ORIGINAL ARTICLE

Running head: AMPLE 2-year Patient-Reported Outcomes: Abatacept vs Adalimumab

Patient-Reported Outcomes from a 2-year Head-to-Head Comparison of Subcutaneous Abatacept versus Adalimumab for Rheumatoid Arthritis

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ORIGINAL ARTICLE

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ORIGINAL ARTICLE

ABSTRACT

Objective. To report 2-year patient-reported outcomes (PROs) from the head-to-head AMPLE trial.

Methods. AMPLE was a Phase IIIb, randomized, investigator-blinded trial. Biologic-naïve patients with rheumatoid arthritis (RA) and an inadequate response to methotrexate (MTX) were randomized to subcutaneous (SC) abatacept (125 mg weekly) or adalimumab (40 mg every 2 weeks), with background MTX. PROs (pain, fatigue, ability to perform work, and ability to perform daily activities) were compared up to Year 2 for patients in each treatment group, as well as those who achieved low disease activity at both Years 1 and 2 ('responders') and those who did not ('non-responders').

Results. 646 patients were randomized and treated with SC abatacept (n = 318) or adalimumab (n = 328). Baseline characteristics were balanced between the two treatment arms. Comparable improvements in PROs were observed in the abatacept and adalimumab groups over 2 years, with both groups achieving clinically meaningful improvements in PROs from baseline. At Year 2, fatigue improved by 23.4 mm and 21.5 mm on a 100-mm visual analog scale with abatacept and adalimumab, respectively. Clinical responders achieved greater improvements in PROs than non-responders.

Conclusion. In biologic-naïve patients with active RA, despite prior MTX, treatment with SC abatacept or adalimumab with background MTX resulted in comparable improvements in PROs, which were highly correlated with physician-reported clinical response endpoints.

ORIGINAL ARTICLE

Keywords: biologics, fatigue, pain, patient-reported outcomes, rheumatoid arthritis

ORIGINAL ARTICLE

Significance & Innovations

- In biologic-naïve patients with active rheumatoid arthritis, despite prior methotrexate (MTX), treatment with subcutaneous abatacept or adalimumab with background MTX resulted in comparable improvements in patient-reported outcomes (PROs), such as pain, fatigue, ability to perform work, and ability to perform daily activities.
- Improvements in these PROs were highly correlated with physician-reported clinical response endpoints, including low disease activity or remission, as assessed by Simplified Disease Activity Index, Clinical Disease Activity Index, or Boolean criteria.

ORIGINAL ARTICLE

Rheumatoid arthritis (RA) can have a major impact on patient-reported outcomes (PROs) that evaluate health, quality of life, and treatment response from the perspective of the patient. PROs thought to have a particularly large impact on the quality of life of patients with RA include pain, fatigue, the ability to perform work, and the ability to perform daily activities (1).

The treat-to-target strategies employed in RA aim to achieve significant improvements in clinical outcomes, with the goal being remission, or if remission cannot be achieved, low disease activity (LDA). However, it remains unclear whether achievement of these goals is associated with meaningful improvements in PROs. It is, therefore, important that PROs are evaluated in conjunction with clinical outcomes, particularly when disease activity is assessed using a measure that does not include a patient-reported component. As both clinical outcomes and PROs are important, it is of interest to investigate how the two are inter-related.

Both the current American College of Rheumatology (ACR) recommendations and the European League Against Rheumatism guidelines recommend methotrexate (MTX) as first-line therapy for RA, with the addition of biologic disease-modifying anti-rheumatic drugs (bDMARDs) in patients who experience an inadequate response to MTX (2,3). Abatacept is a T-cell co-stimulation modulator that has shown efficacy in patients with RA in a wide range of disease and treatment durations (4-11). AMPLE (Abatacept versus Adalimumab Comparison in Biologic-Naïve RA Subjects with Background MTX), the first head-to-head trial comparing bDMARDs in patients with RA receiving MTX, demonstrated non-inferiority for abatacept versus adalimumab by the ACR 20% improvement response (ACR20) at Year 1 (64.8% subcutaneous [SC]

abatacept vs 63.4% adalimumab; estimated difference between treatments: 1.8% [95% confidence interval (CI): −5.6, 9.2]; intent-to-treat [ITT] analysis) (12). In AMPLE, there was a similar time of onset of ACR20 response in both treatment groups, with the response maintained up to Year 2 (13).

AMPLE included a diverse range of PRO analyses and is the first bDMARD head-to-head evaluation of PROs in RA. Comparable improvements from baseline to Year 1 were seen in fatigue with SC abatacept and adalimumab (−23.2% SC abatacept vs −21.4% adalimumab; adjusted treatment difference: −1.8% [95% CI: −5.8, 2.2]) (12); results for pain over 1 and 2 years have also been presented previously (14).

