Adalimumab Efficacy in Patients with Psoriasis Who Received or Did Not Respond to Prior Systemic Therapy: A Pooled Post Hoc Analysis of Results from Three Double-Blind, Placebo-Controlled Clinical Trials

Kim A. Papp1 · April W. Armstrong2 · Kristian Reich3 · Mahinda Karunaratne4 · Wendell Valdecantos4

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Abstract

Introduction There are limited data from randomized controlled clinical trials on the outcomes of biologics after discontinuation of a different systemic therapy. To determine the efficacy of adalimumab in patients who previously received systemic therapy (including failed therapy), we performed a pooled post hoc analysis of Psoriasis Area and Severity Index (PASI) response data from three double-blind, placebo-controlled clinical trials in patients with moderate to severe psoriasis.

Methods Patients from the M02-528, REVEAL, and CHAMPION studies who were previously exposed to systemic treatment were categorized based on their response. The efficacy of adalimumab compared with placebo was analyzed at the end of the double-blind treatment period for the overall pooled intent-to-treat population (N = 1469) and subgroups that received (n = 780) or did not respond to (n = 229) previous systemic pretreatments.

Results Rates for an improvement of ≥75 % from baseline in the PASI score (PASI75 response) were significantly greater (p < 0.001) at week 16 in patients treated with adalimumab compared with patients who received placebo in the overall (72.1 vs. 8.0 %, respectively), previously treated (72.7 vs. 8.5 %), and previously failed treatment (70.4 vs. 8.1 %) groups. PASI75 response rates were similar in the overall group and in patients who did not respond to methotrexate, cyclosporine, or psoralen plus ultraviolet A therapy. Improvements of ≥90 or ≥100 % from baseline PASI score were also higher with adalimumab vs. placebo in previously treated patients. Adverse events were similar among subgroups.

Conclusions Adalimumab was efficacious for the treatment of moderate to severe psoriasis regardless of prior exposure to systemic therapies or failure of those prior therapies.

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Key Points

Patients with psoriasis treated with adalimumab show significant improvement.

Patients with previous exposure to systemic therapies demonstrated improvement comparable to those without prior exposure to systemic therapies.

Patients who did not respond to systemic therapies demonstrated improvement comparable to the general psoriasis population.

1 Introduction

Current treatment guidelines suggest that psoriasis may be treated with topical, ultraviolet (UV)-based, traditional systemic, or biologic therapies, depending on specific patient and disease characteristics [1–3]. The majority of
patients with psoriasis who are prescribed biologic therapy have previously received treatment with other systemic therapies, including methotrexate (MTX), cyclosporine, and psoralein plus UVA (PUVA) therapy. It is of clinical relevance to understand whether patients who have received prior systemic therapy, especially patients who did not respond to previous treatment, will respond to biologics to the same degree as patients who are naive to systemic treatments.

Systemic therapies for the treatment of moderate to severe psoriasis include MTX, which acts as an immunosuppressant and is often a first-line systemic therapy, and cyclosporine, which is a short-term treatment alternative owing to its potential for nephrotoxicity [4]. A third option is PUVA, which uses naturally occurring, photosensitizing psoralein compounds to sensitize cells to the effects of UVA light and form psoralein-DNA crosslinks upon exposure, thus preventing DNA replication [5]. Biologics approved for the treatment of psoriasis have included agents that modulate T cells (e.g., alefacept and efalizumab [both withdrawn from the market]) and inhibitors of tumor necrosis factor (TNF; e.g., adalimumab, etanercept, and infliximab), interleukin-12 and interleukin-23 (e.g., ustekinumab) [6–8], and interleukin-17 (e.g., secukinumab) [9]. Apremilast is a recently approved small-molecule inhibitor of phosphodiesterase 4 [10]. However, there are limited published clinical trial data on the outcomes of systemic biologics after discontinuing a different prior systemic therapy, particularly following failure of the previous therapy.

The efficacy of adalimumab in the treatment of psoriasis was demonstrated in two large, randomized, placebo-controlled phase III trials. In the REVEAL trial, a significantly greater percentage of patients receiving adalimumab achieved an improvement of ≥75 % from baseline in the Psoriasis Area and Severity Index score (PASI75 response) compared with patients receiving placebo (71 vs. 7 %) [11]. In the CHAMPION trial, the superiority of adalimumab over MTX and placebo was demonstrated by a significantly greater percentage of patients receiving adalimumab achieving PASI75 (79.6 %) compared with patients receiving MTX (35.5 %) and placebo (18.9 %) [12].

