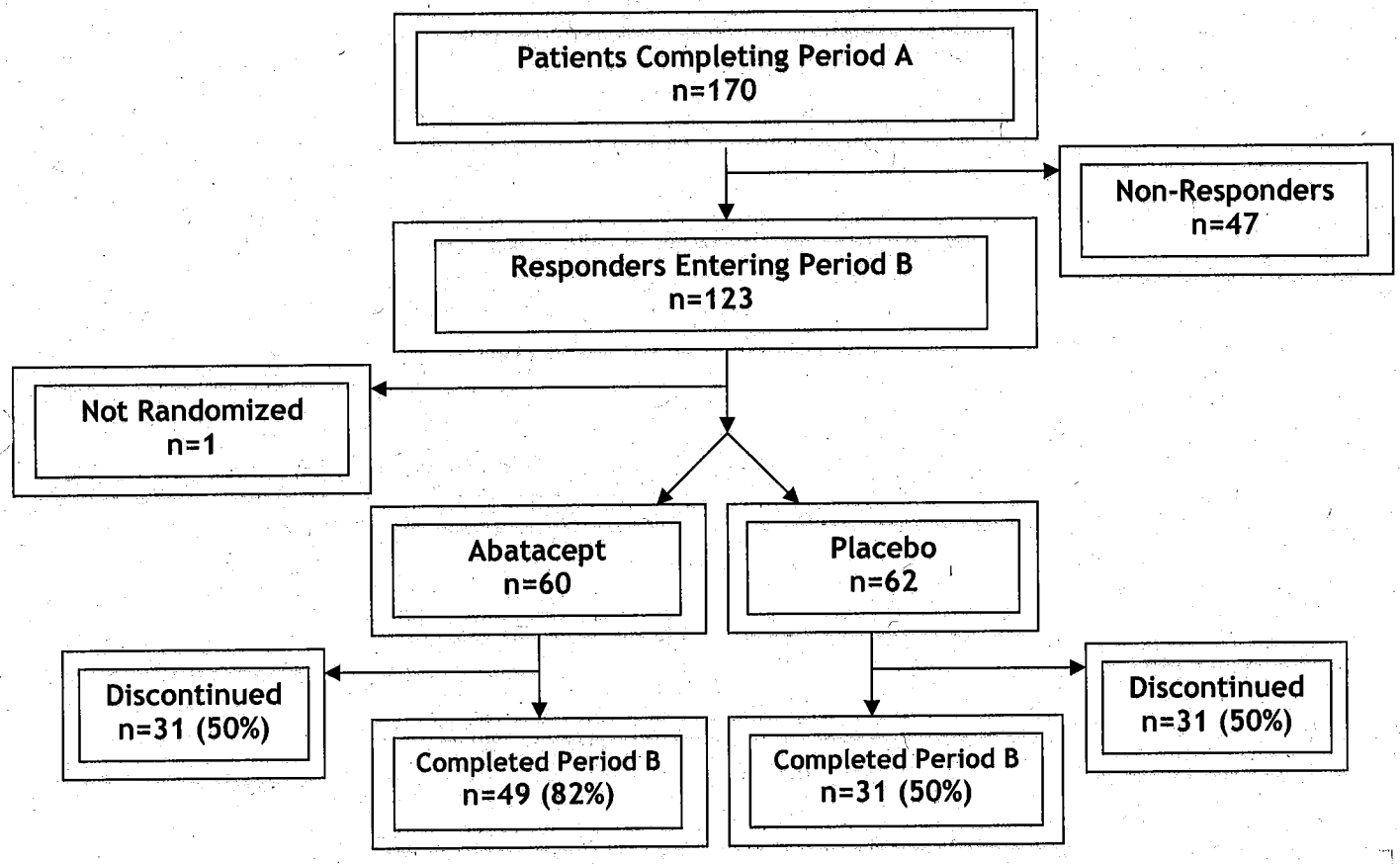
Adapted from Sponsor's Submission, Document Control Number 930016107,1.0, Supplemental Tables S.2.1.2A

6.1.5 Efficacy Findings-Period B

6.1.5.1 Study Conduct-Period B

A total of 122 of the 123 patients meeting the classification of responder in Period A were randomized in a 1:1 ratio to enter the double-blind phase of the study, Period B (Figure 3). One patient withdrew consent and chose not to participate in Period B.

Figure 3. Patient Disposition-Period B



As shown in Table 11, 49 of 60 (82%) patients randomized to the abatacept-treatment arm completed Period B compared to 31 of 62 (50%) patients randomized to the placebo-treatment arm. The most common reason for patient discontinuation in both treatment arms was lack of efficacy.

Table 11. Reasons for Discontinuation from Study-Period B

	Abatacept	Placebo
Number of Patients Completed Period A	60	62
Number of Patients Entering Period B	60	62
Patients Discontinuing Period B, n (%)	11 (18)	31 (50)
Death	0	0
Adverse event	0	0
Lack of Efficacy	10 (17)	31 (50)
Withdrawal of consent	1 (2)	0
Lost to follow-up	0	0
Other	0	0
Patients Completing Period B, n (%)	49 (82)	31 (50)

Adapted from Sponsor's Submission, Document Control Number 930016107, Table 6.1

6.1.5.2 Study Demographics-Period B

As shown in Table 12, the baseline demographic characteristics between the abatacept and placebo treatment arms were well balanced.

Table 12. Baseline Patient Demographic Characteristics-Period B

	Abatacept (n=60)	Placebo (n=62)
Characteristic		
Age (years)		
Mean ± SD	13 ± 3	12 ± 3
Sex, n (%)		
Female	43 (72)	45 (73)
Race, n (%)		
White	46 (77)	49 (79)
Black	5 (8)	4 (7)
Other	9 (15)	9 (15)
Body weight (kg)		
Mean ± SD	42 ± 15	39 ± 14
Geographical region, n (%)		
North America	3 (5)	4 (7)
South America	38 (63)	33 (53)
Europe	19 (32)	25 (40)

Adapted from Sponsor's Submission, Document Control Number 930016107, Table 6.2.1

The disease characteristics for patients in the two treatment arms were adequately balanced at baseline (Table 13). Overall, disease characteristics suggest that patients in the placebo arm may have had slightly less active or aggressive disease. For example, mean and median number of active joints and joints with loss of motion were lower in the placebo group, and more of the placebo patients were RF negative. However, if placebo patients had less active disease, this would be expected to bias the results against abatacept in this study, since the primary endpoint for the study was time to flare and less active patients might be expected to have a longer time to flare and experience fewer flares. Therefore, study results favoring abatacept remain valid.

