Clinical Trial of Human Umbilical Cord Blood-derived Stem Cells for the Treatment of Moderate-to-Severe Atopic Dermatitis: Phase I/IIa Studies

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Key words. Atopic dermatitis • Skin disease • Mesenchymal stem cells • Umbilical cord blood • Clinical trial

ABSTRACT

Mesenchymal stem cells (MSCs) have been proven to be therapeutically effective against atopic dermatitis (AD) in preclinical studies. However, the safety and efficacy of MSCs against AD have not yet been investigated in a clinical study. To establish the safety and efficacy of human umbilical cord blood-derived MSCs (hUCB-MSCs) in AD, thirty-four adult patients with moderate-to-severe AD were enrolled in two phase trials with a follow-up for 1 month and 3 months, respectively. Patients were randomly allocated to receive low dose (2.5 x 10^5) or high dose (5.0 x 10^5) of hUCB-MSCs subcutaneously. An Eczema Area and Severity Index (EASI) score, investigator’s global assessment (IGA) score, Severity Scoring for Atopic Dermatitis (SCORAD) score, adverse effect assessments and serum biomarker levels were evaluated as end points. A single treatment of hUCB-MSCs resulted in dose-dependent improvements in AD manifestation. Fifty-five percent of patients in high dose hUCB-MSC-treated group showed a 50% reduction in the EASI score. The IGA score and SCORAD score decreased by 33% and 50%, respectively, in high dose-treated group. Particularly, the administration of high dose hUCB-MSCs reduced the pruritus score by 58%. The serum IgE levels and number of blood eosinophils were down-regulated by the treatment. No serious adverse events occurred and none of the patients discontinued the trial due to adverse events. This is the first report to demonstrate a marked improvement of AD features with cell therapeutics. These data suggest that the infusion of hUCB-MSCs might be an effective therapy for patients with moderate-to-severe AD. Stem Cells 2016; 00:000–000

SIGNIFICANCE STATEMENT

Atopic dermatitis (AD) is a chronic and relapsing skin disease which has become a major public health issue. The current clinical therapy against AD has been reported to be limited in its efficacy and often accompanied by side-effects. In the present study, we report the efficacy and safety of human umbilical cord blood-derived mesenchymal stem cells (hUCB-MSCs) in patients with moderate-to-severe atopic dermatitis (AD) as a promising alternative therapy. This first-in-class clinical study shows that single subcutaneous injection of hUCB-MSCs improves disease symptoms based on the eval-
Atopic dermatitis (AD) is a chronic and relapsing skin disease accompanied by pruritus, xerosis, and eczematous lesions [1]. AD has become a major public health issue, affecting up to 20% of children and 3-10% of adults [2, 3]. The pathogenesis of AD is a complicated inflammatory process involving a combination of genetic, immunologic, and environmental factors. AD is characterized by excessive type 2 helper T cell (Th2)-mediated inflammatory responses and frequently accompanied by elevated levels of serum IgE and blood eosinophils [4-6]. Although AD has been classified as a Th2 dominant disease, it has been recently reported that other subsets of helper T cells such as Th1, Th17 and Th22 might be involved in the pathogenesis [7, 8]. The treatment and management of AD is complex and depends on the symptoms of patients. The current clinical management of AD generally involves topical steroids and systemic immunosuppressants drugs. However, the efficacy of topical corticosteroids has been reported to be limited for patients with moderate-to-severe AD and is accompanied by side-effects with long-term application [9]. Moreover, systemic immunosuppressants including cyclosporin A have been reported to carry the risk of severe toxicity and side-effects [9, 10]. More recently, new biological agents including anti-IgE (omalizumab), anti-IL-5 (mepolizumab), anti-CD11a (efalizumab) and anti-IL-4R (dupilumab) have been introduced for AD patients. However, their efficacies have been reported to be limited and non-uniform in certain patients with AD in clinical trials [11]. Therefore, there are unmet needs for the development of a novel therapy with safety and efficacy.

