U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	sBLA STN 125118.045
Drug Name:	ORENCIA® (abatacept, BMS-188667)
Indication(s):	For reducing signs and symptoms in pediatric and adolescent patients with moderately to severely active juvenile idiopathic arthritis / juvenile rheumatoid arthritis with polyarticular course
Applicant:	Bristol-Myers Squibb Company
Date(s):	Submitted: June 8, 2007 PDUFA: April 7, 2008
Review Priority:	Standard
Biometrics Division:	Division of Biometrics II
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Keywords: Clinical studies, endpoint analysis

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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

Study IM101033 was conducted in children and adolescents with active polyarticular juvenile rheumatoid arthritis for the pediatric efficacy supplement for abatacept. The study demonstrated a greater effect of abatacept compared to placebo in treating signs and symptoms of juvenile rheumatoid arthritis (JRA) / juvenile idiopathic arthritis (JIA). The effect was measured by time to occurrence of disease flare based on ACR Pediatric 30 (JRA/JIA core set variables). The effect was evident in both the applicant's analyses and the additional analyses conducted by me.

1.2 Brief Overview of Clinical Studies

Study IM101033 was a multi-center, multi-national, randomized, withdrawal, double-blind, placebo-controlled, three-period (4 month open-label lead-in period, 6 month double-blind period, and 5 year ongoing open-label extension period) trial investigating the safety and efficacy of abatacept in children and adolescents with active polyarticular juvenile rheumatoid arthritis. During the double-blind period of the study, 122 patients were randomized to abatacept i.v. (n = 60) or placebo i.v. (n = 62). Eligible patients subsequently entered an open-label extension study. The primary efficacy outcome was the time to disease flare during the double blind period. Key secondary efficacy measures included the proportion of subjects that demonstrate JRA/JIA disease flare, number of joints with limited range of motion, and disease activity as measured by the physician's global assessment of disease severity.

1.3 Statistical Issues and Findings

There were no statistical issues identified during the course of my review. In the primary analysis, patients who dropped out prior to experiencing a disease flare were censored. This was appropriate as artificially counting dropouts as having experienced a flare would have overestimated the treatment effect. In the analysis of the secondary variables, a LOCF strategy was used. Again because the reason for most dropouts was lack of efficacy and the placebo group had more such dropouts, a more conservative imputation method would give more favorable analysis results to the abatacept group. Also since each center enrolled fewer than 5 subjects on the average and the biggest center enrolled less than 10% of the total subjects, I did not consider an assessment of the homogeneity of treatment effects across centers to be meaningful. Also, it is worthwhile to note that analyses for the secondary endpoints were not adjusted for multiplicity.

2. INTRODUCTION

2.1 Overview

2.1.1 Regulatory history

Abatacept was approved for marketing by the US FDA on December 2005 for the treatment of adult rheumatoid arthritis. The trade name for abatacept is Orencia®.

The following is a history of regulatory interaction described in the submission.

> The topic of Pediatric Study Deferral for abatacept was initially discussed at the End-of-Phase 2 meeting with the US Food and Drug Administration (FDA) on 25-Mar-2002 (refer to the FDA meeting minutes dated 25-Mar-2002).
>
> The JRA/JIA study protocol (IM101033) was provided to the FDA on 09-Oct-2003 (IND: 9391, Serial No. 0167) prior to its initiation for review and comments. On 13-Nov-2003, the agency provided agreement (via telephone contact) that the final protocol was appropriately designed to provide the necessary data for evaluation of the safety and efficacy of the product in the children and adolescent population, and recommended few changes to the protocol. A revised protocol (with Amendment 01) was submitted to the agency on 11-Dec-2003 (IND: 9391, Serial No. 0184).
>
> The abatacept Biologics License Application (BLA) for adult RA was approved on 23-Dec-2005. Post-marketing commitment #1 (due on 30-Nov-2006) was the submission of study results from the JRA/JIA study (IM101033); this commitment was fulfilled on 29-Nov-06 by submission of a clinical study report on Periods A and B of the study to the original BLA (STN BL 125118).
>
> Further, Bristol-Myers Squibb (BMS) requested feedback from the FDA on questions related to the planned pediatric Supplemental BLA (sBLA) submission on 11-Apr-2007 (IND: 9391, Serial No. 0437); an e-mail response from the FDA was received on 11-Apr-2007.

2.1.2 Proposed Indication

The proposed indication for abatacept is to reduce signs and symptoms in pediatric and adolescent patients with moderately to severely active juvenile idiopathic arthritis (JIA) / juvenile rheumatoid arthritis (JRA) with polyarticular course who have had an inadequate response to 1 or more disease modifying anti-rheumatic drugs (DMARDs), such as methotrexate (MTX) or tumor necrosis factor (TNF)-antagonists. Abatacept may be used as monotherapy or concomitantly with MTX.

2.2 Data Sources

sBLA STN 125118.045 was submitted on June 8, 2007 and has been loaded into the GSreview tool. The electronic SAS data sets were also provided in the GSreview using the following path:

\\cbsap58\M\eCTD Submissions\STN125118\125118.enx

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 Study Design and Endpoints

Study IM101033 was a multi-national, multi-center, randomized, withdrawal trial to evaluate the safety and efficacy of abatacept in children and adolescents with active polyarticular juvenile rheumatoid arthritis.

The study started with a 4-month, open-label, lead-in phase (Period A). Subjects who met the pre-specified definition of response at the end of Period A entered into the 6-month, randomized, withdrawal, double-blind, parallel group, placebo-controlled treatment phase (Period B) in which the subjects were randomized to continuation of abatacept or switch to placebo. Response criteria for entry into the double blind phase was defined as $\geq$ 30% improvement in at least 3 of the 6 JRA/JIA core set variables and $\geq$ 30% worsening in not more than 1 of the 6 JRA/JIA core set variables.

The ACR pediatric components (JRA/JIA core set variables) were 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
- childhood health assessment questionnaire (CHAQ)
- erythrocyte sedimentation rate (ESR).

All subjects who successfully completed Period B, subjects who flared during Period B, and subjects who did not meet the pre-specified response criteria at the end of Period A were given an option to enter an open-label extension phase (Period C). Subjects who discontinued due to safety reasons were restricted from entering Period C.
In the study Period B, 122 eligible patients were randomized to abatacept or placebo in a 1:1 ratio at 32 centers worldwide including the US, the Europe (Austria, France, Germany, Italy, Portugal, Spain, and Switzerland), and South America (Brazil, Mexico, and Peru).