Here, 2-year results from the AMPLE trial are reported, directly comparing the effects of abatacept and adalimumab on the PROs of pain, fatigue, the ability to perform work, and the ability to perform daily activities, as well as the relationship between these four PROs and clinical outcomes.

PATIENTS AND METHODS

The AMPLE study design and patient inclusion/exclusion criteria (ClinicalTrials.gov Identifier: NCT00929864) have been described previously (13). Briefly, patients had active RA for ≤5 years, as defined by the 1987 American Rheumatism Association criteria for RA, had reported an inadequate response to MTX, were biologic-naïve, and had a Disease Activity Score (DAS)28 (C-reactive protein; CRP) ≥3.2. Patients were randomly assigned (1:1) to either SC abatacept (125 mg every week) or adalimumab (40 mg every 2 weeks), in addition to a stable dose of MTX (15–25 mg/week).

ORIGINAL ARTICLE

This study was conducted in accordance with: the ethical principles of the Declaration of Helsinki; Good Clinical Practice, as defined by the International Conference on Harmonization; and the ethical principles underlying European Union Directive 2001/20/EC and the USA Code of Federal Regulations, Title 21, Part 50 (21CFR50). The laws and regulatory requirements of all countries participating in this study were followed.

PRO assessments. PROs deemed important to patients with RA and assessed in AMPLE were: pain, fatigue, ability to perform work, and ability to perform daily activities; all except pain were evaluated on Day 1, Month 6, Year 1, and Year 2.

Pain. Pain was measured using a 100-mm visual analog scale (VAS), with a minimal clinically important difference (MCID) defined as a change of −10 mm from baseline (14,15). Pain was evaluated at Days 1, 15, 29, and every 4 weeks thereafter during Year 1, and every 3 months during Year 2.

Fatigue. Patient's assessment of the severity of fatigue over the past week was measured using a 100-mm VAS. An MCID was defined as a change of −10 mm from baseline (16).

Ability to perform work. Four components of the Work Productivity and Activity Impairment Questionnaire: Rheumatoid Arthritis (WPAI:RA) were analyzed: absenteeism (work time missed), presenteeism (impairment at work/reduced on-the-job effectiveness), work productivity loss (overall work impairment/absenteeism plus presenteeism), and activity impairment. For baseline values these components are reported as: work time missed, impairment at work, overall work impairment and activity

impairment; for post-treatment values they are reported as: work time gained, reduced impairment while working, overall reduced work impairment, and activity gained. An MCID for WPAI:RA was defined as a 7% absolute change in WPAI score (17).

Ability to perform daily activities. The Activity Limitation Questionnaire was used to assess the number of days out of the past 30 days that a patient was unable (baseline values) or able (post-treatment values) to perform usual activities owing to RA. An MCID was defined as a change of 4 days from baseline (ie, patients able to perform daily activities on 4 additional days) (16).

***Post hoc* analyses: PROs in clinical responders versus non-responders.** *Post hoc* analyses were performed to determine the proportions of patients who achieved clinical responses according to the following criteria: ACR20 response; Clinical Disease Activity Index (CDAI) LDA (score <10), and remission (score <2.8); Simplified Disease Activity Index (SDAI) LDA (score <11), and remission (score <3.3); and Boolean remission (score <1). The four PROs (pain, fatigue, ability to perform work, and ability to perform daily activities) were compared for patients with clinical responses (as defined above) at Month 6, Year 1, and Year 2 ('responders') and those without ('non-responders').

Statistical analysis. All efficacy analyses were performed on the ITT population, which included all patients who were randomized and received ≥1 dose of study drug. Baseline demographics and clinical characteristics were analyzed descriptively. For fatigue and ability to perform daily activities, changes from baseline were summarized by treatment and visit, and 95% CIs for the treatment differences were constructed. For

ORIGINAL ARTICLE

ability to perform work, percentage reduction from baseline in each of the four components of impairment was reported by treatment and visit. Between-treatment group differences in impairment reduction were also assessed using the point estimation and 95% CI. Definitions of MCIDs for individual outcomes are given above. For all patients who completed Day 729 (Year 2), individual responses/non-responses for ACR20 response and remission/LDA (CDAI, SDAI, and Boolean) were calculated using *post hoc* analyses of as-observed data (ie, all data available). All patients who prematurely discontinued the study after receiving study drug, regardless of reason, were considered non-responders at all subsequent visits for the clinical response measures. For all PROs, adjusted mean changes from baseline were summarized by treatment group and were based on an analysis of covariance model with treatment as the main factor, and baseline values with DAS28 (CRP) stratification as covariates.

