

**Abatacept inhibits structural damage progression in rheumatoid arthritis:  
results from the long-term extension of the AIM trial**

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Running title: Abatacept inhibits structural damage progression in RA

Key words: abatacept, rheumatoid arthritis, structural damage, radiography

## Abstract

*Objective.* Assess the effect of abatacept on structural damage progression over 2 years in patients with rheumatoid arthritis (RA) with an inadequate response to methotrexate (MTX).

*Methods.* 539 patients entered an open-label extension of the AIM trial and received abatacept. Radiographic assessment of the hands and feet was performed at baseline, year 1 and year 2. At year 2, each patient's radiographs were scored for progression blinded to sequence and treatment allocation.

*Results.* In patients treated with abatacept for 2 years, greater reduction in structural damage progression was observed in year 2 than in year 1. The mean change in total Genant-modified Sharp scores was reduced from 1.07 units in year 1 to 0.46 units in year 2. Similar reductions were observed in erosion and joint space narrowing scores. Following 2 years of treatment with abatacept, 50% of patients had no progression of structural damage as defined by a change in the total score of  $\leq 0$  compared with baseline. Fifty-six percent (56%) of abatacept-treated patients had no progression during the first year compared with 45% of placebo-treated patients. In their second year of treatment with abatacept, more patients had no progression than in the first year (66% vs 56%).

*Conclusion.* Abatacept has a sustained effect that inhibits structural damage progression. Furthermore, the mean change in radiographic progression in patients treated with abatacept for 2 years was significantly lower in year 2 versus year 1, suggesting that abatacept may have an increasing disease-modifying effect on structural damage over time.

## Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune disease that usually leads to synovial joint damage and consequent disability. Activated T cells play a critical role in the immunopathology of RA.<sup>1</sup> T-cell proliferation and interaction with other cell types, including synovial macrophages, fibroblasts, and B cells, result in the production of proinflammatory cytokines and matrix metalloproteinases that promote synovitis and erosive loss of sub-chondral bone. Thus, targeting T-cell activation is a rational therapeutic approach for the treatment of RA.

T-cell activation requires antigen recognition by the T-cell receptor, referred to as signal 1, as well as a co-stimulatory signal or signal 2.<sup>2</sup> One of the best characterized co-stimulatory pathways involves the interaction of CD28 expressed on T cells with CD80 and CD86 expressed on antigen-presenting cells. Endogenous downregulation of CD28-mediated T-cell co-stimulation occurs through T-cell expression of cytotoxic T-lymphocyte antigen 4 (CTLA-4). CTLA-4 binds to CD80 and CD86 with higher avidity than CD28, thus preventing co-stimulation through this pathway, and is a major down-regulatory signal for T cells.

Abatacept is a soluble, recombinant, fully human fusion protein composed of the extracellular domain of human CTLA-4 and the Fc domain of human IgG1, which has been modified to prevent complement fixation. Abatacept is the first in a class of biologic agents that target the second signal required for full T-cell activation, a mechanism of action that is fundamentally different than any other current biologic RA therapy. The efficacy of abatacept monotherapy was shown in a phase IIa trial in patients with RA with an inadequate response to disease-modifying anti-rheumatic drugs (DMARDs).<sup>3</sup> The efficacy of abatacept added to methotrexate (MTX) was demonstrated in phase IIb and phase III trials of patients with inadequate response to MTX or TNF-targeting agents.<sup>4-6</sup>

Results from the 1-year phase III, randomized, double-blind trial of Abatacept in Inadequate responders to Methotrexate (AIM) trial have been previously reported.<sup>5</sup> Abatacept added to MTX therapy resulted in clinically significant improvements in the signs and symptoms of RA, physical function, and health-related quality of life in patients with inadequate response to MTX. Further, abatacept resulted in a statistically significant slowing of structural damage progression after 12 months of treatment.

Progressive structural damage is associated with increasing disability over time.<sup>7, 8</sup> Thus, the effects of abatacept treatment on radiographic outcomes were assessed over longer-term treatment. Here we present radiographic assessments after 2 years of abatacept treatment in an open-label extension of the AIM trial. These data demonstrate that radiographic progression is significantly inhibited through 2 years. The maintenance of efficacy of abatacept therapy on other clinical endpoints will be described in full in another report.

## Patients and Methods

The study design, baseline characteristics, and results of the 12-month double-blind phase of this trial have been reported previously.<sup>5</sup> Institutional review boards or independent ethics committees approved the clinical protocol, and written informed consent to the study protocol was provided by each patient.