A schematic of the study is presented in the appendix (Figure 12).

The primary efficacy variable was the time to occurrence of JRA/JIA disease flare in the double-blind phase (Period B), defined as the elapsed number of days between the first double-blind dose and the study day that disease flare was confirmed. Flare was defined as:

- ≥ 30% worsening in at least 3 of the 6 JRA/JIA core set variables
- ≥ 30% improvement in not more than 1 of the 6 JRA/JIA core set variables
- ≥ 2 cm (possible up to 10 cm) of worsening must have been present if the Physician or Parent Global Assessment was used to define flare
- worsening in ≥ 2 joints must have been present if the number of active joints or joints with limited range of motion was used to define flare.

The secondary efficacy variables included the following:

- proportion of subjects that demonstrate JRA/JIA disease flare by Day B169
- number of active joints using the definition provided by American College of Rheumatology (ACR) Pediatric 30 (JRA/JIA core set variable)
- number of joints with limited range of motion (JRA/JIA core set variable)
- disease activity as measured by the physician's global assessment of disease severity (JRA/JIA core set variable)
- change in the subject's overall well-being as measured by the parent global assessment of overall well being (JRA/JIA core set variable)
- change in physical function as measured by the disability index of the Childhood Health Assessment Questionnaire (CHAQ) (JRA/JIA core set variable)
- changes in the surrogate markers Erythrocyte Sedimentation Rate (ESR) and C-reactive protein (CRP) (JRA/JIA core set variable).

3.1.2 Patient Disposition and Demographics

Table 1 summarizes the patient disposition during the open-label lead-in period (Period A) and double blind period (Period B).

Table 1 Patient Disposition

	Abatacept	Placebo	Total
Period A			
Entered			190
Completed			170
Responded			123
Period B			
Randomized (ITT)	60	62	122
Completed	49 (81.7%)	31 (50.0%)	80 (65.6%)
Discontinued	11 (18.3%)	31 (50.0%)	42 (34.4%)
AE	0	0	0
LOE	10 (16.7%)	31 (50.0%)	41 (33.6%)
Consent Withdrawal	1 (1.7%)	0	1 (0.8%)

Source: Tables 5.1 and 6.1 of the Clinical Study Report (pages 59 and 72). ITT population included all randomized subjects for whom study medication was administered.

Patient demographics by treatment group were summarized in the appendix (Table 5). In Study IM101033, 77% of the abatacept patients and 79% of the placebo patients were Caucasian, respectively. Seventy-two percent of the abatacept patients and 73% of the placebo patients were female, respectively. The median age of the abatacept patients was 13 years and the median age of the placebo patients was 12.5 years. There were no noticeable imbalances between treatment groups with respect to the demographic variables of race, sex, age, and weight. Also, there were no noticeable imbalances between treatment groups with respect to the baseline efficacy variables of physician global assessment, parent global assessment, childhood health assessment questionnaire disability index, erythrocyte sedimentation rate, and c-reactive protein. However, there were numerical imbalances between groups in the baseline active joints and joints with limited range of motion, although not statistically tested. The median score of active joints for the abatacept patients was 17 (ranged 2 – 48) and the median score for the placebo patients was 9 (ranged 3 – 53). The median score of joints with limited range of motion for the abatacept patients was 14 (ranged 0 – 59) and the median score for the placebo patients was 9 (ranged 2 – 65).

3.1.3 Statistical Methodologies

The difference in the time to disease flare between the abatacept and placebo groups was analyzed using a log-rank test. A Cox proportional hazard regression model with a term for treatment was used to estimate the hazard ratio and its 95% confidence interval. Curves of the distribution of disease flare over time for the two treatment groups were generated using the Kaplan-Meier method. A continuity corrected chi-square test was used to compare proportions of 'disease flare' between the two treatment groups - the continuity correction is often used when sample sizes are small and is generally conservative. An analysis of covariance model with terms for treatment and baseline value as covariate was used for the analysis of secondary efficacy variables such as number of active joints and number of joints with limited range of motion.

The primary analysis was conducted on the intent-to-treat population defined as all randomized subjects taking at least one dose of study medication. In the primary analysis, subjects discontinuing treatment due to reasons other than 'disease flare' were censored at the time of discontinuation. In the analyses of secondary efficacy variables, missing efficacy data were imputed using the last observation carried forward method.

3.1.4 Results and Conclusions

Tables 2 – 4 present the statistical analyses conducted by the applicant and me. I confirmed the applicant's analyses. The following are the results of the analyses.

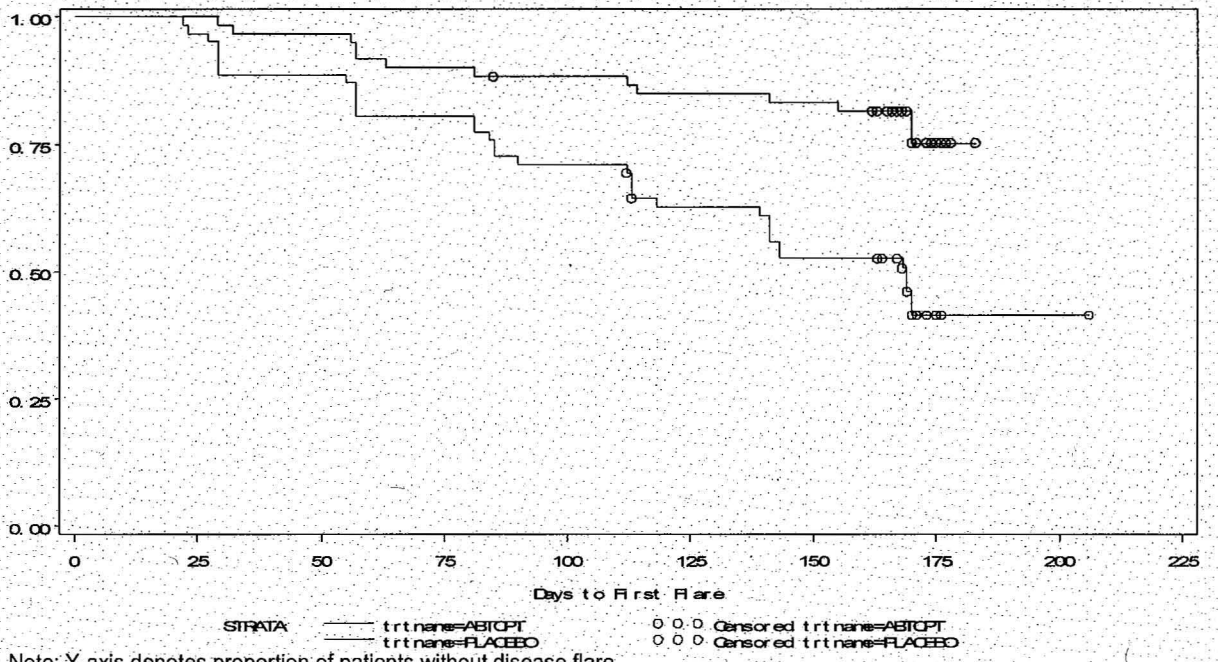
In Study IM101033, a greater treatment effect (as measured by time to disease flare) was achieved by patients receiving abatacept as compared to those receiving placebo. The primary analysis demonstrated superiority of abatacept to placebo based on the log-rank test (Table 2). The table also provided the hazard ratio and its 95% confidence interval estimation based on the Cox proportional hazard regression model with term for treatment. The risk of disease flare for patients in the abatacept group was about one third of the risk for patients in the placebo group. The Kaplan-Meier curves, shown in Figure 1, depicted the significant difference in the time to disease flare among treatments. Based on the Kaplan-Meier curves, the median time in days to disease flare for the placebo group was 169 days with 95% lower confidence bound of 139 days. However, because most patients in the abatacept group did not experience a flare, the median time was not estimable.