Stem cells have been proven to be a promising alternative therapy for intractable diseases through several recent proof-of-concept studies with relatively small size, including embryonic stem cells in macular degeneration (n = 9) [12], hematopoietic stem cells in refractory Crohn’s disease (n = 45) [13], and MSCs in amyotrophic lateral sclerosis or multiple sclerosis (n = 26 and 10, respectively) [14, 15]. Particularly, MSCs have been used for the treatment of immune disorders such as graft-versus-host disease, systemic lupus erythematosus and multiple sclerosis in various clinical studies [15-17]. More recently, studies have revealed that MSCs could be effective for the treatment of AD [18, 19]. Particularly, our previous study demonstrated that subcutaneous administration of hUCB-MSCs can efficiently alleviate AD in an experimental mouse model through the production of multiple soluble factors in response to AD-specific biomarkers including interleukin (IL)-4, a dominant cytokine produced by Th2 cells in AD progression [18]. In the study, AD-induced higher levels of serum IgE, and mast cell degranulation were remarkably suppressed by the administration of hUCB-MSCs. To prove that our findings can be successfully applied in a clinical trial, we aimed to evaluate the safety and therapeutic efficacy of FURESTEM-AD, a stem cell therapeutic derived from human umbilical cord blood, to improve symptoms related with moderate-to-severe AD.

Study design and oversight
This phase 1 study was an open-label, dose escalation trial to evaluate the safety of hUCB-MSCs against moderate-to-severe AD over a 4-week period. The phase 2a study was an open-label, double-blind, randomized controlled trial to assess the efficacy and safety of hUCB-MSCs over a 12-week period. These trials were performed between November 2013 and May 2015 at the Department of Dermatology in Seoul St. Mary’s Hospital. Participants were evaluated every 2 weeks after a subcutaneous administration of hUCB-MSCs at two different doses (low dose; 2.5 x 10⁷ cells or high dose; 5.0 x 10⁷ cells). Clinical-grade hUCB-MSCs were produced according to standard operating procedures under good manufacturing practice condition. This study was approved by the Institutional Review Board of the Catholic University of Korea and was performed in accordance with Good Clinical Practice and the Declaration of Helsinki. Full protocols, detailed methods and strategies for evaluation and statistical analyses are provided in the Supplement 1 and 2.

Participants
For two phase 1/2a studies, 34 participants (7 for phase I and 27 for phase IIa) based on Hanifin and Rajka’s criteria [20] were selected in accordance with inclusion and exclusion criteria (Table S1 in Supplement 1). We enrolled participants with frequent recurrence of AD symptoms not adequately controlled with topical corticosteroids or systemic immunosuppressants. Briefly, major inclusion criteria included patients with moderate to severe AD (SCORAD > 20), ages ≥ 20 years and ≤ 60 years, persistent symptoms (≥ 6 months). Patients were on concurrent medications, including antihistamines, low potent topical steroid (Desonide, 0.05%, class 6) and emollients not containing corticosteroids, during the treatment with hUCB-MSCs and follow-up. Once enrolled, patients were closely monitored at their routine visits: every week up to 4 weeks for phase 1 study and every 2 weeks up to 12 weeks for phase 2a study. All patients were observed for 30 minutes after an injection. Two doses of MSCs were given subcutaneously in participants (phase 1; 3 with a low dose and 4 with a high dose, phase 2a; 14 with a low dose and 12 with a high dose). All participants (20-60 years old) provided an informed consent agreement before entry into the study. At every study visit, severity of AD was assessed by means of scoring parameters.
Randomization
In the phase 1 study, participants were assigned to treatment group in consecutive order on their visit without randomization procedures. In the phase 2a study, participants were randomly assigned (1:1) to receive single treatment of hUCB-MSCs at a low or high dose. A randomization list was generated by a statistician using a randomization program of a SAS system before initiating the clinical trial.

Outcomes
Efficacy
The end point for efficacy was a mean relative reduction in the severity of AD at week 12 evaluated by an Eczema Area and Severity Index (EASI, score range from 0 to 72) [21], Investigator’s Global Assessment (IGA, from 0 to 5) and Scoring Atopic Dermatitis (SCORAD, from 0 to 103) [22]. An additional outcome parameter was the number of participant showing more than 50% reduction in EASI or SCORAD score. Assessments of subjective and objective changes were conducted at every visit by the same investigator. Briefly, these assessments included a full physical examination, vital sign, investigation of concurrent medication, and a blood test.

Safety
During the entire clinical trial period, adverse events or adverse drug events reported by participants or noted by the investigator were documented. The number and severity of adverse events were examined at each visit.

Biomarker evaluations
In the phase 2a study, total serum IgE levels were evaluated in all patients at the first visit (within 1 week before baseline visit) and at week 12 after the hUCB-MSC administration. The number of eosinophils in the blood was assessed at week 0, 2, 4, 8 and 12.