**Patients.** Patients eligible to participate in the AIM trial were at least 18 years of age, met the American Rheumatism Association criteria for RA,<sup>9</sup> and had RA for at least 12 months. All patients were screened for TB. At randomization, all patients had persistent, active RA despite treatment with MTX, with  $\geq 10$  swollen joints,  $\geq 12$  tender joints, and C-reactive protein concentration  $\geq 1.0$  mg/dL. Patients were required to have received MTX therapy at a minimum dose of 15 mg/week for at least 3 months, with the dose having been stable for a minimum of 28

days prior to randomization. A 28-day washout period was required for all other DMARDs. Reduction of MTX dosage in the first 6 months was permitted only in cases of toxicity. Stable dosages of nonsteroidal anti-inflammatory drugs or corticosteroids at  $\leq 10$  mg prednisone/day were allowed, with a stable dosage for 25 days prior to randomization. Adjustment of MTX and/or corticosteroid dosages were permitted after month 6, as was treatment with an additional DMARD if deemed appropriate by the investigator, including hydroxychloroquine, sulfasalazine, gold, or azathioprine.

**Study protocol.** During the first year, patients were randomized to receive a fixed dose of abatacept approximating 10 mg/kg body weight or placebo in a 2:1 ratio. The dose of abatacept was 500 mg for patients weighing less than 60 kg, 750 mg for patients weighing 60 kg to 100 kg, and 1 gram for patients weighing greater than 100 kg. Study medication was infused intravenously over 30 minutes on days 1, 15, and 29, and every 28 days subsequently. Patients completing the double-blind period were eligible to enter an open-label, long-term extension and receive abatacept therapy every 28 days at a dose approximating 10 mg/kg, as described above. The loading dose used in the double-blind period was not utilized here. No premedication was required for the intravenous infusions.

**Radiographic evaluation.** Radiographic assessments of hands, wrists, and feet were performed at baseline, year 1, and year 2, or upon early termination. The trial was powered for radiographic findings at year 1, and the primary endpoint was the change in erosion score, with secondary assessments of joint-space narrowing and total score using the Genant-modified Sharp scoring system. For each patient, baseline, year 1, and year 2 radiographs were all re-read at year 2 by two independent expert readers blinded to the original treatment allocation and the sequence of the films.<sup>10</sup>

The Genant-modified Sharp scoring system (Figure 1) assesses changes in structural damage, assigning scores for erosions of 0 to 3.5 (8 gradations) for 14 sites in each hand and wrist, and 6 sites in each foot.<sup>11, 12</sup> Joint space narrowing (JSN) scores of 0 to 4 (9 gradations) are assigned to 13 sites in each hand and 6 sites in each foot.<sup>12</sup> The erosion and JSN scores are normalized to 145 for a maximum total Genant-modified Sharp score of 290.<sup>12</sup> Inter-reader, intra-class correlation coefficient (ICC) was determined based on the baseline and year 1 readings.<sup>10</sup> Smallest detectable difference (SDD) was determined as 1.96 x standard deviation of the two independent baseline readings.<sup>13</sup>

**Statistical analysis.** The study was powered for change from baseline in Genant-modified Sharp erosion score and used a rank-based analysis of covariance to compare changes between treatment groups at year 1. The radiographic analyses were performed on a modified intent-to-treat population at year 2. The modified intent-to-treat population included patients who were randomized and treated, completed the 1-year double-blind period, and continued to receive at least 1 dose of study medication during the open-label period. Patients who discontinued abatacept treatment during the open-label period were requested to return for follow-up radiography at year 2, regardless of any subsequent new anti-rheumatic therapy prescribed by the investigator. Radiographs were taken at the time of discontinuation in patients who were unwilling or unable to return at year 2. In these patients, 2-year data were imputed using linear extrapolation of the scores of the discontinuation film.

The changes from baseline in total Genant-modified Sharp scores, erosion scores, and JSN scores were graphed as cumulative probability plots to visually present the distribution of all radiographic data. The observed cumulative proportion (scores ranked from the lowest to the highest and presented as a cumulative proportion of all scores) was plotted against the actual change from baseline of each score. The proportion of observations that fall below each possible change from baseline (y-axis) can be read on the x-axis.<sup>14</sup>

## Results

**Patients and study completion.** Of the 652 patients randomized and treated in the double-blind portion of the AIM trial, 433 received abatacept and 219 received placebo (Table 1). As previously reported, baseline demographics and clinical characteristics did not differ significantly between patients in the abatacept and placebo groups.<sup>5</sup> After the 12 month double-blind treatment period, all patients were eligible to receive open-label treatment with abatacept. More patients receiving abatacept treatment (89%) completed the 1-year double-blind phase relative to the placebo group (74%). Of the 547 patients who completed 12 months of treatment, 539 (83% of all randomized and treated patients) were treated with abatacept in the open-label period (378 initially randomized to abatacept [87%] and 161 to placebo [73.5%]). A high retention rate was maintained with open-label abatacept treatment, with 90% of the patients who entered the long-term extension completing 2 years.