The results of several small studies suggest that adalimumab may be an appropriate treatment option for patients who have not achieved an adequate response to prior systemic treatments, underscoring the need for confirmation with additional data [13–18]. In this post hoc analysis, we assessed the efficacy of adalimumab vs. placebo in patients with psoriasis who received systemic therapy (biologics, non-biologics, and/or oral PUVA) before enrolling in the clinical trial, and included patients who experienced failure (i.e., lack of improvement or worsening of psoriasis) with one or more prior therapies.

### 2 Methods

#### 2.1 Data Sources

Pooled data from three double-blind, placebo-controlled efficacy and safety studies of adalimumab for the treatment of moderate to severe psoriasis (N = 1469) were used for this post hoc analysis. Patients from the placebo and adalimumab (80 mg at week 0, then 40 mg every other week [eow] starting at week 1) treatment groups were included in the analysis. Patients who had received a systemic biologic, non-biologic, or oral/topical PUVA were identified; additionally, patients who had not responded to prior treatments were also identified. Assessment of prior treatment outcomes was based on patient self-report rather than medical records or assessment scales. Prior treatment was classified as treatment failure if the patient described his or her psoriasis as the “same” or “worse” after the treatment.

#### 2.2 Study Design and Patients

The designs of the three studies used for this pooled post hoc analysis have been described previously [11, 12, 19]. Study M02-528 [19] was a 12-week phase II study in which 148 patients were randomized in a 1:1:1 manner, with 147 patients receiving the following treatments: adalimumab 80 mg at week 0, followed by 40 mg eow starting at week 1 (n = 45); adalimumab 80 mg at weeks 0 and 1, followed by 40 mg weekly starting at week 2 (n = 50); or placebo (n = 52). PASI responses were evaluated at weeks 1, 2, 4, 8, and 12. The CHAMPION study [12] was a 16-week phase III trial in which 271 patients were randomized in a 2:2:1 manner to receive adalimumab 80 mg at week 0, followed by 40 mg eow starting at week 1 (n = 108); MTX (not included in this analysis) 7.5–25.0 mg weekly starting at week 0 (n = 110); or placebo (n = 53). PASI responses were evaluated at weeks 1, 2, 4, 8, 12, and 16. The REVEAL study [11] was a 16-week (Period A) phase III trial in which 1212 patients were randomized in a 2:1 manner to receive adalimumab 80 mg at week 0, followed by 40 mg eow starting at week 1 (n = 814) or placebo (n = 398). PASI responses were evaluated at weeks 4, 8, 12, and 16.

Inclusion and exclusion criteria were similar for each study, which facilitated combining data from the separate study populations. Patients included adults with moderate to severe plaque psoriasis that affected ≥10 % of body surface area (≥5 % for Study M02-528), who had a Physician Global Assessment (PGA) of at least “moderate” disease severity for the CHAMPION and REVEAL studies, and a PASI score of ≥10 for the CHAMPION
study or a PASI score ≥12 for the REVEAL study. Patients who had previously used systemic TNF antagonists were excluded from both studies; patients who had previously used MTX were excluded from the CHAMPION study. Washout periods for prior treatments were 2 weeks for topicals and phototherapy, 4 weeks for non-biologic systemic therapies (including PUVA in the REVEAL study), 6 weeks for efalizumab in the REVEAL study, and 12 weeks for biologic therapies.

2.3 Study Assessments

The primary efficacy endpoint was PASI75 response at week 16 (except for Study M02-528, which was a 12-week study). The PASI score (range 0–72) assesses the severity of lesions with respect to erythema, induration, and desquamation and the body surface area involved on the head, torso, and upper and lower extremities. Improvements of ≥90 and ≥100 % from baseline in PASI score (PASI90 and PASI100, respectively) were similarly assessed.

Information was collected on the prior use of systemic treatments for psoriasis and patients’ self-reported recollection of their response to treatment. For the M02-528 study, information about prior psoriasis treatments and their effectiveness was collected for the previous 12 months; for the CHAMPION and REVEAL studies, information about all lifetime psoriasis treatment was collected, and response to treatments from the previous 12 months was recorded. Within each category of prior treatment, multiple prior treatments per patient may have been used. For this post hoc analysis, patients who recalled that their psoriasis was the “same or worse” with a prior therapy were considered to have had a lack of response.