Table 2 Applicant's Primary Efficacy Analysis: ITT Population

	Abatacept/Placebo
Hazard Ratio	.31
95% CI	(.16, .59)
p-value	**.0002**

P-value was calculated using log-rank test and the hazard ratio and its 95% confidence interval were calculated based on Cox proportional hazard regression model with a term for treatment.

Figure 1 Reviewer's Kaplan-Meier Curve Estimation: ITT Population



Note: Y-axis denotes proportion of patients without disease flare.

As a supportive analysis, the proportions of disease flare were compared between the abatacept and placebo groups. Patients that discontinued prior to having a disease flare were considered as not having had a disease flare. The proportion of patients experiencing disease flare by the end of Period B in the abatacept group was statistically significantly lower than the proportion in the placebo group (Table 3).

Table 3 Applicant's Supportive Analysis with Proportions of Patients Experiencing Disease Flare : ITT Population

	Abatacept (N=60)	Placebo (N=62)	P-value
Flare Proportion	12/60 (20%)	33/62 (53%)	**<.001**

P-value was calculated using continuity corrected chi-square test.

In my analyses of the secondary efficacy variables, there were statistically significant differences in mean percent change from the baseline to the end of double-blind period (Period B) between the abatacept and placebo groups for the number of active joints, the number of joints with limited range of motion, physician global assessment, childhood health assessment questionnaire (CHAQ), and c-reactive protein (CRP). However, there were no statistically significant differences between the groups for parent global assessment and erythrocyte sedimentation rate (ESR) (Table 4). In their study report, the applicant presented the median percent change scores from baseline with the first and third quartiles although they pre-specified the use of the mean percent change scores with 95% confidence intervals in the statistical analysis plan. Although not completely clear from the report, it seems that their objective with the secondary variables was changed from a formal comparison of the variables between the treatment groups to an informal description of observed trend during Period B. Therefore, I conducted the analysis of covariance (ANCOVA) as planned in the statistical analysis plan. The applicant included the same analyses in the appendix of the study report. However, some of their analyses were different from mine.

Table 4 Reviewer's Analyses for Secondary Efficacy Variables: ITT Population with LOCF Imputation

		Abatacept (n=60)	Placebo (n=62)
Active Joints	Baseline Mean (SD) %Change from Baseline (SE) Diff. from Placebo (95% CI)	5.4 (5.5) 19 (23) -73 (-136, -9)	3.9 (5.9) 92 (22)
Joints with LOM	Baseline Mean (SD) %Change from Baseline (SE) Diff. from Placebo (95% CI)	8.8 (10.7) 6 (16) -58 (-103, -13)	7.4 (12.6) 64 (16)

Phy. Global Assessment	Baseline Mean (SD) %Change from Baseline (SE) Diff. from Placebo (95% CI)	15.9 (12.5) 6 (27) -136 (-211, -62)	12.5 (12.5) 143 (26)
CHAQ Disability Index	Baseline Mean (SD) %Change from Baseline (SE) Diff. from Placebo (95% CI)	.8 (.8) 0 (15) -45 (-87, -3)	.7 (.6) 44 (15)
CRP (mg/dL)	Baseline Mean (SD) %Change from Baseline (SE) Diff. from Placebo (95% CI)	16.5 (23.6) 14 (99) -315 (-591, -39)	17.6 (32.7) 329 (98)
Parent Global Assessment	Baseline Mean (SD) %Change from Baseline (SE) Diff. from Placebo (95% CI)	17.2 (16.2) 121 (95) -51 (-314, 212)	17.1 (16.8) 172 (93)
ESR (mm/hr)	Baseline Mean (SD) %Change from Baseline (SE) Diff. from Placebo (95% CI)	22.2 (20.8) 65 (33) 4 (-87, 95)	23.1 (25.0) 61 (32)

Confidence intervals were calculated using ANCOVA model with terms for treatment and baseline value as covariate.

3.2 Evaluation of Safety

The evaluation of safety was conducted by the clinical reviewer, Keith Hull, M.D.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

I explored the heterogeneity of the treatment effect across age group ('<13 yr.' vs. '≥13 yr.'), race group ('white' vs. 'non-white'), and sex by inclusion of interaction terms in the Cox proportional hazard regression model. In the analyses, there were no statistically significant interactions between treatment and age group, sex or race in the time to disease flare. Kaplan-Meier curves estimated for each subgroup was provided by me in the appendix (Figures 6-11).

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

5.1.1 Statistical Issues

There were no statistical issues identified during the course of my review. In the primary analysis, patients who dropped out prior to experiencing a disease flare were censored. This was appropriate as artificially counting dropouts as having experienced a flare would have overestimated the treatment effect. In the analysis of the secondary variables, a LOCF strategy was used. Again because the reason for most dropouts was lack of efficacy and the placebo group had more such dropouts, a more conservative imputation method would give more favorable analysis results to the abatacept group. Also since each center enrolled fewer than 5 subjects on the average and the biggest center enrolled less than 10% of the total subjects, I did not consider an assessment of the homogeneity of treatment effects across centers to be meaningful. Also, it is worthwhile to note that analyses for the secondary endpoints were not adjusted for multiplicity.