RESULTS

A total of 646 patients were randomized and treated: 318 patients in the SC abatacept group and 328 patients in the adalimumab group. Demographic and baseline clinical characteristics, including PRO measures, were well balanced between the two treatment groups (Table 1). Overall, 79.2% of patients treated with SC abatacept and 74.7% of patients treated with adalimumab completed the 2-year study.

Change in PROs during the study period. Over the 2-year study period, comparable improvements were seen in the SC abatacept and adalimumab treatment groups for most of the four PROs assessed.

Pain. Numerically greater improvements in pain were observed for patients who received abatacept versus adalimumab over 2 years (14). Mean (standard error of the mean) improvements in pain at Year 2 for abatacept versus adalimumab were 53.7% (6.2%) versus 38.5% (6.1%), respectively, with an adjusted mean treatment difference (95% CI) of 15.2% (−1.2, 31.6) (published previously) (14). An MCID in pain was reached from Day 15 for both treatment groups.

Fatigue. Comparable improvements in fatigue were observed in the abatacept and adalimumab treatment groups over 2 years (Figure 1). Adjusted mean change in fatigue reached an MCID (−10 mm) as early as Day 15 in both treatment groups, with improvements being maintained up to Year 2.

Ability to perform work. The four components of the WPAI:RA were found to be similarly improved in patients receiving abatacept and those receiving adalimumab over the 2-year study (Figure 2). In both the abatacept and the adalimumab treatment groups, improvements in the components of reduced impairment while working, overall reduced work impairment, and activity gained, reached an MCID (7%) at all post-baseline assessments (Month 6, Year 1, and Year 2).

Ability to perform daily activities. As seen for the ability to perform work assessments, improvements in patients' ability to perform daily activities over 2 years were similar in both the abatacept and the adalimumab treatment groups (Figure 3).

ORIGINAL ARTICLE

Again, the MCID for ability to perform daily activities of 4 additional days was seen in both treatment groups at all post-baseline assessments (Month 6, Year 1, and Year 2).

PROs in clinical responders versus non-responders. The results of the *post hoc* analyses showed that for each of the four PROs evaluated there was clear separation between patients who achieved clinical response (responders) and those who did not (non-responders), regardless of whether they received abatacept or adalimumab. This was true for each of the six clinical outcomes assessed, except when using Boolean remission to assess the ability to perform daily activities in clinical responders versus non-responders. As pain was assessed more frequently than the other PROs, which were assessed at Month 6, Year 1, and Year 2, the association of pain improvement with clinical response is shown in Figure 4 and Supplemental Figure 1 as a representative example. Adjusted mean improvements in pain reached an MCID as early as Day 15 in both responder and non-responder groups for all LDA and remission criteria; these improvements were maintained up to Year 2 (Figure 4, Supplemental Figure 1). For each PRO and each clinical measure, the number of patients was similar in the two treatment groups, for both responder and non-responder subgroups. Abatacept and adalimumab responders had similar improvements in each PRO over time.

DISCUSSION

Over 2 years of the AMPLE trial, patients treated with SC abatacept or adalimumab on background MTX achieved comparable, clinically meaningful improvements with a

similar onset of response in four PROs: pain (14), fatigue, ability to perform work, and ability to perform daily activities. Furthermore, *post hoc* analysis of the four PROs showed a clear association between clinical response according to several clinical criteria (ACR20 response, CDAI LDA, CDAI remission, SDAI LDA, SDAI remission, and Boolean remission) and improvement in PROs, with the exception of an association between Boolean remission and the ability to perform daily activities.

PROs capture the effects of treatment from a patient's perspective and are critical to ensuring that a clinical response corresponds to benefits that are perceptible and important to the patient (18). Patients and clinicians want RA treatments that rapidly improve health-related quality of life and reduce or halt functional impairment, with improvements maintained over time (19). Pain and loss of physical function are meaningful outcomes that need to be considered by clinicians as important consequences of RA (20); patients also identify fatigue as having a considerable influence on quality of life (21,22).

The results reported here are consistent with data from other published studies of the effect of abatacept on PROs, including ATTEST (Abatacept or infliximab versus placebo, a trial for tolerability, efficacy and safety in treating RA), AIM (Abatacept in inadequate responders to MTX), and ACQUIRE (Abatacept comparison of SC versus intravenous [IV] in inadequate responders to MTX). As in AMPLE, these three abatacept studies included patients with an inadequate response to MTX who were biologic-naïve (5,23-25).