Table 13. Baseline Patient Disease Characteristics-Period B

	Abatacept (n=60)	Placebo (n=62)
Duration of RA (years)		
Mean ± SD	4 ± 4	4 ± 4
Duration of RA Disease		
≤2 years	29 (48)	27 (44)
>2 years to ≤5 years	12 (20)	17 (27)
>5 years to ≤10 years	13 (22)	15 (24)
>10 years	6 (10)	3 (5)
Active Joints		
Mean ± SD	18 ±12	15 ±13
Median (range)	17 (2-48)	9 (3-53)
Joints with LOM		
Mean ± SD	17 ± 13	14 ± 14
Median (range)	14 (0-59)	9 (2-65)
CHAQ Disability Index (0-3)		
Mean ± SD	1.3 ± 0.7	1.2 ± 0.8
Parental Global Assessment (VAS 100 mm)		
Mean ± SD	42 ± 23	40 ± 25
Physician Global Assessment (VAS 100 mm)		
Mean ± SD	54 ± 18	53 ± 21
JIA Disease Onset Category		
JIA Oligoarticular Persistent	0	2 (3)
JIA Oligoarticular Extended	9 (15)	7 (11)
JIA Polyarticular (RF+)	14 (23)	12 (19)
JIA Polyarticular (RF-)	26 (43)	28 (45)
JIA Systemic	11 (18)	12 (19)
ESR (mm/hr)		
Mean ± SD	31 ± 27	31 ± 28
CRP (mg/dL)		
Mean ± SD	3 ± 5	3 ± 3
RF, n (%)		
Negative	41 (68)	50 (81)
MTX Dose ($mg/m^2/wk$)		
Mean ± SD	14 ± 5	13 ± 4

Adapted from Sponsor's Submission, Document Control Number 930016107, Table 6.2.2

Concomitant Medications

The use of concomitant medications was similar between the two treatment arms as expected based on the protocol (Table 14).

Table 14. Concomitant Medications at the Start of Period A

	Abatacept (N=60)	Placebo (N=62)
Patients on Concomitant Medications, n (%)	56 (93)	61 (98)
Methotrexate	49 (81)	47 (76)
Other DMARDs	0	2 (1)
Hydoxychloroquine/Chloroquine	0	1 (<1)
Corticosteroids	28 (47)	27 (44)
NSAIDS	53 (88)	58 (94)
Number of DMARDS		
Mean ± SD	1 ± 0.3	1 ± 0.5

Adapted from Sponsor's Submission, Document Control Number 930016107, Table 6.2.3.2

Extent of Drug Exposure and Treatment Compliance for Period B

As shown in Table 15, the mean duration of exposure during Period B was greater in the abatacept treatment arm compared to the placebo arm (153 days versus 127 days, respectively). The shorter exposure to abatacept for the placebo treatment arm is due to the earlier discontinuation from the study due to the lack of efficacy. During Period B, 2 abatacept-treated patients and 3 placebo-treated patients missed 1 infusion of study drug each. No patient missed more than 1 infusion during Period B.

Table 15. Extent of Abatacept Exposure during Period B

	Abatacept (N=60)	Placebo (N=62)
Days, n (%)		
<30	1 (2)	7 (11)
30 to <60	4 (7)	5 (8)
60 to <90	2 (3)	6 (10)
90 to <120	2 (3)	7 (11)
120 to <150	1 (2)	5 (8)
150 to <180	48 (80)	31 (50)
≥180	2 (3)	1 (2)
Mean Days (± SD)	153 ± 38	127 ± 53
Median Days (Range)	168 (28-196)	159 (21 to 205)

Adapted from Sponsor's Submission, Document Control Number 930016107, Table 7.1

6.1.5.3 Signs and Symptoms-Period B

6.1.5.3.1 Primary Efficacy Endpoint

The primary efficacy endpoint for Study IM101033 was the difference in time to disease flare between the abatacept and placebo treatment arms was statistically significant using the log-rank test (p=0.0002; Table 16). As suggested by the hazard ratio (0.31, 95% CI [0.16, 0.59]), the risk of disease flare for abatacept-treated patients was approximately one-third that of placebo-treated patients.

Table 16. Time to Flare-Period B

Endpoint	Abatacept (N=60)	Placebo (N=62)	Abatacept vs. Placebo Hazard Ratio Estimate* Estimate	95% CI	p-values Log-Rank Test
Flare, n (%)	12 (20)	33 (53)	0.31	0.16,0.59	0.0002

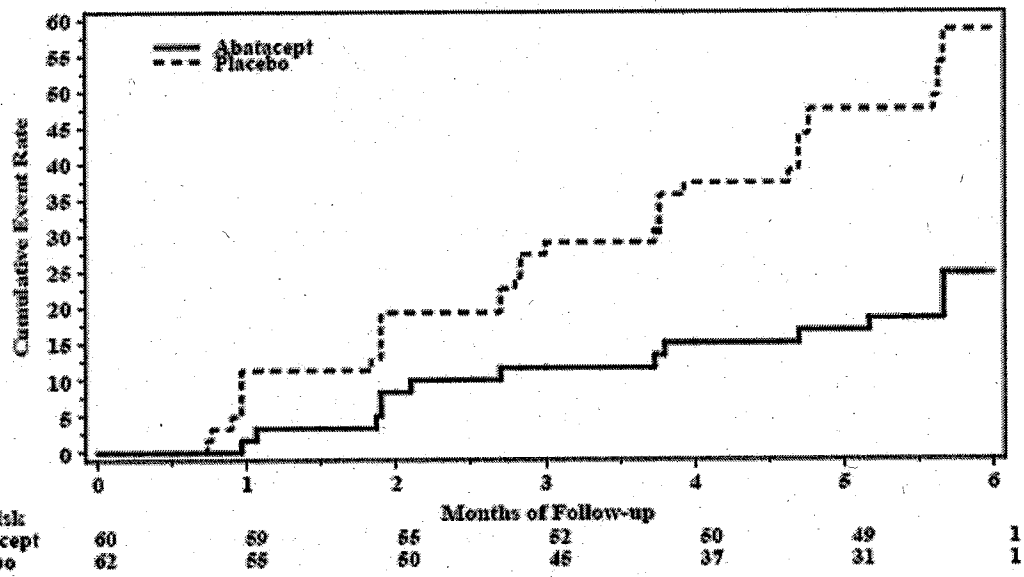
*Cox proportional hazards model with treatment as the only covariate.

Adapted from Sponsor's Submission, Document Control Number 930016107, Table 8.2

As shown in Figure 4, the Kaplan-Meier curves demonstrate that the median time to flare for the placebo treatment arm was approximately 6 months. However, since less than 50% of abatacept-treated patients experienced a disease flare, all that can be derived from the data is that the median time to flare for the abatacept treatment is greater than 6 months (the end of the

double-blind phase) but a definitive median time to flare can not be determined.

Figure 4. Kaplan-Meier Curves of Time to First Flare in Period B



Adapted from Sponsor's Submission, Document Control Number 930016107, Figure 8.2

6.1.5.4 SECONDARY EFFICACY ENDPOINTS

Proportion of Patients with Disease Flare

An additional analysis was performed using the proportion of patients with disease flare at the end of Period B (6 months; Table 17). As expected, these data are consistent with the primary analysis and demonstrated that 12 of 60 (20%) abatacept-treated patients flared by 6-months compared with 33 of 62 (53%) of placebo-treated patients.

Table 17. Proportion of Patients with Disease Flare through Day 169 of Period B

	Abatacept (N=60)	Placebo (N=62)
Patients with Disease Flare, n (%)	12 (20)*	33 (53)

* p<0.01 using Chi-square test

Adapted from Sponsor's Submission, Document Control Number 930016107, Table 8.3.1

Individual Core Set Variables

As shown in Table 18, the individual ACR Pediatric components, which comprise the JIA/JRA core set variables, continued to improve or remained stable for the abatacept-treated patients but worsened for the placebo-treated patients during Period B. This observation held true for each of the individual components of the ACR Pediatric response criteria, demonstrating that no single component drove the composite score result.