5.1.2 Collective Evidence

In reviewing the collective evidence from the applicant's primary and secondary analyses as well as my additional analyses, I conclude that the data provides evidence of efficacy of abatacept in treating signs and symptoms in pediatric and adolescent patients with moderately to severely active JIA/JRA.

5.2 Conclusions and Recommendations

Study IM101033 was conducted in children and adolescents with active polyarticular juvenile rheumatoid arthritis for the pediatric efficacy supplement for abatacept. The study demonstrated a greater effect of abatacept compared to placebo in treating signs and symptoms of juvenile rheumatoid arthritis (JRA) / juvenile idiopathic arthritis (JIA). The effect was measured by time to occurrence of disease flare based on ACR Pediatric 30 (JRA/JIA core set variables). The effect was evident in both the applicant's analyses and the additional analyses conducted by me.

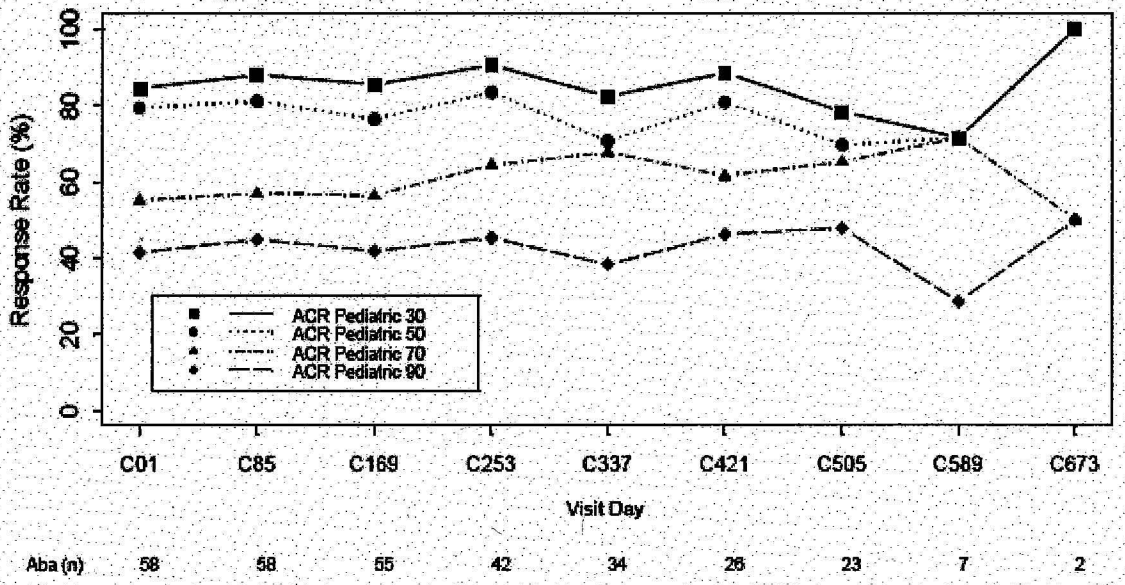
5.3 Review of Clinical Studies of Proposed Label

The following is the portion of the Clinical Study section from the proposed label with the results of pediatric study data analyses.

I found that the results on the primary analyses for time to disease flare are consistent with the reports of the analyses of pediatric efficacy data.

The claim of maintenance of effect measured in the open label extension phase (Period C) is not substantiated considering that the study was not complete and only a partial amount of information was available. Also the presentation of the available data is not most desirable with respect to the claim. The following figures were presented to support the claim by the applicant.

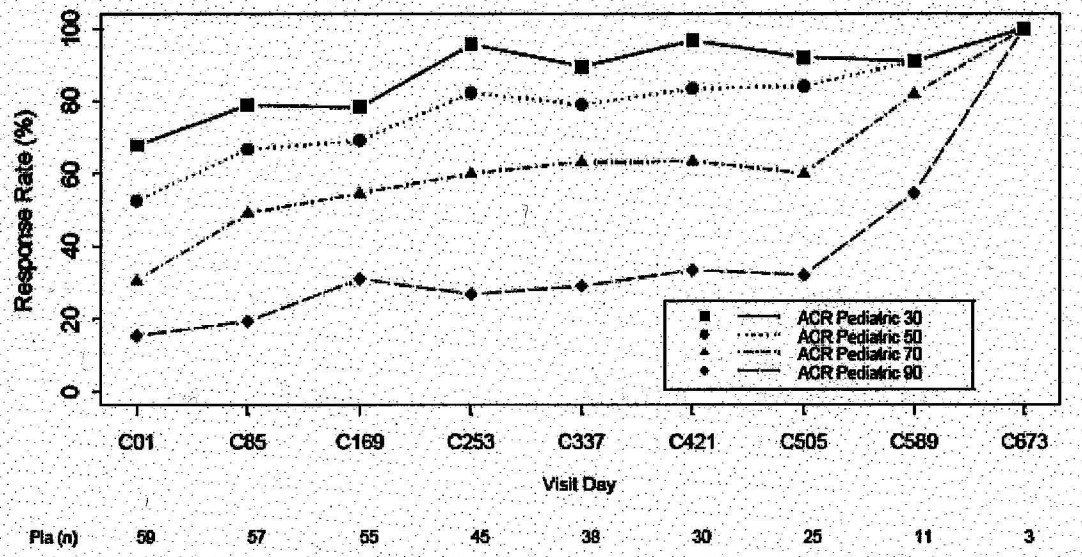
Figure 2 ACR Pediatric (ESR) Response Rates over Time for Period B-Abatacept Cohort



Population: All Treated Subjects in Period C.
All subjects received a fixed dose of abatacept in Period C.
Response information for Period C is derived from observed data.
Classification of response based on value observed at Day A1.
Visit Number C01 = Period B Day 169 LOCF.
Source: Table S.5.1

Source. Figure 7.2A of the Study Report IM101033-LT-CSR-ADDEND01 (pages 59 and 60).

Figure 3 ACR Pediatric (ESR) Response Rates over Time for Period B-Placebo Cohort



Population: All Treated Subjects in Period C.
All subjects received a fixed dose of abatacept in Period C.
Response information for Period C is derived from observed data.
Classification of response based on value observed at Day A1.
Visit Number C01 = Period B Day 169 LOCF.
Source: Table S.5.1

Source. Figure 7.2A of the Study Report IM101033-LT-CSR-ADDEND01 (pages 59 and 60).