Two-year radiographic data were available from 87% of patients who entered the open-label period, which comprises 72% of all randomized and treated patients (467/652 patients; Table 1) Observed data were available for 97% of patients who completed the open-label period; 454/467 patients had radiographs at baseline and at year 2. Baseline and an early termination film were available for the remaining 3% of patients, and 2-year data were imputed by linear extrapolation. The data include baseline and year 2 radiographs of 324 patients treated with abatacept for 2 years (observed data in 315 patients, imputed data in 9 patients). Therefore, the 2-year data represent a majority of randomized patients. As previously reported in an abstract,<sup>10</sup> a high degree of inter-observer agreement was demonstrated by ICC for radiographic assessments at baseline (0.90) and 12 months (0.92) and for change between baseline and 12 months (0.82). The SDDs were 3.5, 2.5, and 5.1, respectively, for erosion, JSN, and total score. These correspond to 1.9%, 1.3%, and 1.3%, respectively, of the maximum values for each of these scores and compare favorably with values reported for other studies.<sup>15, 16</sup>

**Radiographic results—population level data.** Structural damage progression was significantly reduced in patients treated with abatacept over 2 years versus those treated with placebo initially. Baseline erosion and JSN scores were comparable in patients originally randomized to either treatment group. Significantly lower mean changes in radiographic progression were observed in patients treated with abatacept for 2 years, with mean changes in total score, erosion, and JSN scores of 1.55, 0.84, and 0.71 units, respectively, compared to 3.17, 1.48, and 1.69 units in patients treated with placebo for 12 months prior to abatacept open-label therapy (Figure 2 and Table 2).

Patients treated with abatacept for 2 years also had lower median changes in radiographic progression scores. The median change from baseline in total Genant-modified Sharp scores was 0.0 units at year 1 and year 2 with abatacept treatment (Figure 3), versus median changes of 0.46 and 0.51 units at year 1 and year 2, respectively, in patients who received placebo prior to abatacept therapy. Further, the median change in erosion score was 0.0 units in patients treated with abatacept for 2 years, compared to 0.26 units in patients originally in the placebo group.

The mean change in the total score, erosion, and JSN score were lower from year 1 to year 2 (0.46, 0.21, and 0.24 units, respectively) than the mean change in these scores from baseline to year 1 (1.07, 0.62, and 0.45 units, respectively) in patients treated with abatacept for up to 2 years (Table 2). The increasing effect of treatment was consistently observed for both erosions and JSN.

**Radiographic results—patient level data.** Radiographic results at 2 years demonstrate the maintenance of effect of abatacept and MTX on non-progression of structural damage in

patients with no progression at year 1 (Table 3), defined as a change from baseline in total Sharp score of  $\leq 0$ . Overall, 50% of abatacept-treated patients did not progress from baseline through 2 years of treatment (163/324 patients). At 2 years, non-progression in erosions and JSN (change  $\leq 0$ ) was observed from baseline in 56% and 68% of these patients, respectively. In abatacept-treated patients with no radiographic progression at year 1, 79% had no radiographic progression at year 2. Non-progression in erosions and JSN was maintained at 2 years in 83% and 87% of patients with no progression at 12 months.

Non-progression at year 2 was also achieved in patients with initial damage progression on abatacept therapy. Of abatacept-treated patients who demonstrated radiographic progression at year 1, 45% had no progression of structural damage at year 2. Further, 53% of patients originally randomized to placebo with progression at year 1 did not progress at year 2 after receiving abatacept treatment (42/79 patients).

Cumulative probability plots showing the distribution of change from baseline in total Genant-modified Sharp scores for year 1 and year 2 are shown in Figure 3. Comparison of the curves in patients treated in the abatacept group (solid line) versus patients originally randomized to placebo (dotted line) demonstrates that abatacept treatment is associated with results in decreased numbers of patients with progression. Furthermore, the amount of structural damage in patients who progressed is lower in patients treated with abatacept for both year 1 and year 2.

## Discussion

Abatacept has been shown to significantly reduce disease activity in patients with rheumatoid arthritis. The previously described randomized, double-blind, placebo-controlled portion of the phase III study of abatacept in patients with RA with an inadequate response to MTX demonstrated statistically significant improvement in the signs and symptoms of disease, physical function assessed by the health-assessment questionnaire disability index, and health-related quality of life.<sup>5</sup> In addition, abatacept positively impacted the rate of structural damage progression at 12 months, reducing it by approximately 50% compared to placebo. This placebo-controlled radiographic finding from randomized clinical trials provides an assessment of short-term effects on structural damage. However, only long-term radiographic progression has been associated with physical disability.<sup>8</sup> Therefore, it is important to assess longer-term effects on structural damage beyond 1 year of therapy.

The retention rate of patients receiving abatacept treatment was high, with 89% completing the 1-year double-blind portion of the AIM trial,<sup>5</sup> and 90% of the patients entering the long-term extension completing year 2, suggesting the tolerability and durability of response to abatacept. Further, radiographic data were collected from a high percentage of patients, with 2-year data available from 87% of patients entering the open-label period, and observed data for 97% of patients; linear imputation based on baseline and early termination films was used in only 3% of patients.

Of note, an increased proportion of patients randomized to the placebo group withdrew from the double-blind portion of the study (between baseline and year 1) due to lack of efficacy (18% versus 3% in the abatacept group).<sup>5</sup> Patients initially randomized to placebo who discontinued the study during the double-blind period are not included in these calculations. As these patients with worsening disease were not included in the assessment of radiographic outcomes, the structural damage progression in patients initially randomized to placebo may be underestimated. As is standard for assessments of radiographic outcome, readers were blinded to the sequence of the radiographs, thus eliminating bias for the expectation of benefit.