Table 18. Individual ACR Pediatric Components: Median Percent Change from Baseline to Six Months (Study Day 169)

	Abatacept (n=60)	Placebo (n=62)
Active Joints		
Baseline Median	3	2
Post-Baseline Median	1.5	4.5
Median % Change from Baseline	-21	50
% Change Percentile (25^{th}, 75^{th})	(-92, 18)	(0, 100)
Joints with LOM		
Baseline Median	4	3
Post-Baseline Median	3	5
Median % Change from Baseline	0	50
% Change Percentile (25^{th}, 75^{th})	(-46, 0)	(0, 100)
Physician Global Assessment (VAS 100 mm)		
Baseline Median	18	9
Post-Baseline Median	7	21
Median % Change from Baseline	-30	56
% Change Percentile (25^{th}, 75^{th})	(-86, 22)	(-31, 250)
Parental Global Assessment (VAS 100 mm)		
Baseline Median	15	13
Post-Baseline Median	10	17
Median % Change from Baseline	-11	8
% Change Percentile (25^{th}, 75^{th})	(-57, 28)	(-32, 100)
CHAQ Disability Index (0-3)		
Baseline Median	0.5	0.5
Post-Baseline Median	0.5	0.56
Median % Change from Baseline	0	0
% Change Percentile (25^{th}, 75^{th})	(-39, 2)	(-13, 56)
ESR (mm/hr)		
Baseline Median	16	16
Post-Baseline Median	15	21
Median % Change from Baseline	0	21
% Change Percentile (25^{th}, 75^{th})	(-21, 50)	(-14, 92)
CRP (mg/dL)		
Baseline Median	0.5	0.4
Post-Baseline Median	0.3	0.85
Median % Change from Baseline	0	6
% Change Percentile (25^{th}, 75^{th})	(-47, 67)	(-33, 150)

Adapted from Sponsor's Submission, Document Control Number 930016107, Table 8.3.2

Overall, fewer abatacept-treated patients experienced disease flares compared to placebo-treated patients regardless of previous treatment with biologic therapy of concomitant use of MTX. As shown in Table 19, in patients who had previously received prior biologic therapy, 2 of 8 (25%) abatacept-treated patients had a disease flare by the end of Period B compared to 8 of 13 (62%) placebo-treated patients. These results were similar in proportion to the results for the patients who had not received prior biologic therapy.

Table 19. Proportion of Patients with Disease Flare by Prior Biologic Therapy through Period B

Disease Flare	Placebo	Abatacept
Previous Biologics Use; n, (%)	8/13 (62%)	2/8 (25%)
95% CI	(-5, 55)	(35, 88)
No Previous Biologics Use; n, (%)	25/49 (51%)	10/52 (19%)
95% CI	(9, 30)	(37, 65)

Adapted from Sponsor's Submission, Document Control Number 930016107,1.0, Supplemental Table S.2.2.2

Similarly, in patients receiving concomitant MTX, 9 of 48 (19%) abatacept-treated patients experienced a disease flare compared to 24 of 46 (52%) of placebo-treated patients (Table 20). These results were similar in proportion to the results for the patients who were not receiving concomitant MTX therapy.

Table 20.Proportion of Patients with Disease Flare with Concomitant MTX Therapy through Period B

Disease Flare	Placebo	Abatacept
Concomitant MTX Use; n, (%)	24/46 (52%)	9/48 (19%)
95% CI	(38, 67)	(8, 30)
No Concomitant MTX Use; n, (%)	25/49 (51%)	3/12 (25%)
95% CI	(32, 81)	(1, 50)

Adapted from Sponsor's Submission, Document Control Number 930016107,1.0, Supplemental Table 2.2.3

6.1.6 Efficacy Findings-Period C

6.1.6.1 Study Conduct-Period C

A total of 153 patients were enrolled in to the open-label extension phase (Period C) including 117 patients who were enrolled from Period B (58 abatacept-treated patients and 59 placebo-treated patients) and 36 patients who completed Period A but did not have an adequate clinical response. At the time of the data lock, a total of 22 of the 153 (14%) patients enrolled in Period C had discontinued from the study (Table 21). Overall, the majority of patients discontinued from the study in Period C due to lack of efficacy. A total of 10 of the 36 (28%) patients who did not achieve an adequate response in Period A withdrew due to lack of efficacy compared to 2 of 58 (3%) abatacept-treated patients and 5 of 9 (9%) placebo-treated patients from Period B.

Table 21. Reasons for Discontinuation-Period C

	Period A Non-Responders (n=36)	Period B Abatacept (n=58)	Period B Placebo (n=59)
Patients Discontinued, n (%)	13 (36)	3 (5)	6 (10)
Death	0	0	0
Adverse Event	0	0	0
Lack of Efficacy	10 (28)	2 (3)	5 (9)
Lost to Follow-up	1 (3)	0	0
Withdrawal of Consent	2 (6)	0	0
Other	0	1 (2)	1 (2)

Adapted from Sponsor's Submission, Document Control Number 930019991, Table 5.1

6.1.6.2 Study Demographics-Period C

The demographic characteristics of the patients in Period C are shown in Table 22. Interestingly, Period A non-responders were slightly less likely to be white females, and more likely to be of other ethnicities. However, because the number of patients in these subgroups was small, definitive conclusions regarding potential differences in efficacy related to race or gender cannot be made.

Table 22. Baseline Patient Demographic Characteristics-Period C

	Period A Non-Responders (n=36)	Period B Abatacept (n=58)	Period B Placebo (n=59)
Age (years)			
Mean ± SD	13 ± 3	12 ± 3	12 ± 3
Sex, n (%)			
Female	23 (64)	41 (71)	42 (71)
Race, n (%)			
White	23 (64)	44 (76)	46 (78)
Black	5 (14)	5 (9)	4 (7)
Other	8 (22)	9 (15)	9 (15)
Body weight (kg)			
Mean ± SD	42 ± 15	42 ± 15	42 ± 15
Geographical region, n (%)			
North America	6 (17)	2 (3)	4 (7)
South America	22 (61)	38 (66)	33 (56)
Europe	8 (22)	18 (31)	22 (37)

Adapted from Sponsor's Submission, Document Control Number 930019991, Table 5.3.1

The disease characteristics for patients entering Period C are shown in Table 23, below.

Table 23. Disease Characteristics for Patients entering Period C at Baseline

	Period A Non-Responders (n=36)	Period B Abatacept (n=58)	Period B Placebo (n=59)
Duration of RA (years)	5 ± 4	4 ± 4	4 ± 4
Mean ± SD			
Duration of RA Disease			
≤2 years	14 (39)	28 (48)	25 (42)
>2 years to ≤5 years	8 (22)	12 (21)	16 (27)
>5 years to ≤10 years	10 (28)	12 (21)	15 (25)
>10 years	4 (11)	6 (10)	3 (5)
Active Joints			
Mean ± SD	15 ±14	18 ±11	15 ±13
Median (range)	10 (2-56)	17 (2-48)	9 (3-53)
Joints with LOM			
Mean ± SD	17 ± 18	17 ± 12	15 ± 14
Median (range)	10 (1-67)	14 (0-45)	9 (2-65)
CHAQ Disability Index (0-3)			
Mean ± SD	1.1 ± 0.9	1.3 ± 0.7	1.3 ± 0.8
Parental Global Assessment (VAS 100 mm)			
Mean ± SD	44 ± 25	42 ± 23	40 ± 25
Physician Global Assessment (VAS 100 mm)			
Mean ± SD	51 ± 22	53 ± 18	52 ± 21
JIA Disease Onset Category			
JIA Oligoarticular Persistent	0	0	2 (3)
JIA Oligoarticular Extended	3 (8)	9 (16)	6 (10)
JIA Polyarticular (RF+)	8 (22)	13 (22)	12 (20)
JIA Polyarticular (RF-)	16 (44)	25 (43)	26 (44)
JIA Systemic	9 (25)	9 (16)	12 (20)
ESR (mm/hr)			
Mean ± SD	31 ± 22	31 ± 27	32 ± 28
CRP (mg/dL)			
Mean ± SD	4 ± 5	3 ± 5	3 ± 4
RF, n (%)			
Negative	30 (83)	4 (69)	47 (80)
MTX Dose (mg/m^2/wk)			
Mean ± SD	13 ± 5	13 ± 5	13 ± 4