ORIGINAL ARTICLE

The results presented here are also consistent with published PRO data for adalimumab (26-28). In the ARMADA (Anti-TNF research study program of the monoclonal antibody adalimumab) trial, patients who had an inadequate response to MTX and were treated with adalimumab plus MTX demonstrated significant improvements in physical function from baseline to Year 4 (mean Health Assessment Questionnaire-Disability Index [HAQ-DI]: 0.7 and 1.5, respectively [$p<0.001$]) (26). Similarly, in the DE019 adalimumab study, patients who had an inadequate response to MTX who received up to 10 years of adalimumab plus MTX therapy demonstrated a reduction in mean HAQ-DI from 1.4 at baseline to 0.7 at Year 10, while 42% of patients achieved HAQ-DI <0.5 (normal functionality) at Year 10 (27). In the PREMIER study, significant improvements from baseline to Year 2 in HAQ-DI ($p<0.0001$), Short-Form 36 Health Survey physical component summary score ($p<0.0001$), Patient Global Assessment ($p<0.0001$), and pain ($p<0.0001$) scores were reported by patients with early RA treated with adalimumab plus MTX versus patients treated with MTX monotherapy (28).

The goal of current treat-to-target strategies in patients with RA is the achievement of remission, but with the recognition that LDA may be an acceptable alternative if remission is not achievable, particularly for those with advanced established disease (29). By correlating clinical response with PROs that are important to both physicians and patients, such as pain, fatigue, work productivity, and activity impairment, the achievement of how a good clinical response translates into meaningful benefits for the patient in their daily life can be better understood. Greater reductions in

the signs and symptoms of RA (ACR20 response) and disease activity (LDA or remission, as assessed by SDAI, CDAI, or Boolean criteria) were associated with greater improvements over 2 years in the four PROs assessed (except for ability to perform daily activities when assessed by Boolean remission), with comparable benefits observed with SC abatacept and adalimumab.

Concerning the effect of RA on the ability to maintain employment, previous studies have found greater disease activity to be significantly correlated with higher numbers of missed work hours (absenteeism), greater work impairment (presenteeism), and greater activity impairment (30,31). It is unclear how relatively small changes in disease activity, such as from LDA to remission, can impact PROs. Nonetheless, reaching an MCID in pain, fatigue, or physical function results in significantly greater improvements in work productivity compared with patients who did not achieve MCID in these outcomes (32). Furthermore, a recent study reported worse work productivity in patients achieving LDA than in those achieving disease remission (33).

Limitations to this analysis should be considered. Although the AMPLE trial was powered to compare abatacept and adalimumab directly, it was a single-blinded, rather than double-blinded, design, which may have introduced bias (14). An additional limitation was the *post hoc* nature of the analyses that compared PROs in patient subgroups based on clinical response.

In summary, this study demonstrated that in biologic-naïve patients with RA, treatment with SC abatacept or adalimumab is associated with comparable improvements in PROs that are considered particularly important in RA (pain, fatigue,

work productivity, and activity limitation). Furthermore, improved PROs were associated with physician-reported clinical responses.

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ORIGINAL ARTICLE

Table 1. Baseline demographics and patient-reported outcomes

	SC abatacept + MTX (n = 318)	Adalimumab + MTX (n = 328)
Age, years	51.4 (12.6)	51.0 (12.8)
Women, %	81.4	82.3
Race		
White, %	80.8	78.0
Disease duration, years	1.9 (1.4)	1.8 (1.4)
HAQ-DI score	1.5 (0.7)	1.5 (0.7)
DAS28 (CRP) score	5.5 (1.1)	5.5 (1.1)
Pain score	63.1 (22.3)	65.5 (21.8)
Fatigue score	60.6 (25.0)	60.1 (25.4)
Ability to perform work score, %		
Work time missed	10.9 (21.5)	13.5 (25.1)
Impairment at work	47.2 (28.5)	51.4 (27.7)
Overall work impairment	50.2 (29.5)	54.4 (29.6)
Activity impairment	56.3 (24.6)	57.1 (25.9)

ORIGINAL ARTICLE

Ability to perform daily activities score, days	11.7 (10.4)	12.4 (10.3)

Values represent mean (standard deviation) unless stated differently. Pain and fatigue measured on a visual analog scale 100-mm scale; ability to perform work assessed using the Work Productivity and Activity Impairment Questionnaire: Rheumatoid Arthritis; ability to perform daily activities assessed as the number of days that patients were unable to perform normal activities during the past 30 days using the Activity Limitation Questionnaire. Baseline fatigue, ability to perform work, and ability to perform daily activities scores presented for patients with available data at 2 years (abatacept and adalimumab, respectively: fatigue: n = 310 and n = 315; work time missed: n = 137 and n = 130; impairment at work, overall work impairment and activity impairment: n = 134 and n = 126; ability to perform daily activities: n = 308 and n = 310).