A problem with the graphs is that a patient could be an ACR responder at some visit days and not at the other visit days, and it is difficult to determine if a patient maintains an effect measured by the ACR response over a clinically meaningful period of time. In addition, this portion of the study is ongoing. Thus, patients have variable amounts of data collected over time. After a discussion with the clinical reviewer, Dr. Keith Hull, I generated the following graphs to better describe the maintenance of the effect. My analyses focus on tracking the response status of patients who were responders at the entry of the open label period and evaluating how many of them maintained the effect over an extended period. However, since the study is ongoing, it is hard to rely on my graphs because attrition of patients across days could be simply due to the nature of ongoing study rather than due to dropout or non-response.

Figure 4 ACR Pediatric (ESR) Response Rates over Time for Period B-Abatacept Cohort with ACR Responders at B169

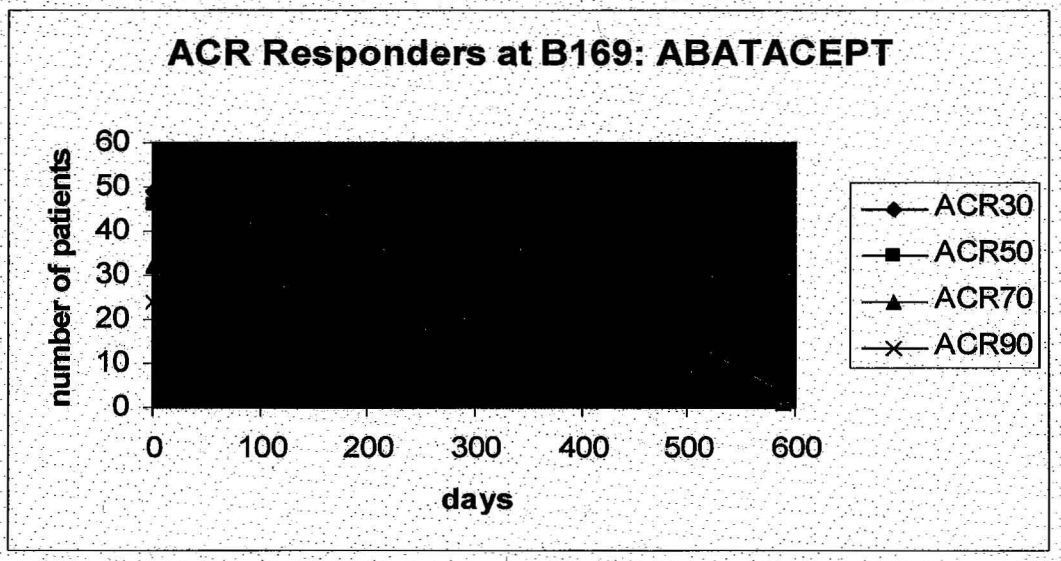
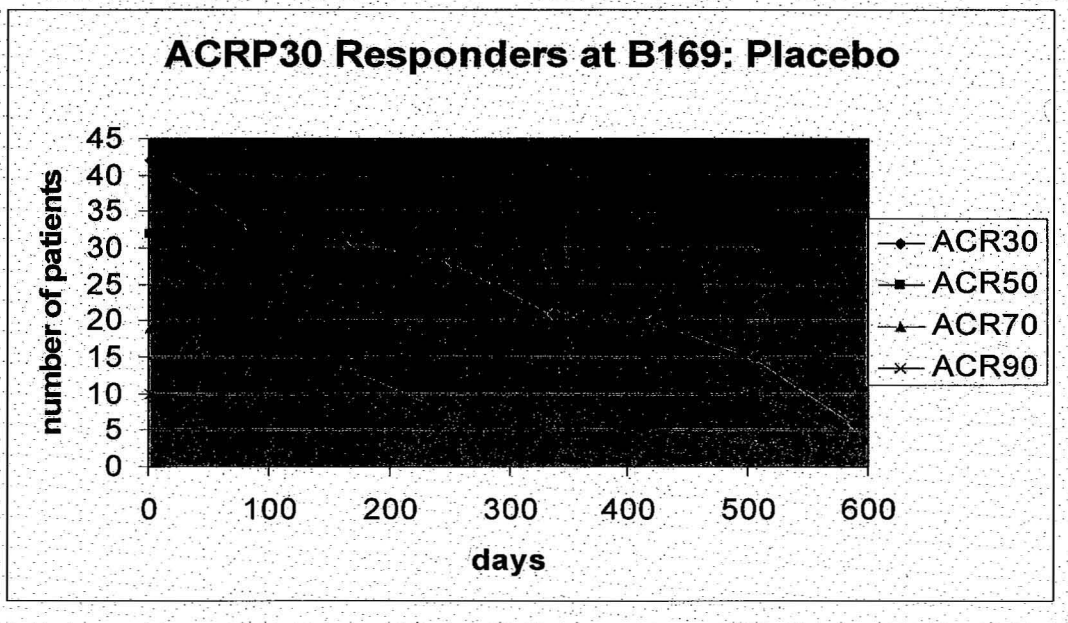


Figure 5 ACR Pediatric (ESR) Response Rates over Time for Period B-Placebo Cohort with ACR Responders at B169

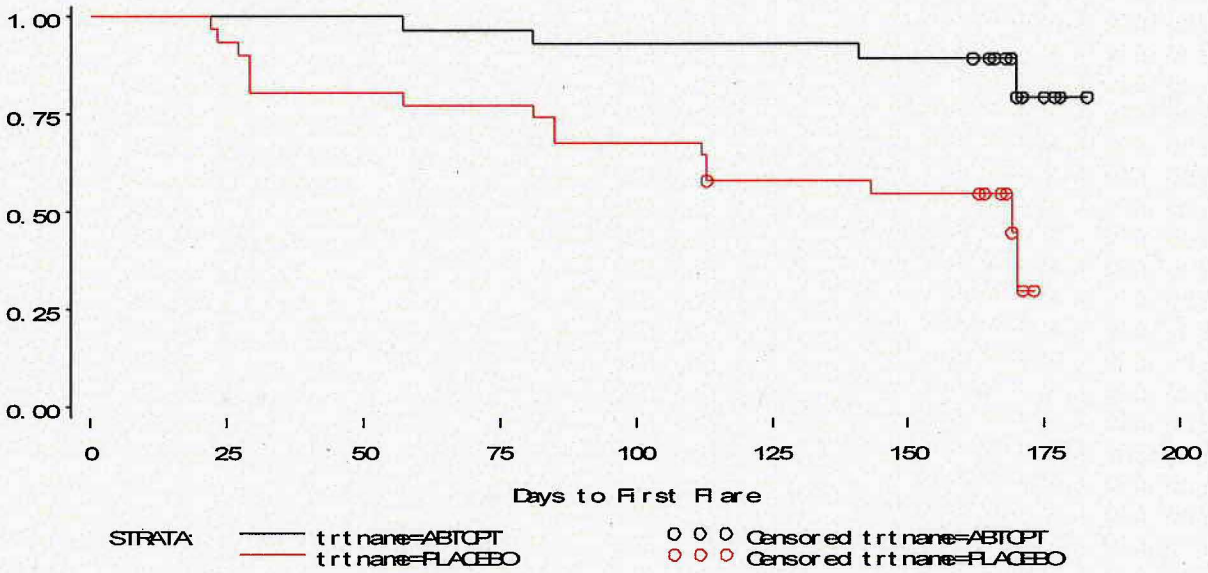


APPENDIX

Table 5 Patient Demographic and Baseline Characteristics for Study IM101033 (ITT Population Entered Double Blind Period)