Adapted from Sponsor's Submission, Document Control Number 930019991, Table 5.3.2

Extent of Drug Exposure and Treatment Compliance for Period C

A total of 95 out of 153 (62%) of the patients enrolled during the open-label extension phase (Period C) had received at least 390 days (approximately 14 months) of abatacept therapy (Table 24). The mean total duration of exposure to abatacept during Period C was 444 days for all patients treated in Period C. A total of 132 out of 153 (86%) patients treated with open-label abatacept during Period C did not miss an infusion. Of the patients who missed infusion during Period C, 15 missed 1 infusion and 6 missed 2 infusions. No patients missed more than 2 infusions during Period C.

Table 24. Extent of Abatacept Exposure during Period C

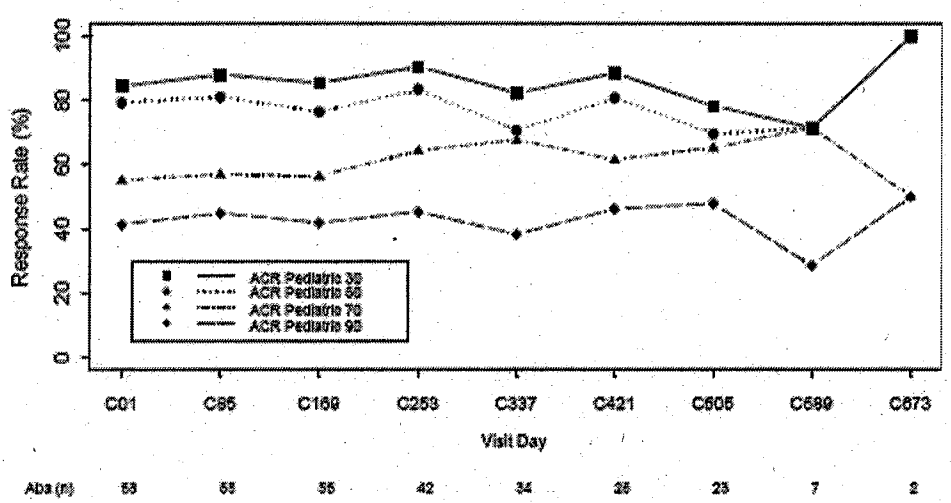
	Period A Non-Responders (n=36)	Period B Abatacept (n=58)	Period B Placebo (n=59)
Days, n (%)			
30 to <60	2 (6)	0	0
60 to <90	2 (6)	0	0
90 to <120	0	1 (2)	2 (3)
120 to <210	3 (8)	1 (2)	3 (5)
210 to <300	2 (6)	13 (22)	9 (15)
300 to <390	4 (11)	9 (16)	7 (12)
390 to <480	11 (31)	10 (17)	8 (14)
≥480	12 (33)	24 (41)	30 (51)
Mean Days (mean ± SD)	430 ± 211	440 ± 166	457 ± 177
Median Days (Range)	431 (56, 735)	437 (112, 729)	497 (111, 729)

Adapted from Sponsor's Submission, Document Control Number 930019991, Table 6.1

6.1.6.3 Signs and Symptoms-Period C

As shown in Figure 5, thus far, to data cut-off, the ACR Pediatric response rates have been maintained throughout Period C in abatacept-treated patients from Period B demonstrating that the clinical efficacy of abatacept therapy has been durable. The decreasing number of patients at successive study time points in this period reflects the staggered nature of enrollment, since this portion of the study is ongoing.

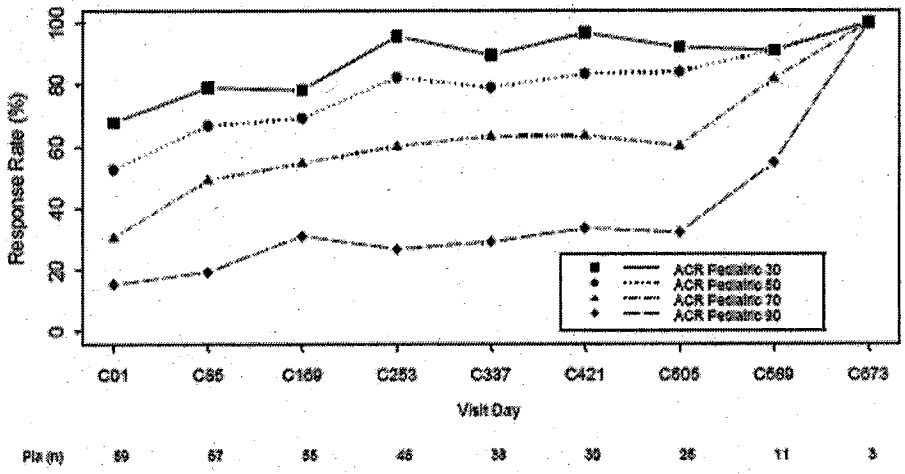
Figure 5. ACR Pediatric Response Rates for Abatacept-Treated Patients from End of Period B through End of Period C



Adapted from Sponsor's Submission, Document Control Number 930019991, Figure 7.2A

Figure 6, below, shows that patients who received placebo during Period B (and thus experienced worsening) subsequently responded to open-labeled abatacept during Period C and experienced improvement in ACR responses.

Figure 6. ACR Pediatric Response Rates for Placebo-Treated Patients from End of Period B through End of Period C



Adapted from Sponsor's Submission, Document Control Number 930019991, Figure 7.2B

Table 25 shows that at Day 169 of Period C (Day C169), the ACR Pediatric 30, 50, 70, and 90 response rates for the Period B placebo-treated patients were 78%, 69%, 55%, and 31%, respectively, which was similar to the response rates for Period B abatacept-treated patients (86%, 76%, 56%, and 42% respectively). A relatively high proportion of patients who had entered the open-labeled extension phase as inadequate responders from Period A ultimately experienced treatment benefit with abatacept, as evidenced by achievement of a ACR Pediatric 30, 50, 70, and 90 responses of 50%, 31%, 19%, and 6%, respectively, at the same time point (Table 25).

Table 25. ACR Pediatric Response Rates at Day C169-Period C

ACR Pediatric Response	Period A Non-Responders (n=32)	Period B Abatacept (n=55)	Period B Placebo (n=55)
ACR Pediatric 30, n (%)	16 (50)	47 (86)	43 (78)
ACR Pediatric 50, n (%)	10 (31)	42 (76)	38 (69)
ACR Pediatric 70, n (%)	6 (19)	31 (56)	30 (55)
ACR Pediatric 90, n (%)	2 (6)	23 (42)	17 (31)

Data from Period C presented in this submission represents interim results (through data cut-off of 12-8-06) from this long-term open-label extension. Results from the period thus far suggest that:

1. Patients taking abatacept for prolonged periods (i.e. patients who responded in Period A, were randomized to abatacept in Period B, and continued on treatment in Period C) continued to benefit from abatacept treatment;
2. Patients who initially responded to abatacept but were randomized to withdraw from abatacept were able to respond to abatacept at a level similar to initial exposure when treatment was re-started after they experienced flare;
3. Many patients who had initially not responded well to abatacept (non-responders in Period A) were able to experience treatment benefit with more prolonged exposure to abatacept.