DAS28 (CRP) = Disease Activity Score 28 (C-reactive protein); HAQ-DI = Health Assessment Questionnaire-Disability Index; MTX = methotrexate.

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Figure captions

Figure 1. Mean improvements in patient fatigue over 2 years.

Intent-to-treat population. All patients with baseline and post-baseline measurements were used for this analysis. Error bars represent standard error of the mean. MCID = minimal clinically important difference; VAS = visual analog scale.

Figure 2. Mean improvements in patient ability to perform work,* over 2 years.

* As assessed by the Work Productivity and Activity Impairment Questionnaire: Rheumatoid Arthritis.

Intent-to-treat population. All patients with baseline and post-baseline measurements were used for this analysis. Error bars represent standard error of the mean. MCID = minimal clinically important difference.

Figure 3. Mean improvements in patients' activity limitation,* over 2 years.

* Number of days that patients are able to perform normal activities during the past 30 days, as assessed by the Activity Limitation Questionnaire.

Intent-to-treat population. All patients with baseline and post-baseline measurements were used for this analysis. Error bars represent standard error of the mean. MCID = minimal clinically important difference.

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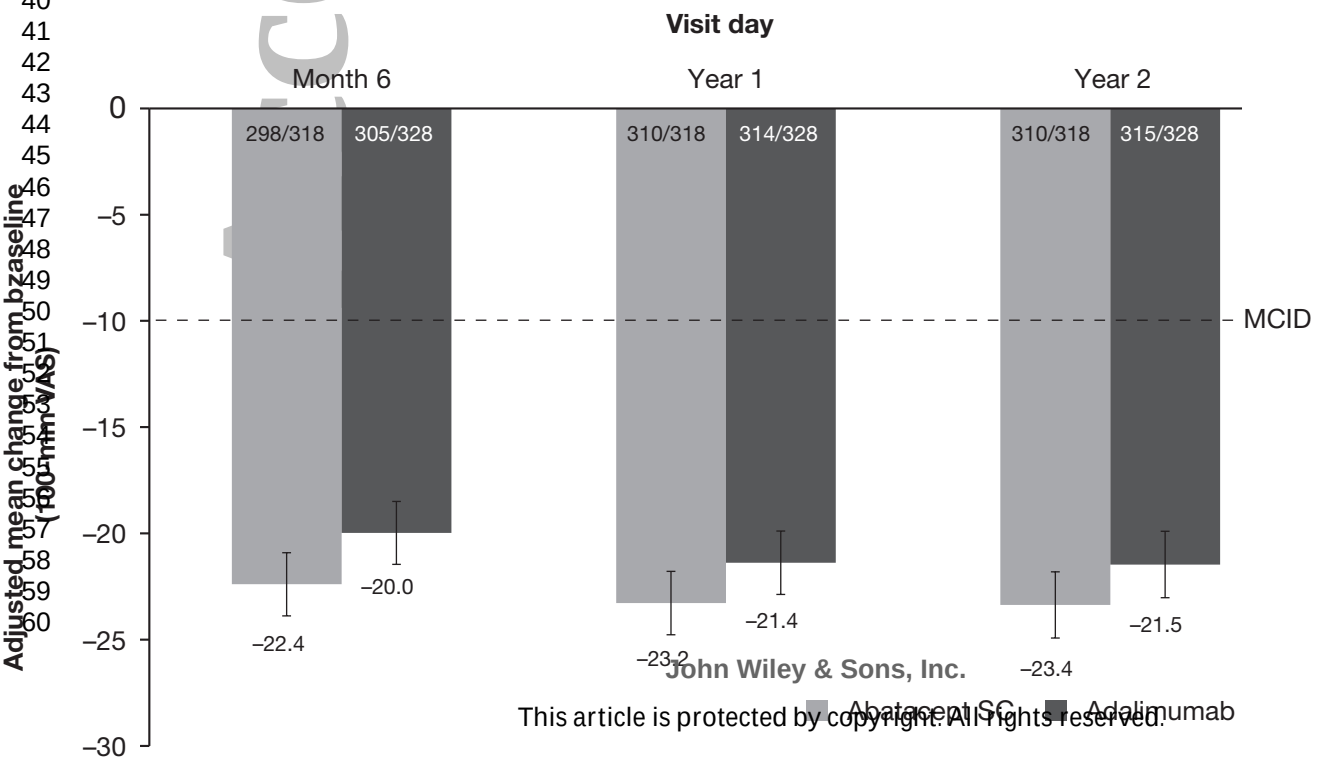
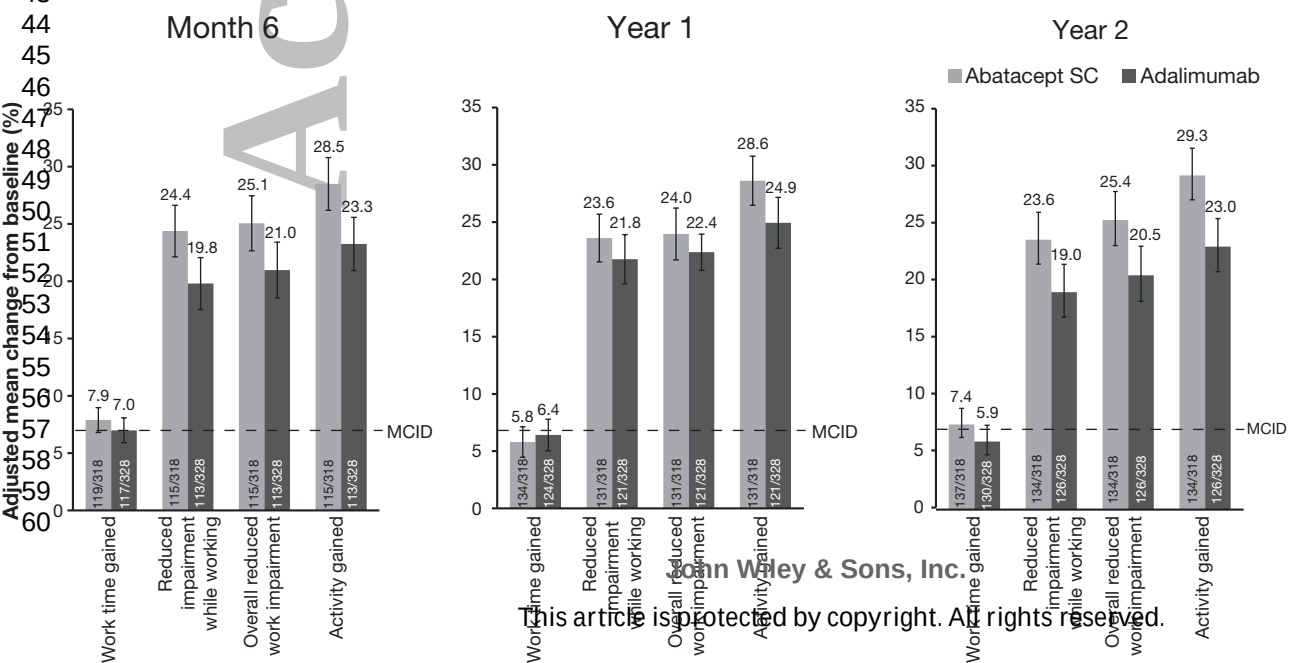
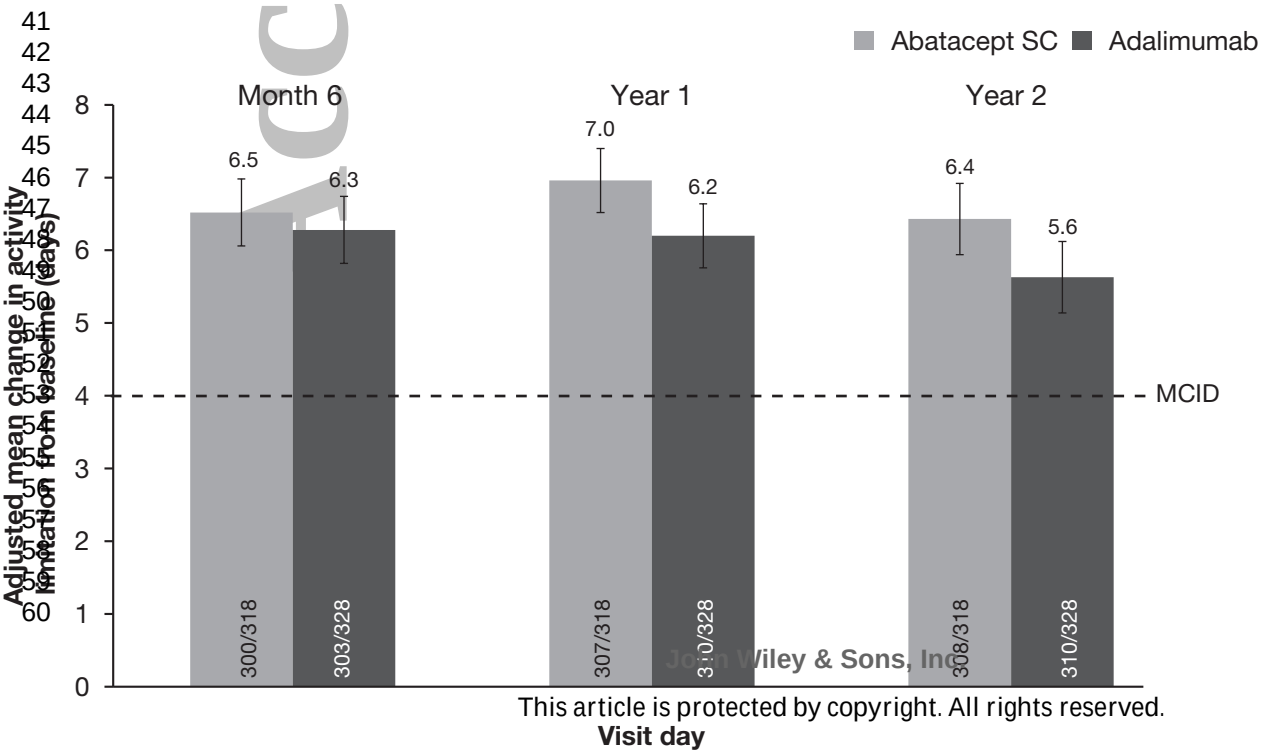
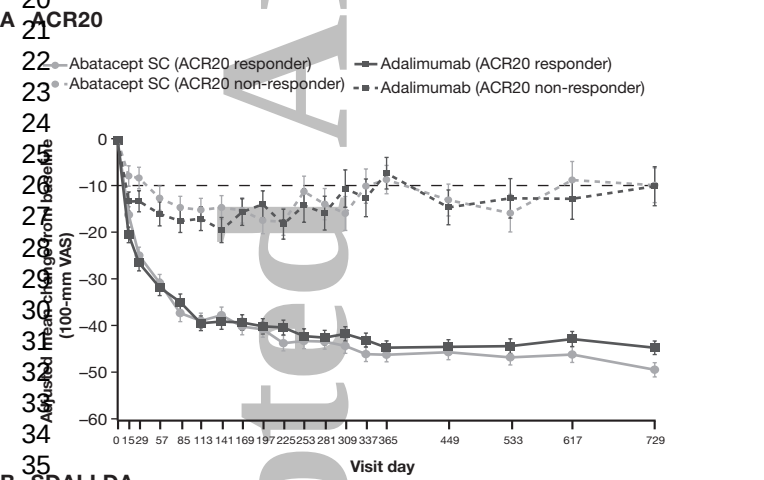
Figure 4. Improvements in patient pain over 2 years in responder and non-responder patient subgroups, defined by clinical response criteria: (A) ACR20 response, (B) SDAI LDA, and (C) SDAI remission.