2.4 Statistical Analyses

Efficacy data from the first 16 weeks (12 weeks for M02-528) of the double-blind period of each study were pooled and analyzed. Efficacy analyses were conducted using the intent-to-treat population, and nonresponder imputation was used for missing PASI data (i.e., patients with missing PASI data were counted as nonresponders). The Fisher exact test was used to calculate p-values for differences between treatment groups.

3 Results

3.1 Patients

Baseline demographics and clinical characteristics were similar between treatment groups; the majority of patients were male and white, and the mean disease duration was 18–19 years (Table 1). The clinical characteristics of the treatment groups included in this analysis were typical of patients with moderate to severe plaque psoriasis. Psoriasis treatments received within the previous 12 months were comparable between the placebo and adalimumab treatment groups, with the majority of patients receiving treatment with topical therapies (Table 2). The rates of responses to prior therapies (i.e., failure [“same or worse”] or improvement) were similar in the placebo and adalimumab groups in the trials analyzed here (Table 3).

3.2 Efficacy Assessments

Patients treated with adalimumab achieved significantly higher PASI75 response rates compared with patients receiving placebo, regardless of whether they had previously received systemic treatment or had not responded to previous systemic therapy (Fig. 1). By 4 weeks (first evaluation), PASI75 response rates were significantly greater (p < 0.001) in patients treated with adalimumab compared with patients receiving placebo in all treatment groups (overall, 19.4 % [187/966] vs. 1.4 % [7/503]; prior treatment, 21.7 % [111/511] vs. 1.5 % [4/269]; and prior failures, 15.6 % [25/160] vs. 0 % [0/69]; Fig. 1a). At 16 weeks, a significantly higher (p < 0.001) percentage of patients treated with adalimumab compared with those

| Table 1 Baseline demographics and clinical characteristics | Placebo (n = 503) | Adalimumab (n = 966) |
|---------------------------------------------------------|-----------------|---------------------|
| Age, mean ± SD, years                                   | 45 ± 13         | 44 ± 13             |
| Male, %                                                 | 65              | 67                  |
| White, %                                                | 91              | 92                  |
| Body weight, mean ± SD, kg                             | 93 ± 23         | 92 ± 23             |
| Psoriasis duration, mean ± SD, years                    | 19 ± 11         | 18 ± 12             |
| BSA affected, mean ± SD, %                              | 26 ± 15         | 27 ± 16             |
| PASI score, mean ± SD                                   | 19 ± 7          | 19 ± 7              |
| Psoriatic arthritis, %                                  | 28              | 27                  |

BSA body surface area, PASI Psoriasis Area and Severity Index, SD standard deviation

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receiving placebo achieved PASI75 in all treatment groups (overall, 72.1 % [664/921] vs. 8.0 % [36/451]; prior treatment, 72.7 % [357/491] vs. 8.5 % [21/247]; and prior failures, 70.4 % [107/152] vs. 8.1 % [5/62]; Fig. 1b). Similar results between adalimumab and placebo were observed for PASI90 and PASI100 responses. At 4 weeks, PASI90 response rates were significantly greater ($p \leq 0.001$) in patients treated with adalimumab compared with patients receiving placebo overall (4.6 % [44/966] vs. 0 % [0/503]) and in patients who had previously received systemic therapy (4.3 % [22/511] vs. 0 % [0/269]); improvement was not significantly different with adalimumab vs. placebo for patients who had not responded to prior therapy (1.3 % [2/160] vs. 0 % [0/69]; Fig. 1a). No statistically significant difference in PASI100 response rates was observed between adalimumab and placebo at 4 weeks. At 16 weeks, however, significantly higher ($p \leq 0.001$) percentages of patients treated with adalimumab compared with placebo (46.9 % [15/32] vs. 0 % [0/17]; $p = 0.001$); however, PASI100 responses with adalimumab compared with placebo (18.8 % [6/32] vs. 0 % [0/17]) were numerically greater but not statistically significantly different. The sample sizes of patients with failure of previous cyclosporine or PUVA therapy were extremely small. At week 16, the percentage of patients achieving PASI75 who did not respond to previous therapy with cyclosporine or PUVA was numerically higher in patients treated with adalimumab (71.4 % [5/7] and 83.3 % [5/6], respectively) compared with patients receiving placebo (20.0 % [1/5] and 50.0 % [2/4], respectively; Fig. 2); similar patterns were observed with PASI90 and PASI100 response rates.