Because data from Period C are preliminary, and only small numbers of patients have experienced prolonged treatment with abatacept thus far, definitive conclusions cannot yet be made.

6.1.7 Efficacy Conclusions

Analysis of the primary and secondary endpoints of Study IM101033 provides statistically strong and consistent evidence for the efficacy of abatacept in treating the signs and symptoms of patients with JIA/JRA in patients who have had an inadequate response to one or more DMARDs.

During the lead-in phase (Period A), 123 out of 190 (65%) patients treated with open-label abatacept achieved an ACR Pediatric 30 response rate (Table 7). An improvement was seen in each of the individual components that comprise the ACR Pediatric response composite score demonstrating that the clinical effect was not due to a single component driving the composite score. Subset analyses also demonstrated that abatacept was clinically effective in patients regardless of whether they had previously had an inadequate response to a biologic agent (Table 8). A total of 76% of "biologic naïve" patients demonstrated an ACR Pediatric 30 response, which is comparable to the etanercept JRA study. Additionally, 39% of patients who had previously failed biologic therapy, generally considered to have more refractory disease, responded to abatacept therapy, thus providing an additional therapeutic option for this subset of patients. Also, the data during Period A demonstrated that abatacept was clinically effective regardless of whether the patient was receiving concomitant MTX, although the data suggest that there is a somewhat higher response for patients using concomitant MTX (TABLE 9).

At the end of the 6-month randomized, double-blind, withdrawal phase (Period B), 53% of placebo-treated patients had experienced a disease flare compared to only 20% of abatacept-treated patients (Table 17). Subset analysis demonstrated that only 25% of the abatacept-treated patients who had previously had an inadequate response to biologic therapy experienced a disease flare which was comparable to the "biologic-therapy naïve" abatacept-treated patients that experienced a disease flare (19%; Table 19). These data suggest that abatacept therapy is effective in patients who have previously had an inadequate response to other biologic DMARDs.

Efficacy data collected during Period C demonstrated that the proportion of patients achieving ACR Pediatric 30/50/70 responses was maintained out to Day C169 supporting the conclusion that abatacept's treatment effect was durable (Figure 5 and Table 25).

Overall, these data provide substantial evidence that abatacept is effective for reducing the signs and symptoms of moderately to severely active polyarticular-course JIA/JRA in patients who have had an inadequate response to one or more DMARDs.

7. INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

The safety assessment of abatacept in patients with JIA/JRA is based on the patients enrolled in Study IM101033. As outlined above, this trial was a multicenter, double-blind, randomized withdrawal study consisting of 3 phases or periods: Period A was a 4-month, open-label lead-in phase; Period B was a double-blind, randomized withdrawal 6-month phase; and Period C is the ongoing, 5-year follow-up, open-label extension phase. Baseline demographics and disease activity suggest that the study enrolled patients representative of those seen in clinical practice with JIA/JRA including a proportion of patients who were on concomitant background DMARD therapy e.g., MTX, corticosteroids, and NSAIDs. Consequently, this study allows for a reasonable assessment of abatacept as it is likely to be used in clinical practice.

An adverse event (AE) was defined as any new untoward medical occurrence or worsening of a pre-existing medical condition in a patient administered study drug. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of study drug, whether or not the event was considered causally related to the use of the product.

Individual investigators monitored patients for clinical and laboratory evidence of AEs on a routine basis throughout the study. The investigators recorded any AE providing an assessment that included the date of onset, description, severity, time course, duration and outcome, relationship of the adverse event to study drug, an alternate etiology for events not considered "probably related" to study drug, final diagnosis (if known), and any action(s) taken. All AEs were recorded regardless of whether the AE was elicited in response to a query, observed by site personnel, or reported spontaneously by the patient. All AEs were followed to their conclusion.

Serious adverse events (SAE) were reported to the sponsor by telephone within 24 hours of occurrence or notification to the site. A SAE was defined as any event that met any one of the following criteria:

- Life-threatening or results in death
- Hospitalization
- Prolongation of hospitalization
- Malignancy
- Congenital anomaly
- Persistent of significant disability/incapacity
- Important medical event requiring medical or surgical intervention to prevent a serious outcome
- Spontaneous or elective abortion

7.1.1 Deaths

No deaths were reported in any of the three phases of Study IM101033.

7.1.2 OTHER SERIOUS ADVERSE EVENTS

There were a total of 6 SAEs reported during the lead-in phase (Period A). Three patients reported a flare of their underlying JIA/JRA, and the remaining 3 patients were diagnosed separately with an ovarian cyst, varicella infection, and acute lymphocytic leukemia (ALL).

The patient diagnosed with ALL was a 7-year-old white male who was originally diagnosed with JRA in July 2004 and started abatacept-treatment in April 2005. In July 2005 he was referred to a hematologist due to a decreasing hemoglobin concentration. A bone-marrow biopsy was performed shortly thereafter and revealed ALL. The patient is currently receiving chemotherapy for treatment of the ALL. The patient had received four infusions of abatacept prior to discontinuation from the study and had been treated with MTX 10 mg/wk since the initial diagnosis of JRA in July 2004. Given the patient's very brief exposure to abatacept therapy prior to diagnosis, it seems unlikely that abatacept treatment would be causally related to the development of this patient's ALL and more likely that the patient already had incipient disease prior to beginning study treatment. Although it is difficult to ascertain when the patient first developed ALL, hematologic malignancies may present with a similar presentation as JRA/JIA and is generally included in the differential diagnosis.

There were no SAE reported for abatacept-treated patients during Period B; however, 2 placebo-treated patients reported SAEs: 1 case of a hematoma and 1 case of varicella infection.

A total of 9 out of 153 (6%) patients reported a SAE during the open-label extension phase of the study (Period C). Of the 9 patients reporting SAEs, 2 patients had received abatacept and 4 patients had received placebo during Period B, and 3 patients had entered as non-responders from Period A. The SAEs included arthritis/flare of disease, torticollis, pyrexia, erysipelas, gastroenteritis, nausea/vomiting, and food allergy. A 17-year-old female, weighing 54 kg, inadvertently received an abatacept infusion of 750 mg instead of the intended 540 mg, and although the patient did not experience an associated AE, the event was coded as an SAE of overdose.

7.1.3 Study Discontinuations Due to Adverse Events

One patient discontinued study drug due to a SAE of ALL (discussed above) during Period A. There were no patients from either treatment arm who discontinued the study due to an AE during Period B or Period C.

7.1.4 Infections

A total of 4 out of 190 (2%) patients developed one or more of a pre-specified list of infections of interest during Period A. Two subjects each developed herpes simplex and varicella infections. Three out of the four infections were assessed as mild or moderate and one of the cases of varicella infection was classified as a SAE (see above). All the infections had a typical clinical presentation, resolved with treatment, and did not result in study drug discontinuation.