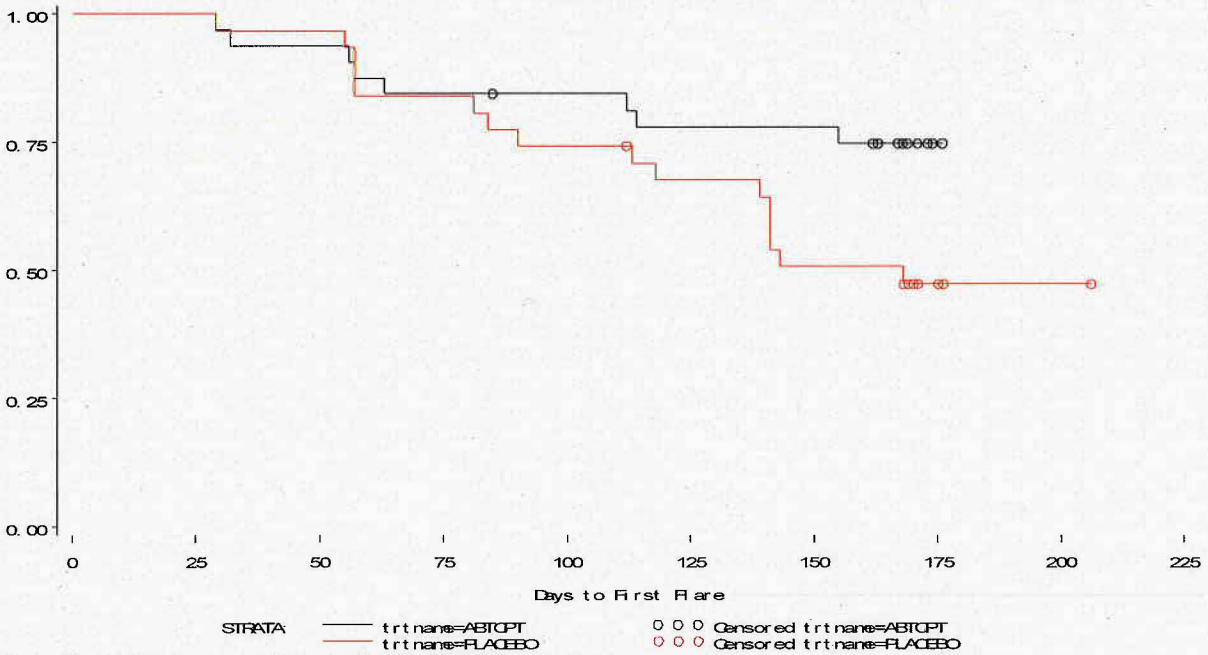
	Abatacept (N=60)	Placebo (N=62)
Gender n (%)		
Female	43 (72%)	45 (73%)
Male	17 (28%)	17 (27%)
Race n (%)		
White	46 (77%)	49 (79%)
Black	5 (8%)	4 (7%)
Native Hawaiian/Other Pacific Islander	1 (2%)	0 (0%)
Other	8 (13%)	9 (14%)
Age (years)		
Median	3.0	3.0
Range	6 – 17	5 – 17
Weight (kg)		
Median	41.0	37.9
Range	16.0 – 77.1	14.9 – 74.8
Number of Active Joints		
Median	17	9
Range	2 – 48	3 – 53
Number of Joints with LOM		
Median	14	9
Range	0 – 59	2 – 65
CHAQ Disability Index		
Median	1.3	1.1
Range	0.0 – 2.6	0.0 – 2.9
Parent Global Assessment		
Median	44.5	43.0
Range	0.0 – 92.0	1.0 – 95.0
Physician Global Assessment		
Median	52.0	50.5
Range	18.0 – 99.0	10.0 – 98.0
ESR (mm/hr)		
Median	26.0	23.5
Range	1.0 – 129.0	1.0 – 120.0
CRP (mg/dL)		
Median	1.2	0.9
Range	0.0 – 26.0	0.0 –16.1

Figure 6 Reviewer's Kaplan-Meier Curve Estimation: ITT Subgroup of Patients Age Less Than 13



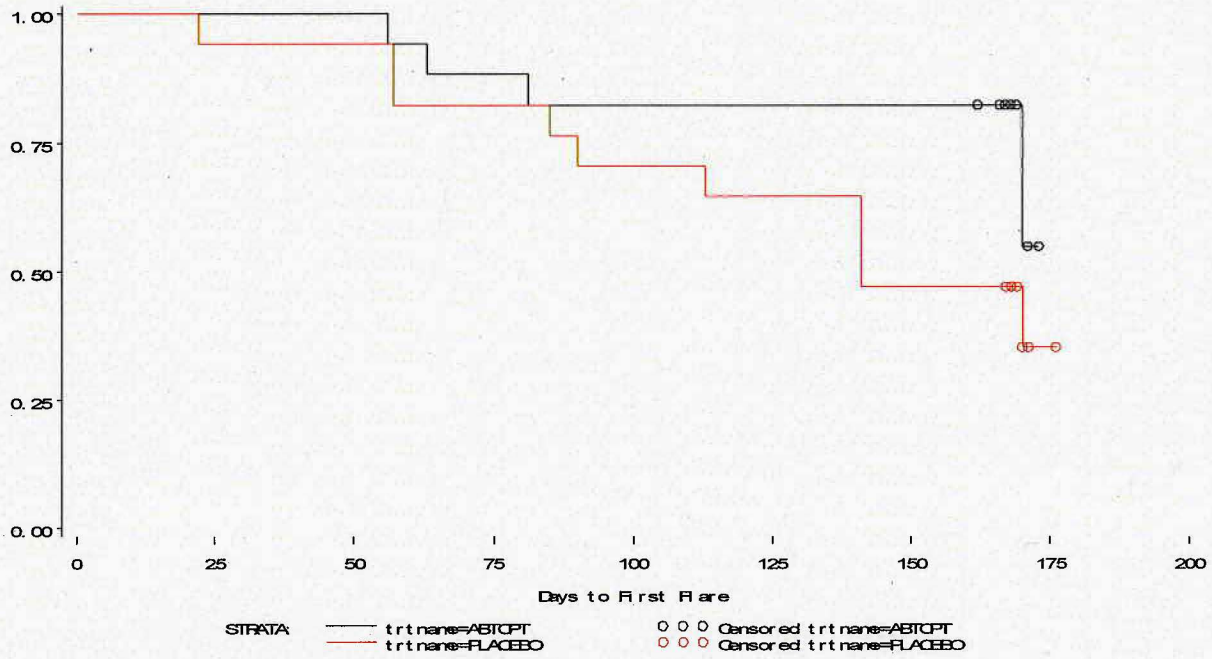
Note: Y-axis denotes proportion of patients without disease flare.