### 3.3 Safety

Generally, adverse event (AE) occurrence was similar across groups. Among the patients who reported AEs, most reported typically mild to moderate AEs (Table 4). Serious AEs occurred in $\leq 3 \%$ of patients in any group; serious infections occurred in $\leq 1 \%$ of patients in any group. No patients developed tuberculosis during the double-blind randomized periods described in this analysis. One patient receiving adalimumab and one receiving placebo had malignancies other than lymphoma, hepatosplenic T-cell

### Table 2 Psoriasis treatment within the previous 12 months

| Type of treatmenta, n (%) | Placebo (n = 503) | Adalimumab (n = 966) |
|---------------------------|------------------|---------------------|
| Topical                   | 380 (75.5)       | 743 (76.9)          |
| Phototherapy              | 89 (17.7)        | 176 (18.2)          |
| Systemic non-biologic     | 121 (24.1)       | 232 (24.0)          |
| Acitretin                 | 20 (4.0)         | 33 (3.4)            |
| Tazarotene                | 17 (3.4)         | 17 (1.8)            |
| Cyclosporine              | 18 (3.6)         | 32 (3.3)            |
| Methotrexite              | 45 (8.9)         | 94 (9.7)            |
| Other                     | 31 (6.2)         | 76 (7.9)            |
| Systemic biologic         | 63 (12.5)        | 106 (11.0)          |
| Alefacept                 | 23 (4.6)         | 34 (3.5)            |
| Efalizumab                | 20 (4.0)         | 30 (3.1)            |
| Other                     | 24 (4.8)         | 43 (4.5)            |
| Laser                     | 3 (0.6)          | 4 (0.4)             |

a Patients may have received multiple previous treatments; therefore, the sums may exceed 100 %

### Table 3 Response to prior psoriasis treatment within the previous 12 months

| Prior treatment, n (%) | Placebo group in current analysis | Adalimumab group in current analysis |
|------------------------|-----------------------------------|-------------------------------------|
|                        | Prior response: same or worse     | Prior response: better              |
|                        |                                   |                                     |
| Phototherapy           | 49 (55.1)                         | 40 (44.9)                           |
| Systemic non-biologic  | 47 (38.8)                         | 74 (61.2)                           |
| Systemic biologic      | 21 (31.8)                         | 45 (68.2)                           |
lymphoma, leukemia, nonmelanoma skin cancer, or melanoma.

4 Discussion

This analysis confirmed that adalimumab is efficacious for the treatment of moderate to severe psoriasis in patients who have received prior systemic therapy, including patients who did not respond to previous treatment.

PASI75 response rates for patients treated with adalimumab who had previous exposure to, or lacked a response to, other systemic therapies or phototherapy were similar to the overall population. The effect was evident at the earliest assessment (week 4) and was maintained through the end of the analysis period (week 16). Similar patterns were observed for PASI90 and PASI100 response rates. This finding demonstrates that adalimumab is an efficacious treatment option for patients who received prior systemic therapy regardless of their prior treatment responses. There were no unexpected differences in safety profiles between adalimumab and placebo for the assessed groups that were based on experience with prior psoriasis therapy.