During Period B, a total of 1 out of 60 (2%) abatacept-treated patients developed an infection of interest, herpes simplex, which was of mild intensity and resolved without treatment or study drug interruption. In contrast, 3 out of 60 (5%) of placebo-treated patients developed 5 infections (2 herpes simplex, 1 cellulitis, and 1 varicella with encephalitis).

A total of 11 infections were reported in 10 out of 153 patients (7%) during Period C. The infections included 3 cases of varicella, 2 cases of Herpes simplex, 2 cases of tooth abscess, and 1 case each of "viral infection", cellulitis, pneumonia, and Staphylococcal infection. All of the infections except one were of mild or moderate intensity and had a typical clinical presentation. One case of varicella was deemed severe in intensity and resolved in 15 days.

7.1.5 Neoplasms: Benign, Malignant, and Unspecified

A total of 5 neoplasms were reported during Period A; 4 neoplasms were benign and did not necessitate study drug discontinuation. The one malignant neoplasm was a diagnosis of ALL and is discussed above.

There were no neoplasms reported for abatacept-treated patients during Period B; however, 1 placebo-treated patient developed a benign skin papilloma.

No malignant neoplasms were reported during Period C. Two benign neoplasms, skin papilloma of the lips and hand, were reported in 1 patient.

7.1.6 Autoimmune Disorders

Two patients reported an autoimmune-related symptom during Period A: 1 case of erythema nodosum and 1 case of vitiligo. Both cases were of moderate intensity. No autoimmune-related events occurred during Period B. One patient, who entered the study with a previous diagnosis of vitiligo, reported a worsening of vitiligo during Period C.

7.1.7 Infusional AEs

Infusional AEs were pre-specified as "peri-infusional" AEs (within 24 hours following start of infusion) and "acute infusional" AEs (within 1 hour after the start of infusion), which are a subset of the peri-infusional AEs.

A total of 30 out of 190 (16%) experienced a peri-infusional AE, the most frequently reported was headache (7%). The majority of peri-infusional AEs were of mild or moderate intensity, although, one patient reported a severe case of thoracic pain that resolved without treatment and did not result in study drug interruption or discontinuation. A total of 8 out of 190 (4%) patients reported an acute infusional AE, of which all but 1 (headache) were mild in intensity and none were reported as serious. There were no cases of anaphylaxis reported during Period A.

The frequency of peri-infusional AEs was similar between abatacept- and placebo-treated patients (3% and 3%, respectively). All events were mild or moderate in intensity. Approximately 2% of abatacept-treated patients reported an acute infusional AE compared to 3% of placebo-treated patients. All of the acute infusional AEs for abatacept-treated patients were reported as mild in intensity. There were no cases of anaphylaxis reported during Period B.

Peri-infusional AEs were reported in 12 out of 152 (8%) patients during Period C. All AEs were considered mild or moderated in intensity except for one case of hypersensitivity reaction that occurred within 1 hour after the start of the abatacept infusion. This AE is also listed as an acute infusional AE and is described below. A total of 4 out of 153 (3%) patients reported an acute infusional AE during Period C. Of the 4 patients, 3 had received abatacept and 1 patient receive placebo during Period B. None of the AEs resulted in discontinuation of study drug. The acute infusional AE that occurred in the patient, who had received placebo during Period B, was reported as severe in intensity (edema, pruritus, and rash due to allergic reaction). She was treated with diphenhydramine and hydrocortisone and the symptoms resolved.

As discussed in section 7.1.11, 2 of the 4 patients who developed an acute infusional reaction during Period C were seropositive for anti-product antibodies. One patient presented with hypersensitivity of severe intensity and one patient presented with urticaria and hypertension of moderate intensity.

Both patients recovered with treatment and neither of the infusional reactions met the criteria for a SAE nor required discontinuation from the study. It is difficult to draw firm conclusions concerning the relationship between the development of anti-product antibodies and infusion-related AEs due the small number of patients who seroconverted in this study; however, it is not unreasonable for clinicians to have an increased index of suspicion for infusion-related reactions in seropositive patients.

7.1.8 Common Adverse Events

As shown in Table 26, 133 out of 190 (70%) of patients reported an AE during Period A. The infections and infestations SOC had the highest number of AEs (36%) and the most common single AE was headache (13%). The majority of the AEs were mild to moderate in intensity.

Table 26. Adverse Events in ≥3% of Patients during Period A

System Organ Class Preferred Term	Abatacept N=190
Total Subjects with AE, n (%)	133 (70)
Infections, n (%)	68 (36)
URI	14 (7)
Nasopharyngitis	11 (6)
Rhinitis	8 (4)
Influenza	7 (4)
Pharyngitis	6 (3)
Sinusitis	6 (3)
Gastrointestinal Disorders, n (%)	66 (35)
Nausea	19 (10)
Diarrhea	17 (9)
Abdominal Pain Upper	10 (5)
Abdominal Pain	9 (5)
Vomiting	7 (3)
Aphthous Stomatitis	6 (3)
Mouth Ulceration	6 (3)
Respiratory, Thoracic & Mediastinal Disorders, n (%)	32 (16)
Cough	17 (9)
Pharyngolaryngeal Pain	8 (4)
Nervous System Disorders, n (%)	30 (16)
Headache	25 (13)
Dizziness	7 (4)
Musculoskeletal and CT Disorders, n (%)	10 (5)
General Disorders & Administration Site Conditions, n (%)	26 (14)
Pyrexia	12 (6)
Skin and Subcutaneous Tissue Disorders, n (%)	18 (10)
Injury, Poisoning and Procedural Complications, n (%)	13 (7)
Blood and Lymphatic System Disorders, n (%)	11 (6)
Musculolskeletal & Connective Tissue Disorders, n (%)	10 (5)
Eye Disorders, n (%)	9 (5)
Renal and Urinary Disorders, n (%)	6 (3)
Vascular Disorders, n (%)	6 (3)
Reproductive and Breast Disorders, n (%)	5 (3)

Adapted from Sponsor's Submission, Document Control Number 930016107, Supplemental Table S.6.16

As shown in Table 27, there were a greater number of AEs reported in abatacept-treated patients (62%) compared to placebo-treated patients (55%) during Period B. The infections and infestations SOC had the highest number of AEs for both the abatacept (45%) and placebo (44%) treatment arms. The most common single AE for that abatacept treatment arm was influenza, which affected 8% of abatacept-treated patients compared to 7% of placebo-treated patients. The majority of the AEs were mild to moderate in intensity and no patient in the abatacept treatment arm had an AE that was reported as severe or very severe intensity.

Table 27. Adverse Events in ≥3% of Abatacept-Treated Patients and Higher Frequency Than Placebo-Treated Patients during Period B

System Organ Class Preferred Term	Abatacept N=60	Placebo N=62
Total Subjects with AE, n (%)	37 (62)	34 (55)
Infections, n (%)	**27 (45)**	**27 (44)**
Influenza	5 (8)	4 (7)
Bacteriuria	4 (7)	0
Nasopharyngitis	4 (7)	3 (5)
Gastroenteritis	3 (5)	1 (2)
Sinusitis	3 (5)	2 (3)
Gastrointestinal Disorders, n (%)	**10 (17)**	**9 (15)**
Abdominal Pain	3 (5)	1 (2)
Mouth Ulceration	2 (3)	0
Respiratory, Thoracic & Mediastinal Disorders, n (%)	6 (10)	3 (5)
Asthma	2 (3)	0
Pharyngolaryngeal Pain	2 (3)	1 (2)
Rhinorrhea	2 (3)	0
Nervous System Disorders, n (%)	3 (5)	2 (3)
Headache	3 (5)	1 (2)
Musculoskeletal and CT Disorders, n (%)	3 (5)	2 (3)
Renal and Urinary Disorders, n (%)	**3 (5)**	**1 (2)**
Vascular Disorders, n (%)	3 (5)	1 (2)

Adapted from Sponsor's Submission, Document Control Number 930016107, Supplemental Table S.6.20

As shown in Table 28, 111 out of 153 (73%) of patients reported an AE during Period 3. The infections and infestations SOC had the highest number of AEs (54%) and the most common single AE was upper respiratory tract infection (12%) and vomiting (11%). The majority of the AEs were mild to moderate in intensity.