Figure 7 Reviewer's Kaplan-Meier Curve Estimation: ITT Subgroup of Patients Age Greater Than or Equal to 13



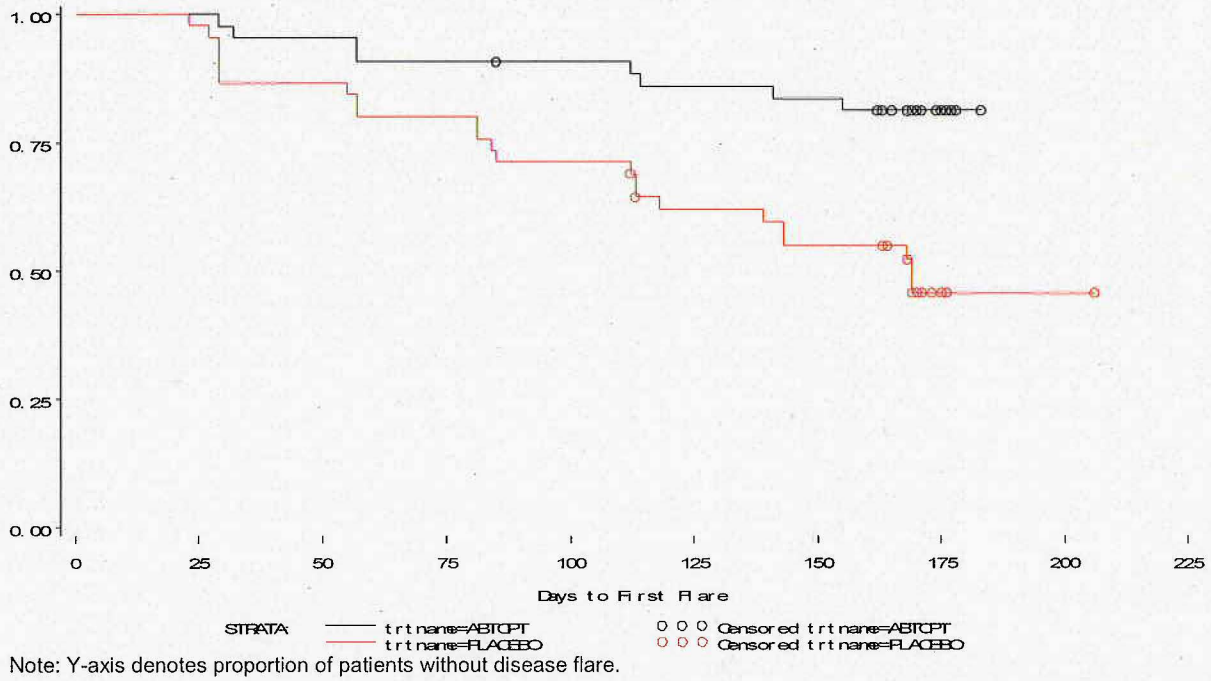
Note: Y-axis denotes proportion of patients without disease flare.

Figure 8 Reviewer's Kaplan-Meier Curve Estimation: ITT Subgroup of Male Patients



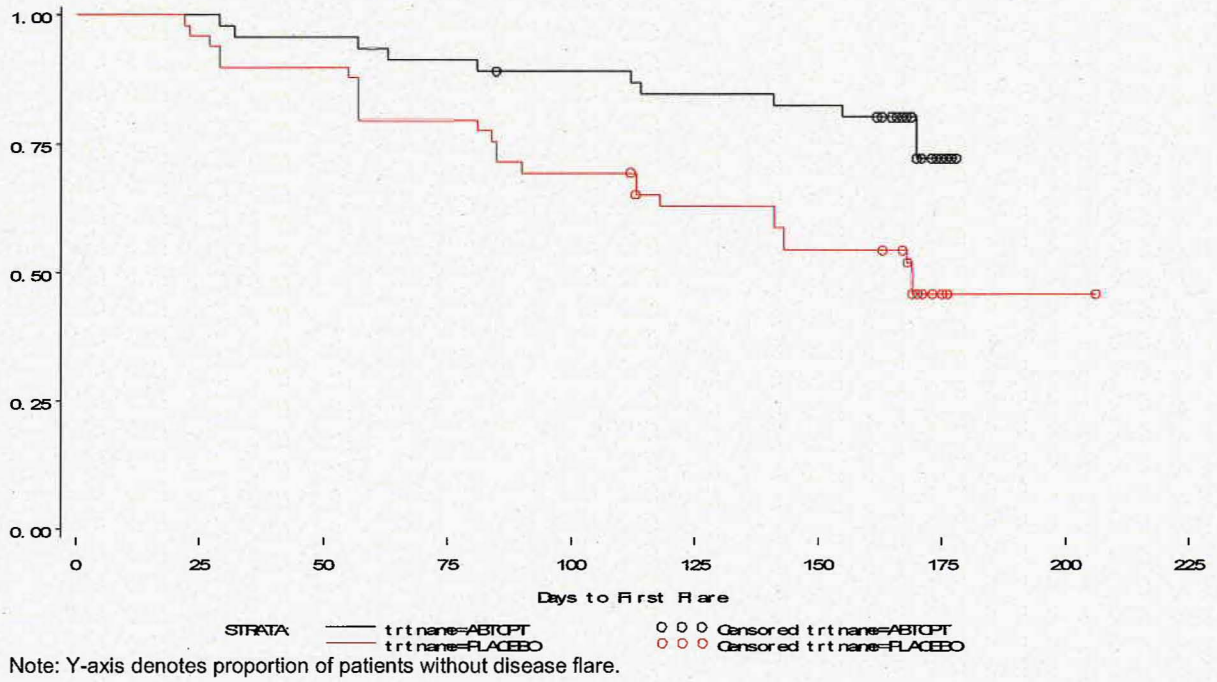
Note: Y-axis denotes proportion of patients without disease flare.