Only a few small studies to date have examined the effectiveness of adalimumab in patients who had an inadequate therapeutic response to other systemic therapies [15–18]. Of these studies, two evaluated the efficacy of adalimumab in patients who changed therapy from another TNF antagonist [15, 16]. A third study included patients who previously did not respond to conventional systemic therapies and up to two TNF antagonists (etanercept and infliximab) and, in some cases, also did not respond to treatment with efalizumab [17]. A fourth study examined patients who began treatment with adalimumab after failure of a variety of systemic therapies, including MTX, cyclosporine, PUVA, retinoids, fumaric acid esters, hydroxymercabadam, and biologics [18]. In an open-label uncontrolled study in 50 patients whose prior etanercept
| Patients, n (%) | Overall | Prior exposure to systemic therapies | Lack of response to systemic therapies |
|----------------|---------|-------------------------------------|--------------------------------------|
|                | Placebo (n = 503) | Adalimumab (n = 966) | Placebo (n = 269) | Adalimumab (n = 511) | Placebo (n = 69) | Adalimumab (n = 160) |
| AE             | 297 (59) | 615 (64) | 162 (60) | 311 (65) | 47 (68) | 96 (60) |
| Serious AE     | 8 (2)   | 18 (2)  | 1 (<1)  | 10 (2)   | 0      | 4 (3)  |
| AE leading to discontinuation | 11 (2) | 18 (2)  | 5 (2)   | 8 (2)    | 5 (7)  | 5 (3)  |
| Severe AE      | 15 (3)  | 27 (3)  | 5 (2)   | 12 (2)   | 2 (3)  | 6 (4)  |
| Drug-related AE| 87 (17) | 221 (23) | 55 (20) | 122 (24) | 14 (20) | 31 (19) |
| AE leading to death | 0      | 0       | 0       | 0        | 0      | 0      |
| Infection      | 118 (23) | 287 (30) | 63 (23) | 154 (30) | 20 (29) | 42 (26) |
| Serious infection | 4 (1)  | 5 (1)   | 0       | 3 (1)    | 0      | 1 (1)  |
| Legionella infection | 0     | 0       | 0       | 0        | 0      | 0      |
| Diverticulitis | 0       | 1 (<1)  | 0       | 0        | 0      | 0      |
| Opportunistic infection (excluding oral candidiasis and TB) | 0     | 0       | 0       | 0        | 0      | 0      |
| Oral candidiasis | 0     | 0       | 0       | 0        | 0      | 0      |
| TB             | 0       | 0       | 0       | 0        | 0      | 0      |
| Parasitic infection | 0     | 0       | 0       | 0        | 0      | 0      |
| Reactivation of hepatitis B | 0    | 0       | 0       | 0        | 0      | 0      |
| PML            | 0       | 0       | 0       | 0        | 0      | 0      |
| Malignancy     | 2 (<1)  | 6 (1)   | 0       | 2 (<1)   | 0      | 1 (1)  |
| Lymphoma       | 0       | 0       | 0       | 0        | 0      | 0      |
| HSTCL          | 0       | 0       | 0       | 0        | 0      | 0      |
| NMSC           | 1 (<1)  | 4 (<1)  | 0       | 2 (<1)   | 0      | 1 (1)  |
| Melanoma       | 0       | 1 (<1)  | 0       | 0        | 0      | 0      |
| Leukemia       | 0       | 0       | 0       | 0        | 0      | 0      |
| Malignancy other than lymphoma, HSTCL, leukemia, NMSC, or melanoma | 1 (<1) | 1 (<1)  | 0       | 0        | 0      | 0      |
| Allergic reaction (including angioedema and anaphylaxis) | 3 (1)  | 13 (1)  | 3 (1)   | 7 (1)    | 0      | 1 (1)  |
| Lupus-like reactions and SLE | 0     | 0       | 0       | 0        | 0      | 0      |
| Vasculitis     | 0       | 0       | 0       | 0        | 0      | 0      |
| Sarcoidosis    | 0       | 1 (<1)  | 0       | 1 (<1)   | 0      | 1 (1)  |
| Autoimmune hepatitis | 0     | 0       | 0       | 0        | 0      | 0      |
| Myocardial infarction | 1 (<1) | 1 (<1)  | 1 (<1)  | 0        | 0      | 0      |
| Cerebrovascular accident | 0    | 0       | 0       | 0        | 0      | 0      |
| CHF            | 0       | 1 (<1)  | 0       | 0        | 0      | 0      |
| Pulmonary embolism | 0     | 0       | 0       | 0        | 0      | 0      |
| Interstitial lung disease | 0    | 0       | 0       | 0        | 0      | 0      |
| Intestinal perforation | 0     | 0       | 0       | 0        | 0      | 0      |
| Pancreatitis   | 0       | 2 (<1)  | 0       | 1 (<1)   | 0      | 0      |
| Stevens–Johnson syndrome | 0    | 0       | 0       | 0        | 0      | 0      |
| Erythema multiforme | 0    | 0       | 0       | 0        | 0      | 0      |
| Psoriasis worsening or new onset | 11 (2) | 10 (1)  | 5 (2)   | 4 (1)    | 3 (4)  | 3 (2)  |
| Demyelinating disorder | 0     | 0       | 0       | 0        | 0      | 0      |
| Amyotrophic lateral sclerosis | 0    | 0       | 0       | 0        | 0      | 0      |
| Reversible posterior leukoencephalopathy | 0    | 0       | 0       | 0        | 0      | 0      |
| Hematologic disorders (including pancytopenia) | 1 (<1) | 2 (<1)  | 1 (<1)  | 1 (<1)   | 1 (1)  | 0      |
| Liver failure/event | 2 (<1) | 2 (<1)  | 0       | 1 (<1)   | 0      | 0      |