Table 28. Adverse Events in ≥3% of Patients during Period C

System Organ Class Preferred Term	Abatacept N=153
Total Subjects with AE, n (%)	111 (73)
Infections, n (%)	83 (54)
URI	19 (12)
Nasopharyngitis	14 (9)
Rhinitis	11 (7)
Sinusitis	11 (7)
Pharyngitis	10 (7)
Influenza	9 (6)
Gastroenteritis	7 (5)
Tonsillitis	7 (5)
Viral Infection	5 (3)
Bacteriuria	4 (3)
Paronychia	4 (3)
Gastrointestinal Disorders, n (%)	46 (30)
Vomiting	16 (11)
Nausea	12 (8)
Diarrhea	11 (8)
Abdominal Pain	6 (4)
Abdominal Pain Upper	6 (4)
Mouth Ulceration	6 (4)
General Disorders & Administration Site Conditions, n (%)	24 (16)
Pyrexia	14 (9)
Respiratory, Thoracic & Mediastinal Disorders, n (%)	21 (14)
Cough	12 (8)
Pharyngolaryngeal Pain	7 (5)
Rhinorrhea	4 (3)
Skin and Subcutaneous Tissue Disorders, n (%)	20 (13)
Injury, Poisoning and Procedural Complications, n (%)	19 (12)
Musculoskeletal and CT Disorders, n (%)	18 (12)
Blood and Lymphatic System Disorders, n (%)	15 (10)
Eosinophilia	7 (5)
Nervous System Disorders, n (%)	15 (10)
Headache	11 (7)
Dizziness	6 (4)
Renal and Urinary Disorders, n (%)	12 (8)
Hematuria	5 (3)
Reproductive and Breast Disorders, n (%)	8 (5)
Investigations, n (%)	7 (5)
ALT increased	5 (3)
Eye Disorders, n (%)	6 (4)
Metabolism and Nutrition Disorders, n (%)	4 (3)

Adapted from Sponsor's Submission, Document Control Number 930019991, Table 8.6.1

7.1.9 Clinical Laboratory Evaluations

7.1.9.1 Hematologic and Blood Chemistry

Overall there were very few patients with laboratory abnormalities in hematologic and blood chemistry parameters that met the pre-defined criteria for marked laboratory abnormalities (as per Sponsor's submission, Document Contorl Number 930016107, Appendix 7.1) during Period A. During Period B, the frequency of laboratory abnormalities that met these criteria were also few and occurred in similar frequency in the abatacept and placebo treatment arms. For both Period A and Period B, laboratory findings meeting the criteria for marked laboratory abnormalities were low in number and observed only at a single time point, and did not interrupt study drug dosing. The changes observed in hematologic and blood chemistry laboratories were small in magnitude and number, and without a consistent pattern. During Period C, fewer than 10% of patients had laboratory parameters that met the definition of a marked laboratory abnormality. The most frequently occurring markedly abnormal laboratories were low fasting glucose (25%), elevation of eosinophils (24%), and elevated creatinine (21%). The elevation of eosinophils was often associated with upper respiratory infection or other infections but none of the elevations were associated with SAEs, infusional AEs, or changes in efficacy. Blood ALT, AST, creatinine levels remained stable during abatacept treatment during Period C. Several patients had elevated AST or ALT levels during the study from both abatacept- and placebo-treated patients but these levels were less than 5x ULN and did not necessitate interruption/discontinuation from study drug.

7.1.9.2 ANA and anti-dsDNA Antibodies

A total of 12 out of 113 (11%) patients who were negative for ANA at baseline seroconverted to a positive ANA during Period A. Conversely, 15 out of 54 (28%) patients who were positive for ANA at baseline subsequently tested negative for ANA during Period A. Similarly, a small proportion of patients (9 out of 146 or 6%) who were negative for anti-dsDNA antibodies at baseline seroconverted to a positive anti-dsDNA antibody during Period A. Conversely, 13 out of 25 (52%) patients who were positive for anti-dsDNA antibodies at baseline subsequently tested negative for anti-dsDNA antibodies during Period A. Seroconversion to either ANA or anti-dsDNA antibodies was not associated with any clinically significant findings such as AEs or a lupus-like syndrome. The clinical significance of patients who are ANA or anti-DNA antibody positive at one point in time and then subsequently testing negative is not well understood but it is not thought to confer a clinical benefit.

A total of 2 out of 34 (6%) abatacept-treated patients and 1 out of 25 (4%) placebo-treated patients who were negative for ANA at the beginning of Period B seroconverted to ANA positive by the end of the double-blind phase.

Conversely, 2 out of 15 (13%) abatacept-treated patients and 6 out of 14 (43%) placebo-treated patients who were positive for ANA at the beginning of Period B subsequently tested negative for ANA by the completion of the double-blind phase. A total of 1 out of 43 (2%) abatacept-treated patients and none of the placebo-treated patients who were negative for anti-dsDNA antibodies at baseline seroconverted to a positive anti-dsDNA antibody during Period B. Conversely, 6 out of 7 (86%) abatacept-treated patients and 2 out of 3 placebo-treated patients who were positive for anti-dsDNA antibodies at baseline subsequently tested negative for anti-dsDNA antibodies during Period B. Seroconversion to either ANA or anti-dsDNA antibodies was not associated with any clinically significant findings such as AEs or a lupus-like syndrome. The clinical significance of patients who are ANA or anti-dsDNA antibody positive at one point in time and then subsequently testing negative is not well understood but it is not thought to confer a clinical benefit.

Two out of 14 (14%) patients who were negative for ANA at baseline seroconverted by the end of Period C and 1 out of 14 (7%) patients who were negative for anti-dsDNA antibodies seroconverted to positive by the end of Period C.

7.1.10 Vital Signs and Physical Findings

Mean values for all vital sign parameters were within normal range and remained stable throughout Period A and Period B. While there were no AE reports of hypertension reported during Period A, there was one case of hypertension that was reported as an AE for an abatacept-treated patient during Period B. The patient was a 16-year-old female who developed hypertension of mild intensity, which resolved without interruption or discontinuation of study drug. Overall, there were 14 patients meeting the criteria of significant or severe hypertension during Period B. Eleven of the 14 cases were single incidences and did not qualify for a diagnosis of chronic hypertension. Overall, there did not appear to be a safety signal seen between abatacept and development of hypertension.

Mean values for all vital sign parameters were within normal range and remained stable throughout Period C. A total of 43 out of 153 (28%) of patients met the pre-specified criteria for having significant or severe hypertension during Period C. The majority of these events occurred on only one or two occurrences and mostly during the peri-infusional period. Two patients reported hypertension as an AE during Period C. Overall, there did not appear to be a safety signal seen between abatacept and development of hypertension.