Statistical analyses
Descriptive statistics were used for demographics, clinical characteristics and safety variables. To compare the statistical significance in the occurrence of adverse events between the two dosage groups, a Chi-square or Fisher’s exact test were used with a 95% confidence interval. Considering the exploratory nature of this trial, all the evaluations were conducted in the set of patients without relevant protocol deviations (per protocol [PP] set). A paired t-test was performed to assess the statistical significance of the relative and absolute change in scores compared to the score documented at the baseline visit. A Fisher’s exact test was conducted to determine the statistical significance of the number of participant showing more than a 50% reduction in EASI or SCORAD score between the two dosage groups at the 95% exact confidence interval. For an efficacy assessment, when a participant missed a visit, relevant data were set to missing without imputation. This trial is registered with ClinicalTrials.gov, number NCT01927705.

RESULTS
Participants
Of the 34 enrolled participants, 31 completed the study (Figure 1). The three cases of withdrawal from the study had nothing to do with adverse events. The demographic and clinical characteristics of the participants assessed at baseline visit were similar between the two groups of different doses (Table 1).

Response to treatment
At week 12, the single administration of hUCB-MSCs demonstrated improvement from baseline in a visual comparison of AD symptoms, involving skin lesions on the neck, trunk, and legs of participants, compared to the baseline (Fig. 2A). Interestingly, the hUCB-MSC treatment resulted in a dose-dependent reduction in the EASI score (Fig. 2B, Table 2 and Fig. S1 in Supplemental Information 1). In particular, the infusion of high dose hUCB-MSCs (5.0 x 10⁷ cells) markedly reduced the EASI score, representing a reduction of 55% at week 12 (Table 2). Six (55%) patients in the high dose hUCB-MSC-treated group and five (36%) patients in the low dose (2.5 x 10⁷ cells)-treated group achieved an EASI-50 response (Fig 2C and Table 2). In addition, three (27%) patients in the high dose group reached an EASI-75 response. The percentage decrease in the EASI score during the whole period of study was consistently greater in the high dose group than in the low dose group. At week 12, a significant difference between high and low dose groups was observed (P = 0.0327, Fig 2B). While the injection of low dose hUCB-MSCs led to a slight reduction of the EASI score after marked reduction during first two weeks after injection, high dose hUCB-MSCs exerted a continuous, gradual therapeutic effect until week 12, resulting in a greater significant reduction by the end of study compared to week 2 (P = 0.0016, Fig 2B). Moreover, a significant improvement from baseline in the absolute EASI score was observed as early as week 4 in high dose-treated group (P = 0.028, Fig S1 in Supplemental Information 1). Similar responses were observed in the relative change of the IGA score (Fig 2D, Table 2 and Fig S2 in Supplemental Information 1). The low dose hUCB-MSC treatment as well as the high dose reduced the IGA score. The relative changes from the baseline IGA score were significant at week 12, achieving a 33% reduction in the high dose-treated group and 19% reduction in the low dose group (P < 0.001 for both groups, Fig 2D). Although reduction levels were similar between the two groups until week 6, only the high dose-treated group demonstrated continuous improvement, whereas the score in the low dose-treated group remained at a stable level till the end of the study (Fig 2D and Fig S2 in Supplemental Information 1). We also noted a significant reduction in the absolute IGA scores.

score as early as week 6 in both groups (P = 0.0111 for the low dose group and P = 0.0437 for the high dose group, Fig S2 in Supplemental Information 1).

In addition, the SCORAD score and its sub-category scores were consistently decreased in a dose-dependent manner. Particularly, in the high dose treated group, the intensity score for the AD lesion was reduced by 51%, pruritus score by 58% and insomnia score by 65% at week 12, resulting in a 50% reduction in the SCORAD score and 45% of the participants reaching SCORAD-50 efficacy (Fig 3A-F and Table 2). Of the sub-category scores in the SCORAD index, the extent criteria and intensity criteria exhibited significant differences between the two groups in their percentage change at week 12 (P = 0.0414 for extent criteria and P = 0.0077 for intensity criteria). Moreover, significant changes in the absolute SCORAD score were noted at week 2 in the high dose group (P = 0.0013) and at week 4 in the low dose group (P = 0.0274) (Fig S3 in Supplemental Information 1). The pruritus score was significantly reduced as early as week 2 and persisted until the end of the study follow-up with greater efficacy in the high dose group. These findings suggest that hUCB-MSCs can markedly and consistently improve AD symptoms in efficacy parameters in a dose-dependent manner and that their efficacy can be observed at the earliest visit after the administration with gradual and persistent effects in high dose-treated group.