Abatacept therapy resulted in inhibition of structural damage progression over time. After 2 years of treatment, a significant reduction in structural damage progression was observed in

patients treated with abatacept for 2 years relative to placebo for 12 months plus abatacept for 12 months.<sup>8</sup> Lower mean changes in total Genant-modified Sharp scores at both 12 months and year 2 were 1.07 versus 2.4 units, and 1.55 versus 3.17 units, respectively. Notably, abatacept had a clear benefit on both erosion and JSN scores.

The treatment effect for abatacept relative to placebo was an approximately 50% reduction in mean structural damage progression in the first year of the study. The rate of structural damage progression when patients had received placebo treatment for 2 years can be estimated by linear extrapolation from the 12-month data of patients randomized to placebo. Patients in the placebo group progressed >2 units in year 1 and can be projected to progress 4-5 units over 2 years using linear extrapolation. Overall, patients receiving abatacept treatment for 2 years progressed ~1.5 units versus the expected progression of ~4.5 units if placebo treatment had been continued for the second year. Thus, the effect of abatacept treatment in the second year of treatment would hypothetically reduce the radiographic progression by an estimated two-thirds when compared to patients with established disease receiving MTX alone.

Fewer abatacept-treated patients had progression of structural damage, and, overall, 50% of patients receiving abatacept treatment did not have radiographic progression over 2 years. In addition, 79% of abatacept-treated patients with no progression at year 1 maintained non-progression of structural damage at year 2, demonstrating a durable effect on radiographic outcomes with abatacept therapy. In addition, 45% of patients with some progression at year 1 had no progression in year 2. As the overwhelming number of patients entering the second year of treatment completed the year, we are not reporting on a selected group of responders.

The increasing effect of abatacept treatment on structural damage progression is consistent with other efficacy data; the proportion of patients with ACR 50 and 70 responses were statistically significantly increased from 6 months to 12 months in this study.<sup>5</sup> The ACR 20, 50, and 70 responses; improvement in physical function; and improvement in both the physical and mental components of the SF-36 health-related quality of life scale in patients treated with abatacept for up to 3 years will be described in full in a future report.

It is difficult to compare results across clinical trials with other treatments that have described radiographic outcomes. Confounding factors include the treatment and disease history of each study population, differing rates of radiographic progression for the control group in each trial, and the use of different scoring systems for the measurement of radiographic damage. The current study assessed the efficacy of abatacept in patients with established RA and long duration of disease, whereas several trials of other biologic therapies, such as those targeting TNF, involved patients with early RA (e.g., the ERA trial of etanercept<sup>17</sup> and the PREMIER trial of adalimumab<sup>18</sup>) or MTX-naïve patients (the TEMPO trial of etanercept<sup>19</sup>). The Sharp-modified Sharp and the van der Heijde-modified Sharp scoring systems utilized in the trials of TNF-targeting agents,<sup>16, 17, 20</sup> as well as the Genant-modified Sharp scoring system utilized here and in the interleukin-1 receptor antagonist and rituximab studies,<sup>18, 21</sup> all have differences in joints assessed, scales applied, and maximum achievable scores. Thus, Sharp-, van der Heijde-, and Genant-modified Sharp scores cannot be directly inter-converted, although they correlate moderately well cross-sectionally and longitudinally. In addition, the definition of structural damage progression varied among studies, including progression defined as change  $\geq 0$  or the SDD among readers.<sup>16-18, 20, 21</sup> The Genant-modified scoring system employed in this study showed high inter-reader agreement (0.90 – 0.92 cross-sectionally and 0.82 for change) and high sensitivity to change (SDD) for erosion (3.5), JSN (2.5), and total score (5.1).<sup>10</sup>

The inhibition of structural damage progression with abatacept has clinical implications for the prevention of disability over time. The association of progression of structural damage and impaired physical function over the long term has been well correlated, and is strongest in

established disease.<sup>7,8</sup> Impacting the rate of joint destruction with continued abatacept treatment is likely to impede progressive functional disability, and thus may have increasing benefit for patients over time. Further study in this and other patient populations will assess the efficacy of abatacept therapy over longer periods of time.

### **Competing interest statement**

HG has been reimbursed by Bristol-Myers Squibb, Amgen, Wyeth, Novartis, Merck, Sanofi-Aventis, Lilly, GSK, Roche, and Genentech for speaking fees and honoraria. HK has also received research funding from these organizations. HG is a founder and share holder of Synarc, Inc., and serves as a member of the board of directors. RW has been reimbursed >\$10,000 by Bristol-Myers Squibb and Schering-Plough for speaking fees and honoraria. J-C Becker is an employee of Bristol-Myers Squibb, and has shares with the company. RA is an employee of Bristol-Myers Squibb, and has shares with the company. GV is an employee of Bristol-Myers Squibb, and has shares with the company. JT is an employee of Bristol-Myers Squibb, and has shares with the company. JK has been reimbursed >\$10,000 by Bristol-Myers Squibb for speaking fees and honoraria. CP is an employee and shareholder of Synarc, Inc., and is a provider of central image analysis, molecular marker assays, and subject recruitment for global clinical trials for numerous pharmaceutical and biotechnology companies across a broad range of therapeutic areas.