7.1.11 Immunogenicity

In the Phase 3 trials studying abatacept in adult patients with RA, 34 of 1993 (1.7%) patients developed binding antibodies to the entire abatacept molecule or to the CTLA-4 portion of abatacept. Because trough levels of abatacept can interfere with assay results, a subset analysis was performed that demonstrated 9 of 154 (5.8%) patients that had discontinued treatment with ORENCIA for over 56 days developed antibodies. Samples with confirmed binding activity to CTLA-4 were subsequently assessed for the presence of neutralizing antibodies and found that 6 of 9 (67%) evaluable patients had developed neutralizing antibodies; however, no correlation of antibody development to clinical response or adverse events was observed.

In the present study, abatacept infusions were intentionally interrupted when patients were randomized to receive placebo infusions during Period B. Therefore, the analyses of immunogenicity for this study included the development of anti-abatacept and anti-CTLA-4 antibodies as well as the analysis comparing patients who received placebo versus abatacept during Period B. Serum was obtained for assessment of anti-abatacept and anti-CTLA4 antibodies on Days 1, 57, 113 (or at discontinuation) during Period A; Days 85 and 169 (or at flare/discontinuation) during Period B; and at 3 month intervals during Period C. Any patient that discontinued from treatment was to have samples collected 28, 56, and 85 days after their last dose of study drug.

The antibody response to abatacept or the CTLA-4 portion of the abatacept fusion protein (termed CTLA4-T or 'tip') was determined using 2 validated ELISA tests. Seropositivity was confirmed and specificity of the reactivity defined by a competition assay. Samples that were positive for anti-CLTA4 antibodies were further evaluated for neutralizing activity. Immunogenicity data were available from 188 of the 190 patients during Period A; 108 patients (54 abatacept-treated; 54 placebo-treated) during Period B; and 143 of the 153 subjects who entered Period C.

A total of 40 patients were found to be seropositive. Of these patients, 2 out of 162 (1%) patients had developed anti-abatacept antibodies, and 39 out of 188 (21%) patients developed anti-CTLA4-T antibodies. Of note, 1 patient was seropositive for both antibodies. Titers for anti-CTLA4 antibodies in seropositive patients ranged from 25 to 199, and patients who were seropositive for anti-abatacept antibodies had titers of 420 and 22,499. Patients who had received placebo for the entire 6-months of Period B had a greater incidence anti-abatacept and/or anti-CTLA4 antibodies (22 of 54 (41%) patients) compared to those patients treated with abatacept during Period B (7 of 54 (13%) patients). A total of 3 out of 23 (13%) of patients from Period A and 2 out of 14 (14%) patients from Period B who discontinued from the study and were followed for up to 85 days after their last dose of study drug had seroconverted.

Overall, anti-abatacept and anti-CTLA4 antibodies appeared to be transient with the majority of seropositive patients having antibodies only at a single visit. Of the 40 patients with a positive antibody response, 26 (65%) had only single instances of seropositivity and remained seronegative during continued abatacept treatment in Periods B and C, or after the re-initiation of abatacept therapy in Period C. A total of 5 out of 25 (20%) patients who continued to Period C from Period B were seropositive; 3 of 18 (17%) placebo-treated patients and 2 of 7 (29%) abatacept-treated patients. Additionally, 13 samples from 10 patients were found to be positive for antibodies with neutralizing activity to abatacept. It is difficult to truly ascertain the clinical significance of the neutralizing activity in this study due to the small number of patients exhibiting neutralizing antibodies; however, there did not appear to be a demonstrable consequence on the maintenance of efficacy or safety.

A total of 18 out of the 22 placebo-treated patients during Period B re-initiated abatacept infusions during Period C and 3 of the 18 (17%) patients developed SAEs: gastroenteritis, synovial cyst and erysipelas, and recurring nausea and vomiting. Also, 2 of the 4 patients who developed an acute infusional reaction during Period C were seropositive. One patient presented with hypersensitivity of severe intensity and one patient presented with urticaria and hypertension of moderate intensity. Both patients recovered with treatment and neither of the infusional reactions met the criteria for a SAE nor required discontinuation from the study. There were no autoimmune disorders reported in seropositive patients during Period A, Period B or Period C and no observable relationship between seropositive status and clinical efficacy.

In summary, patients who had an interruption in their abatacept therapy for up to 6-months (i.e., those patients randomized to receive placebo during Period B) had a higher incidence of anti-abatacept and anti-CTLA-4 antibodies compared to than patients who continued abatacept therapy. Approximately 65% of patients who were positive for anti-abatacept/anti-CTLA-4 antibodies only had a single occurrence of seropositivity. Overall, seropositive patients did not appear to be at an increased risk for AEs, including infusion-related reactions, or to experience limited efficacy; however, it is difficult to draw firm conclusions due the small number of patients who seroconverted in this study. It in interesting to note that while concomitant MTX has been shown to inhibit antibody formation to adalimumab and infliximab, concomitant MTX did not appear to prevent the development of anti-CTLA-4 antibodies in placebo-treated patients during Period B.

7.1.12 120 Day Safety Update

Overall, the types of events reported during the 120 day safety update period were similar to those reported during the earlier study periods. Of the 132 patients entering the safety update period, 116 (88%) patients were still participating at the time of the cut-off date, and 16 (12%) patients had discontinued (2 due to AEs). There were no deaths or malignancies reported during this period.

A total of 16 SAEs were reported for 10 patients. There were 5 cases of joint pain, 1 case of "flat feet" that was reported due to the patient being hospitalized for tarsal prosthesis surgery, 1 case of abdominal pain of moderated intensity lasting 19 days associated with vomiting and pyrexia of 1 day duration, 1 case on bacterial meningitis that resolved with antibiotic treatment and did not require interruption of drug dosing, 1 case of hypersensitivity of moderate intensity that lasted 1 day. Lastly, a 12 year-old male developed temporal lobe epilepsy and was ultimately diagnosed with multiple sclerosis and was discontinued from further abatacept treatment.

A total of 332 AEs were reported for 92 patients during the safety update period. The majority of these were of mild or moderate intensity. Abatacept therapy had to be interrupted in 6 patients due to an AE and 2 patients discontinued the study due to an AE (1 case each of multiple sclerosis and infusional-related AE). Four patients reported an AE related to an autoimmune disorder: the 1 case of multiple sclerosis discussed above, 1 case of Raynaud's phenomenon, and 1 case of worsening vitiligo which was diagnosed prior to the patient entering the study, 1 case of neutropenia that is currently continuing. Neutropenia was observed in abatacept trials in adult patients with RA.

Infusional reactions were reported for 2 patients. One case of hypersensitivity reaction resolved without further treatment and did not interrupt further treatment, and 1 case of hypersensitivity was associated with urticaria and bronchospasm, resulting in discontinuation from the study.

9. OVERALL ASSESMENT

9.1 Conclusions

In total, the data from the double-blind and open-label periods of Study IM101033 demonstrate that abatacept, with or without concomitant MTX, provides an acceptable risk-benefit ratio and is clinically effective in treating the signs and symptoms of JIA/JRA in patients who have had an inadequate clinical response to other DMARDs.

9.2 Recommendations

It is the recommendation of this reviewer to approve the BLA supplement STN#: 125118/45 and to allow the inclusion of data to the package insert describing the results of the randomized withdrawal Study IM101-033. Additionally, it is my recommendation to request the sponsor to agree to a post-marketing commitment to create and maintain a database of at least 500 patients for a minimum of 3 years.