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therapy failed, 40% achieved a PASI75 response at week 12 with adalimumab [16]. In an open-label retrospective study in 13 patients treated with adalimumab after failure of etanercept, PASI75 was achieved by two patients (15%) at week 12 and by three patients (23%) at week 24 [15]. In an open-label study of 30 patients whose psoriasis was unresponsive to conventional systemic treatments and did not respond to all other biologics, 87% achieved a PASI75 response at week 12 with treatment with adalimumab [17]. In a retrospective study of 21 patients whose prior systemic therapy failed, 38% achieved a PASI75 response at week 16 with treatment with adalimumab [18]. These studies were neither placebo controlled nor randomized; thus, the results should be viewed with caution.

Two larger studies evaluated the efficacy of adalimumab in patients who had previously not responded to other systemic therapies that included biologics [13, 14]. In patients who either never responded, lost response, or were intolerant to prior TNF antagonist treatment (n = 282), PASI75 response was achieved in 53.8%, 65.7%, and 50.0% of patients, respectively, following treatment with adalimumab for 16 weeks [13]. The current findings are consistent with data from the PROGRESS trial, a 16-week, open-label phase IIIb trial in which 61, 49, and 48% of patients (n = 152) with a suboptimal response to MTX, etanercept, or phototherapy, respectively, achieved a PGA of “clear” or “minimal” at week 16 of treatment with adalimumab [14].

Although the current study included a large population from placebo-controlled double-blind studies, the results were obtained by a post hoc analysis of data pooled from three different trials, with the resultant possibility of heterogeneity; additionally, the statistical analyses were not adjusted for multiple comparisons. Although no data were collected after week 16, patients could continue adalimumab for 252 weeks in an open-label extension study (NCT00195676) [20]. Whereas response to adalimumab for this analysis was defined as PASI75, response to prior therapy was based on patient recall, which may be less reliable than data from medical records. It should be kept in mind that the definition of treatment failure or contraindication in clinical trials may not exactly correspond to the definitions in clinical practice, which may be influenced by the specific reimbursement system available to the patient. Data were unavailable for prior reimbursement status, the doses of prior therapies, and whether those dosages were optimized. The analysis did not include representative samples of patients who experienced treatment failure with several therapies that are currently widely used; for example, patients who received prior TNF antagonists were excluded from the trials. The pre-specified washout periods did not reflect clinical practice, in which patients may need treatment immediately following failed therapies. For some prior treatment subgroups (i.e., cyclosporine and PUVA), the number of patients who experienced treatment failure was small and may be responsible for the lack of significance in these groups.

### 5 Conclusion

Adalimumab was efficacious for the treatment of moderate to severe psoriasis regardless of prior exposure to or the lack of a response to treatment with systemic therapies. The PASI75, PASI90, and PASI100 responses for each subgroup based on prior treatment were similar to those of the overall population.

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### Compliance with Ethical Standards

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**Table 4 continued**

| Patients, n (%) | Overall | Prior exposure to systemic therapies | Lack of response to systemic therapies |
|----------------|---------|-------------------------------------|--------------------------------------|
|                | Placebo (n = 503) | Adalimumab (n = 966) | Placebo (n = 269) | Adalimumab (n = 511) | Placebo (n = 69) | Adalimumab (n = 160) |
| Administration-related medication error | 0 | 0 | 0 | 0 | 0 | 0 |
| Injection-site reaction | 26 (5) | 69 (7) | 16 (6) | 40 (8) | 1 (1) | 10 (6) |

*AE* adverse event, *CHF* congestive heart failure, *HSTCL* hepatosplenic T-cell lymphoma, *NMSC* non-melanoma skin cancer, *PML* progressive multifocal leukoencephalopathy, *SLE* systemic lupus erythematosus, *TB* tuberculosis
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