### **Funding**

This study was funded by Bristol-Myers Squibb.

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## Figure Legends

**Figure 1.** Genant-modified Sharp scoring system. Coloured areas indicate sites used to evaluate Erosion and Joint Space Narrowing (JSN) Scores. Each site was evaluated in 0.5 unit increments as indicated. Erosion and JSN Scores are normalized to 145 for a maximum Total Score of 290.

**Figure 2.** Mean change from baseline in Total (A), Erosion (B), and Joint-Space Narrowing (C) Genant-modified Sharp scores for patients at 12 months and 2 years. \*Placebo patients were switched to abatacept after 12 months. All patients received background MTX.

**Figure 3.** Cumulative probability distribution of changes from baseline in Genant-modified total Sharp scores by treatment at year 1 (A) and year 2 (B). The solid line represents abatacept-treated patients (A and B) and the dotted line represents placebo treated patients (A) or placebo-treated for 12 months then abatacept-treated for 12 months (B). All patients received background MTX.

**Table 1.** Number of subjects with radiographic assessments on day 365 and day 729.

	<b>Abatacept (N = 376)</b>	<b>Placebo (N=160)</b>
<b>Subjects included in analyses</b>		
Day 365	328 (87.2%)	144 (90.0%)
Baseline and day 365	328 (87.2%)	144 (90.0%)
Day 729	324 (86.2%)	143 (89.4%)
Baseline and day 729	315 (83.8%)	139 (86.9%)
Imputation on day 729*	9 (2.4%)	4 (2.5%)
<b>Subjects not included in the analyses</b>		
No day 365 value <sup>†</sup>	2 (0.5%)	1 (0.6%)
No day 729 value <sup>‡</sup>	6 (1.6%)	2 (1.3%)

\*Subjects are discontinued and qualified for imputation requirement.

<sup>†</sup>Two subjects in abatacept group had evaluative radiographic assessment outside the pre-specified visit window of day 365, and 1 subject in the placebo group had no radiographic assessment on day 365.

<sup>‡</sup>Subjects had evaluative radiographic assessment outside the pre-specified visit window of Day 729.

**Table 2.** Yearly mean changes in Genant-modified Sharp scores. Baseline is day 1 of study. All randomized and treated patients who entered the open-label period and had radiographs at baseline and year 1. Baseline and year 1 radiographs were re-read at day 729. Placebo patients were switched to abatacept in the long-term extension (year 2). All patients received background MTX.

	$\Delta$ Baseline to year 1	$\Delta$ Baseline to year 2	$\Delta$ Year 1 to year 2
<b>Total Score</b>			
<b>Abatacept</b>	1.07	1.55	0.46
<b>Placebo/abatacept</b>	2.40	3.17	0.75
<b>Erosion Score</b>			
<b>Abatacept</b>	0.62	0.84	0.21
<b>Placebo/abatacept</b>	1.44	1.48	0.25
<b>Joint Space Narrowing Score</b>			
<b>Abatacept</b>	0.45	0.71	0.24
<b>Placebo/abatacept</b>	0.95	1.69	0.50

**Table 3.** Non-progressors in structural damage measured by Genant-modified Sharp scores in patients on abatacept therapy for 2 years. All patients received background MTX.

<b>Percentage of non-progressing patients*</b>		
<b>Outcome</b>	<b>Baseline to year 1 (n=328)</b>	<b>Baseline to year 2 (n=324)</b>
<b>Erosion (%)</b>	61	56
<b>Joint-space narrowing (%)</b>	74	68
<b>Total (%)</b>	56	50
<b>Percentage of non-progressing patients in year 2<sup>†</sup></b>		
<b>Outcome</b>	<b>Non-progressors at end of year 1 remaining non-progressors<sup>†</sup></b>	<b>Progressors at end of year 1 becoming non-progressors</b>
<b>Erosion (%)</b>	83	49
<b>Joint-space narrowing (%)</b>	87	52
<b>Total (%)</b>	79	45

\*Defined by a change in the total score of  $\leq 0$  from baseline to year 1.

<sup>†</sup>Defined by a change in the total score of  $\leq 0$  from year 1 to year 2.

Figure 1.