Figure 9 Reviewer's Kaplan-Meier Curve Estimation: ITT Subgroup of Female Patients



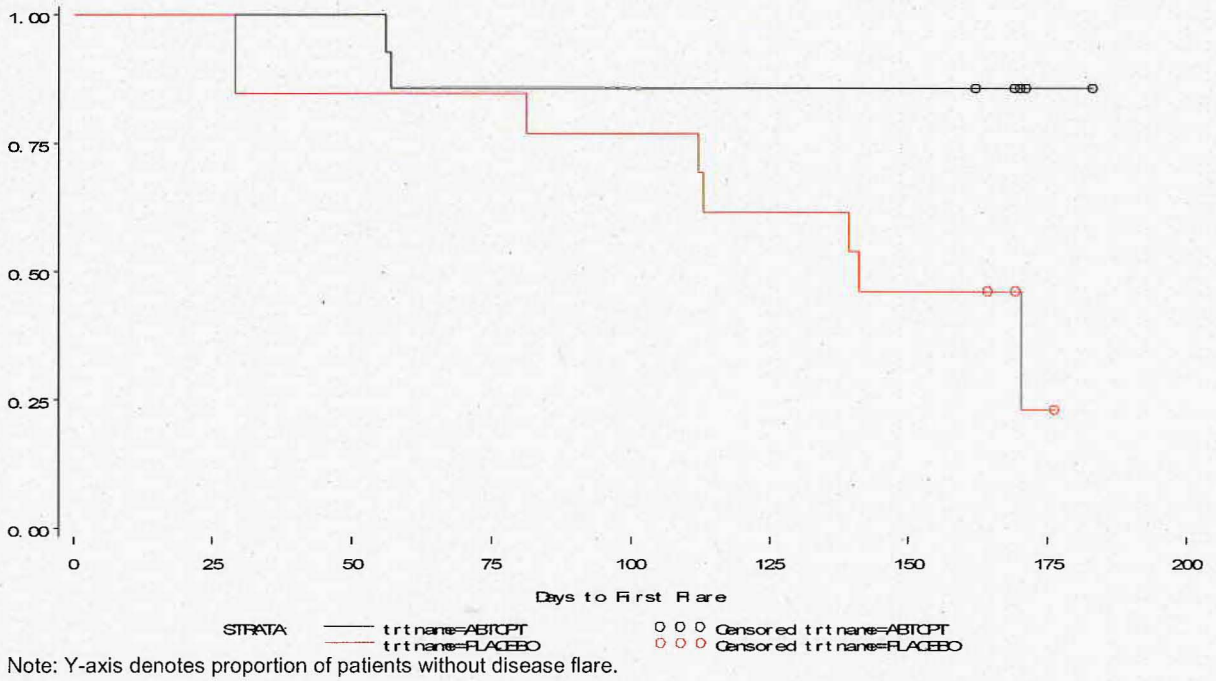
Note: Y-axis denotes proportion of patients without disease flare.

Figure 10 Reviewer's Kaplan-Meier Curve Estimation: ITT Subgroup of White Patients



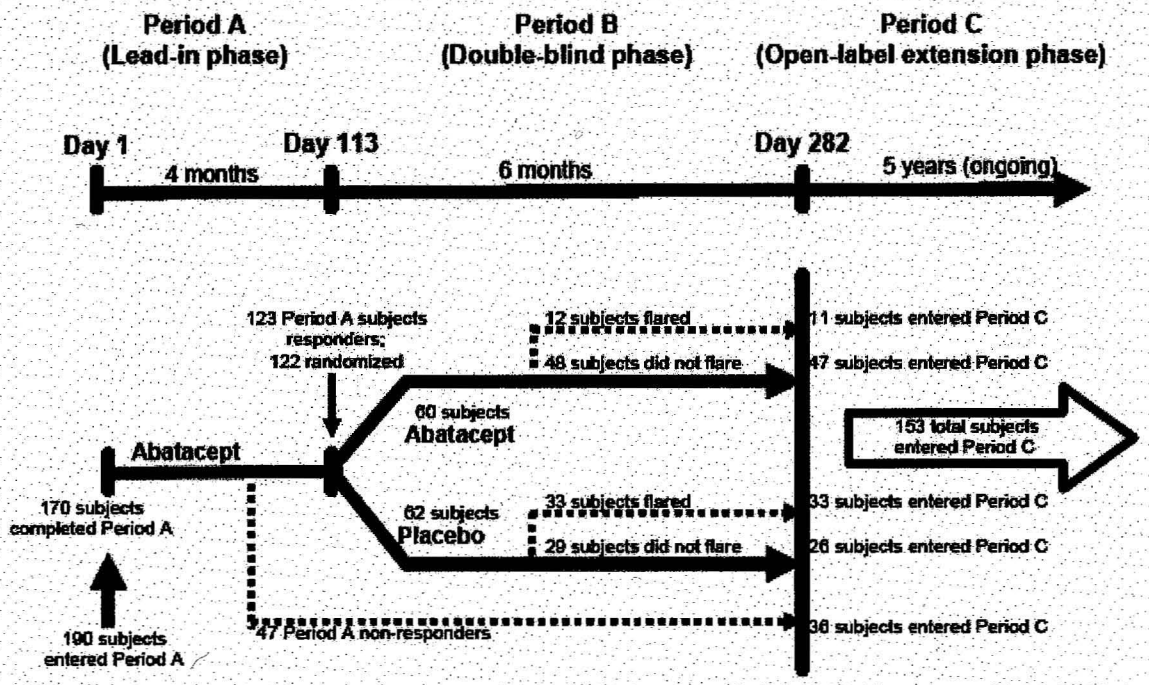
Note: Y-axis denotes proportion of patients without disease flare.

Figure 11 Reviewer's Kaplan-Meier Curve Estimation: ITT Subgroup of Non-White Patients



Note: Y-axis denotes proportion of patients without disease flare.

Figure 12 Schematic of Study Design



Source: IM101033 Addendum to Final Clinical Study Report

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