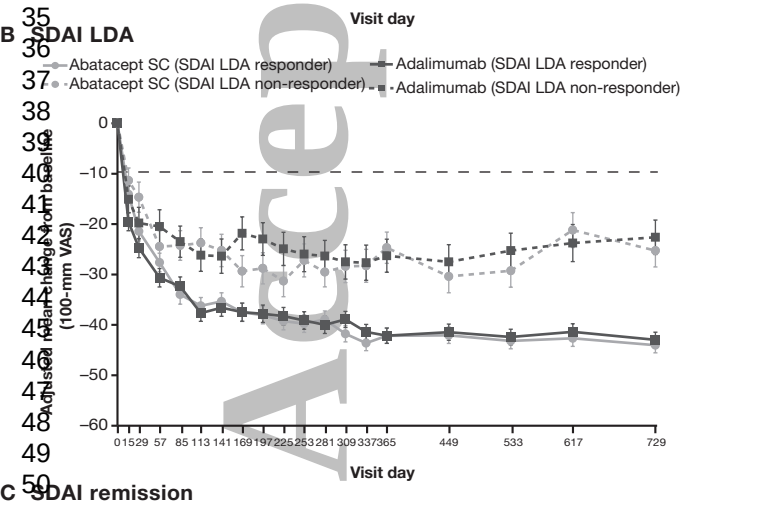
Intent-to-treat population. All patients with baseline and post-baseline measurements were used for this analysis. Error bars represent standard error of the mean. ACR20 = American College of Rheumatology 20% improvement response; LDA = low disease activity; MCID = minimal clinically important difference; SDAI = Simplified Disease Activity Index; VAS = visual analog scale.