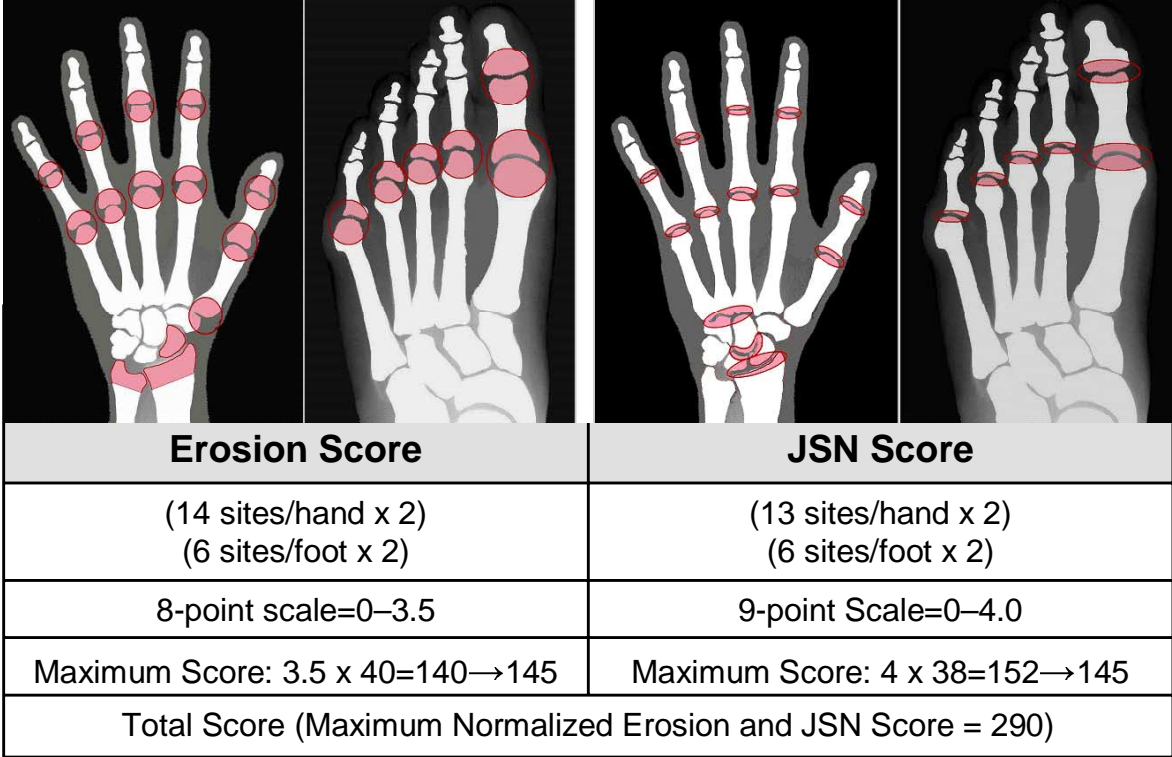
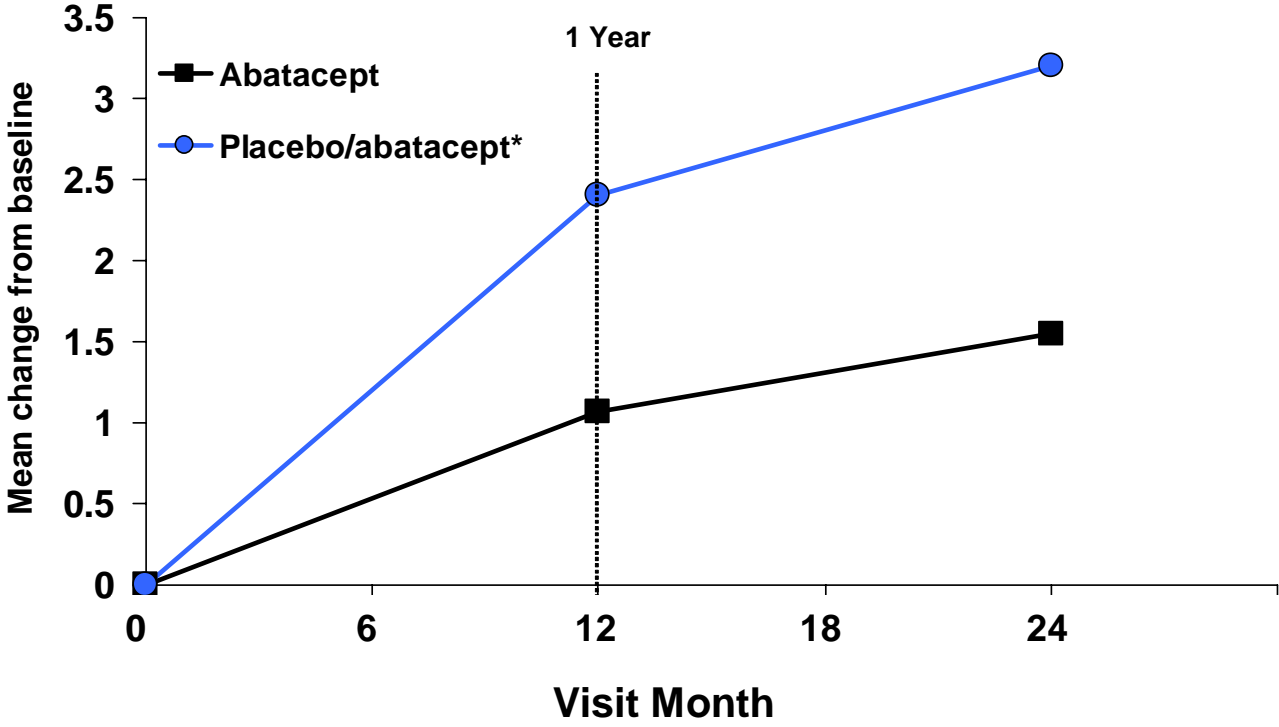


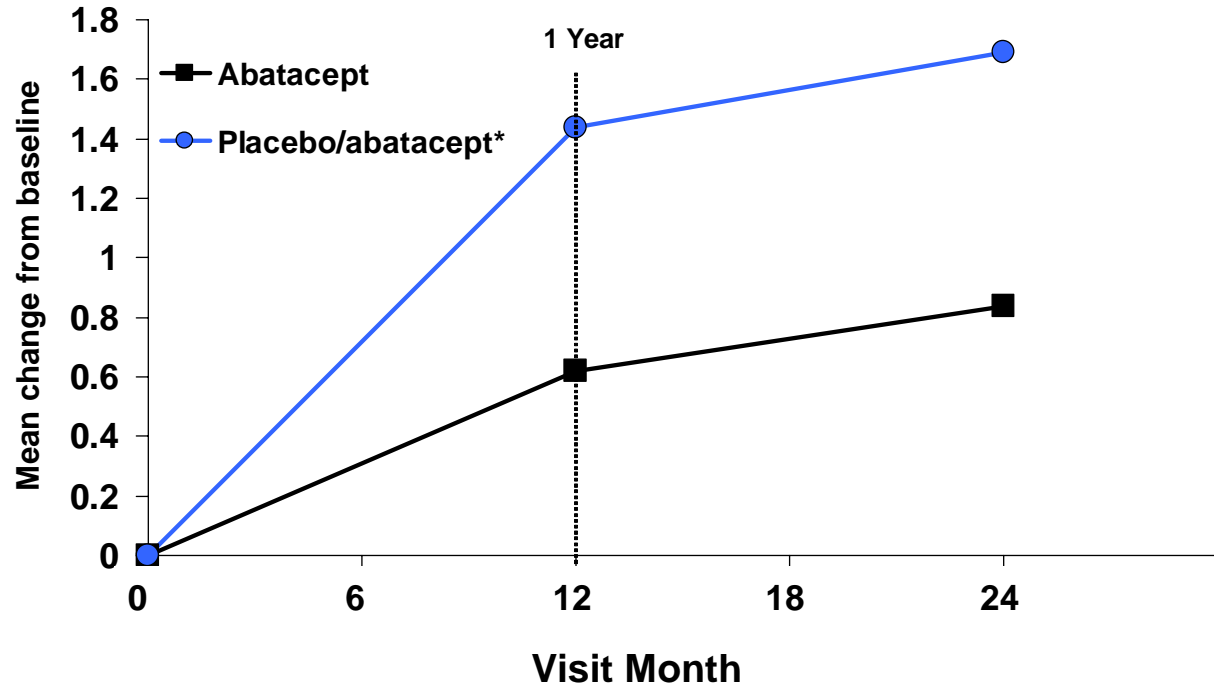
Figure 2A.