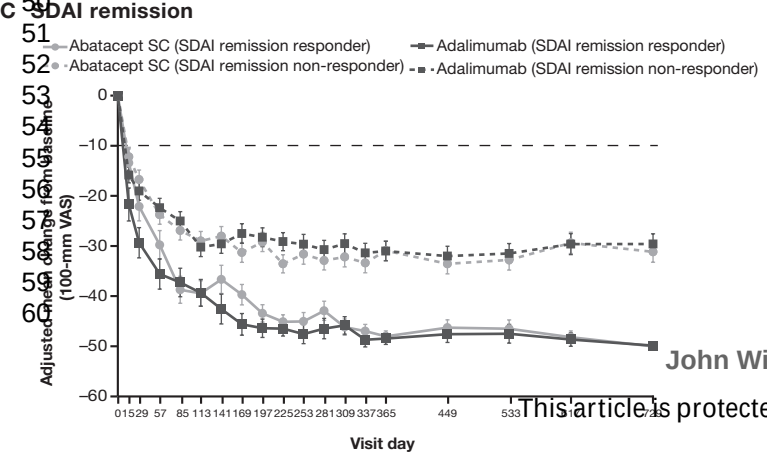




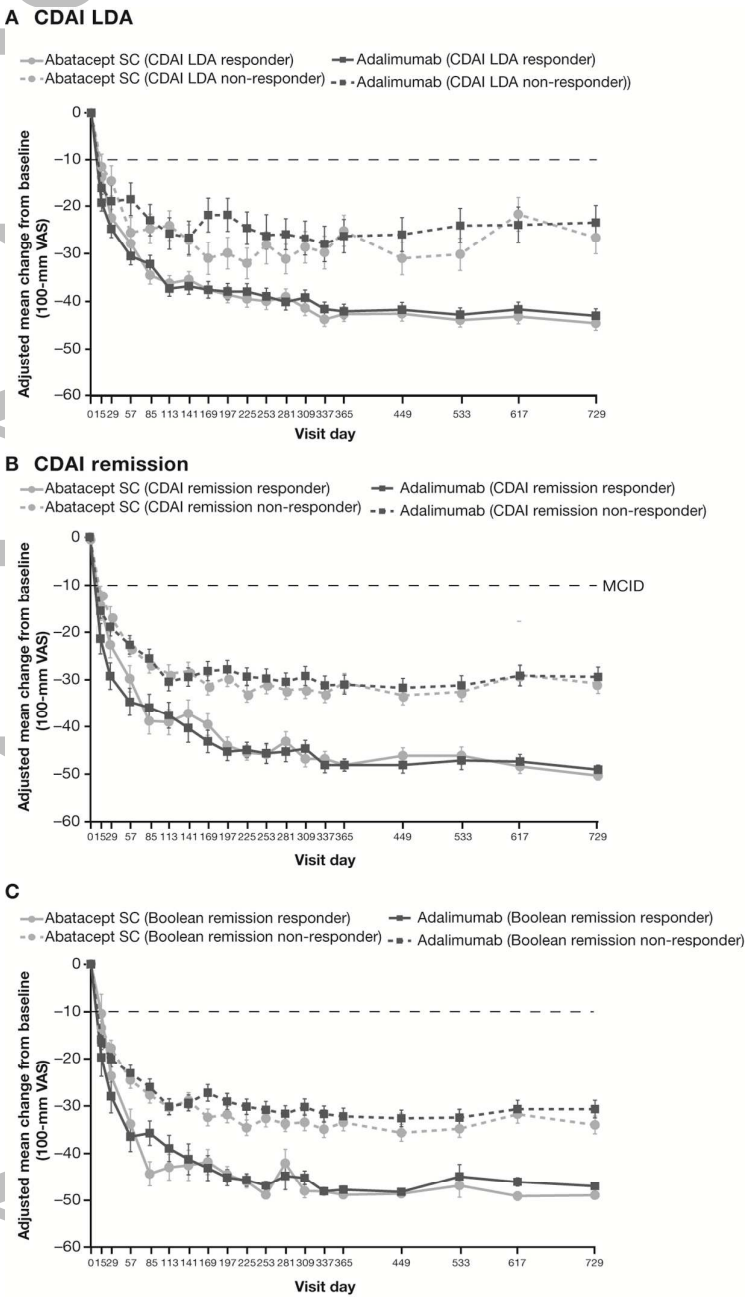








Supplemental Figure 1. Improvements in patient pain over 2 years in responder and non-responder patient subgroups, defined by clinical response criteria: (A) CDAI LDA, (B) CDAI remission, and (C) Boolean remission.



Intent-to-treat population. All patients with baseline and post-baseline measurements were used for this analysis. Error bars represent standard error of the mean. CDAI =

Clinical Disease Activity Index; LDA = low disease activity; MCID = minimal clinically important difference; VAS = visual analog scale.