A) Total





## B) Erosion



### C) JSN

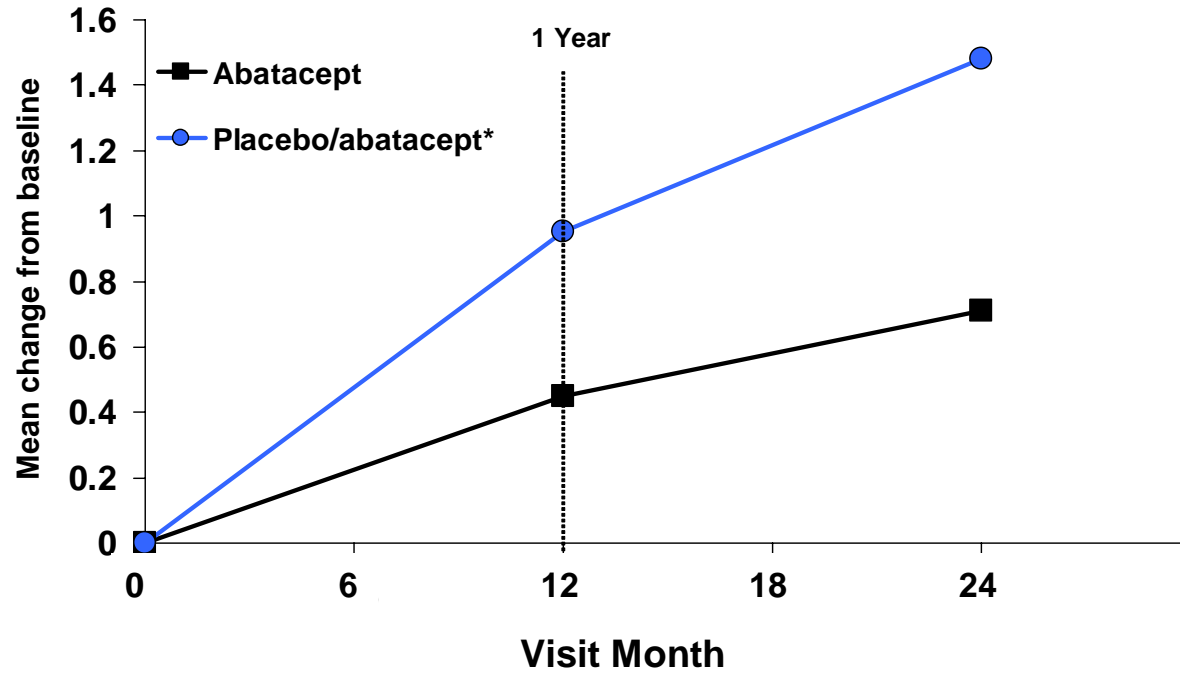
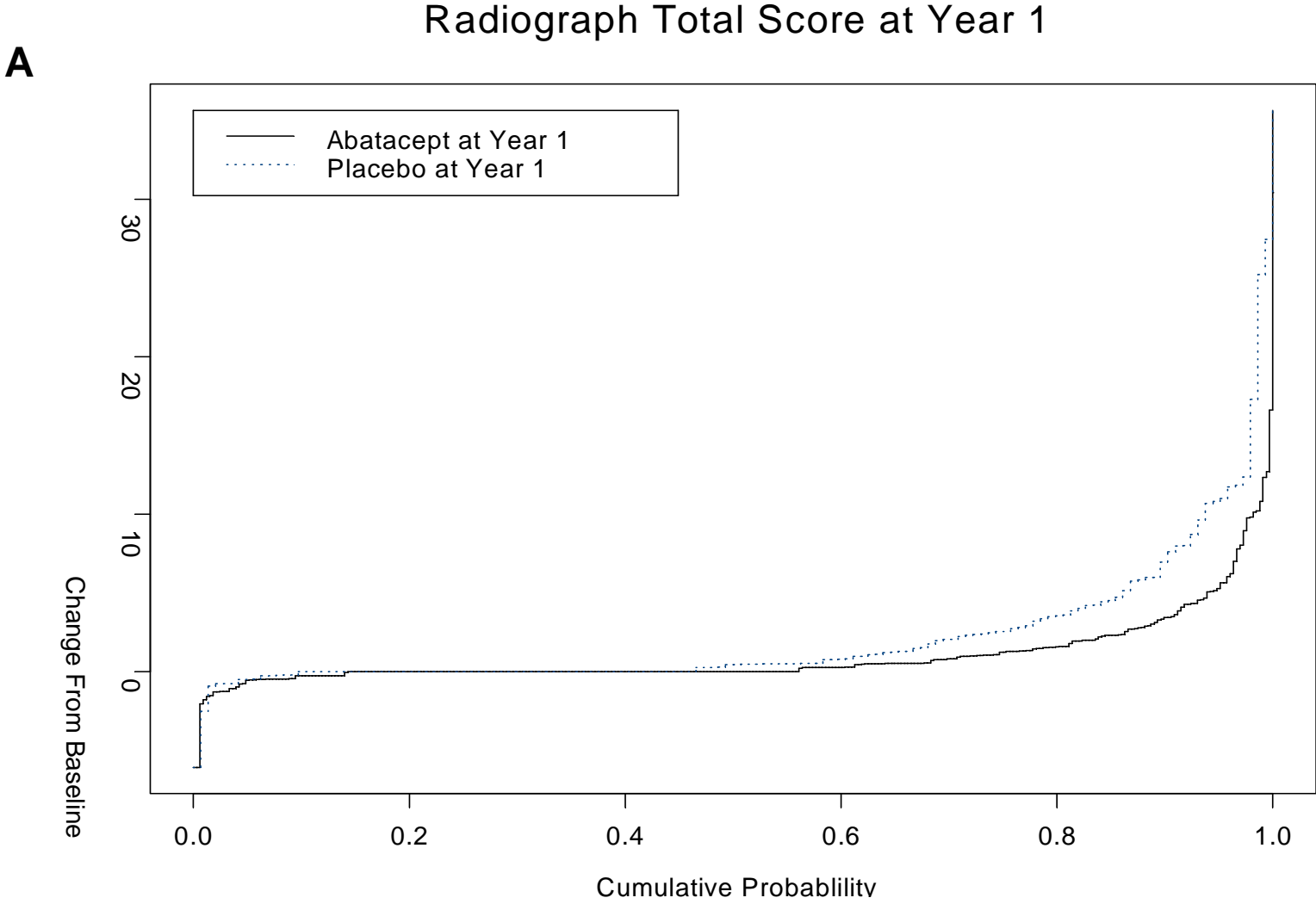


Figure 3A.



**B**

### Radiograph Total Score at Year 2