**Biomarkers**

Importantly, along with an improvement in disease severity evaluated by multiple parameters, the treatment with hUCB-MSCs showed a consistent reduction in the level of crucial biomarkers. All the dosages of the hUCB-MSC administration down-regulated the levels of serum total IgE as well as blood eosinophil counts (Fig 4A and B). At weeks 8 and 12, the decrease in blood eosinophil number was significant in the high dose hUCB-MSC-treated group compared to the number recorded at the baseline visit (P = 0.0452 at week 8 and P = 0.0041 at week 12, Fig 4B).

**Safety**

No severe or serious adverse events were observed in this study. Most of the adverse events resulted from the study drug were local reactions evoked by administration site reactions, such as induration, bruising, erythema, or pain around the injection site (Table 3). One skin infection occurred in each dose group and only one gastrointestinal disorder was observed. These infectious or gastrointestinal adverse events were transient and mild in severity. There was no discontinuation due to adverse events (Table 3). Taken together, these safety assessment results indicate that the hUCB-MSCs were well tolerated in this study.

This is the first-in-class evaluation of a cell therapy in patients with AD. The single treatment of hUCB-MSCs in adults with moderate-to-severe AD demonstrated remarkable improvements in disease symptoms in the 12-week trials. The efficacy of hUCB-MSCs was consistently observed in various criteria assessed by different scoring parameters. Particularly, the hUCB-MSC treatment rapidly ameliorated pruritus, which directly contributes to an improvement in quality of life of AD patients. Moreover, in most of the assessments, the hUCB-MSC treatment had a dose-dependent therapeutic effect. The symptoms were improved during the first two weeks of the treatment regardless of the administered dosage. Particularly, after two weeks, patients treated with high dose hUCB-MSCs showed further improvement by the end of the study. These results strongly suggest that greater efficacy might be observed by applying higher dose or multiple infusions of hUCB-MSCs. Of the participants who responded to the survey via telephone, 12 out of 16 patients indicated their intention to receive repeated hUCB-MSC therapy. They reported that the treatment seemed to be effective in reducing pruritus and insomnia shortly after the administration of study drug.

Despite the recent advances in the development of therapies for allergic diseases including AD, most of the treatments so far are limited, not uniformly effective and often accompanied by adverse reactions or inconvenience. Therefore, physicians are trying to find new effective and safe drug for controlling symptoms of patients with moderate to severe AD. More recently, dupilumab, a human monoclonal antibody that blocks IL-4 and IL-13, was reported to be remarkably effective against moderate to severe AD, with 85% of the patients reaching EASI-50 criteria in the 12 week study [23, 24]. In the study, all the study drugs were administered subcutaneously once a week, that is, 11 times in 12 week trial. Therefore, one can envision that it is difficult to compare the efficacy of dupilumab with the results from the present study. Moreover, while promising results using monoclonal antibody drugs have been reported in the treatment of immune disorders and cancer, clinical trials and research have found limitations related with the function and safety of these drugs. For example, unexpected clinical responses resulted from Fc receptor polymorphisms or the recruitment of effector cells into target tissue can be associated with differing outcomes [25]. In addition, monoclonal antibodies have been reported to have various modes of actions in vitro, leading to an unclear action once administered into patients [26]. Therefore, the safety and efficacy of dupilumab should be further confirmed in long-term follow-up studies.

MSCs, the major stem cells in the field of cell therapy, have been used in the clinic for more than 10 years. To date, MSCs for cell therapy have been proven to be safe [15, 17, 27, 28]. In this study, no serious adverse events...
or exclusion from the PP due to adverse events occurred. Moreover, few adverse events were observed. Mainly mild and transient events occurred that were related with injection site responses. Furthermore, a long-term follow-up study of 34 participants who received medicinal drug in the present study will be conducted up to 3 years to secure the long-term safety of allogeneic stem cells including oncogenicity. One of the major hurdles in stem cell therapy is not understanding the exact mechanisms by which injected cells might exert their efficacy against a target disease. Several candidate factors have been suggested as a key factor against immune-related diseases [29-32]. However, findings from our previous study elucidated the precise mechanisms of hUCB-MSC administration, representing a concerted action of two crucial factors from hUCB-MSCs: prostaglandin E2 (PGE2) and transforming growth factor (TGF)-β1, to regulate the degranulation of mast cells [18]. Moreover, in the study, we demonstrated that a subcutaneous route of hUCB-MSC injection can be more effective than an intravenous route to reduce gross and histological signatures of AD in mouse model. These findings led us to conduct the present study using subcutaneous route for the administration of hUCB-MSCs. In the present study, we proved that a subcutaneous administration of hUCB-MSCs can be successfully used for the treatment of AD and is well tolerated without any safety issues.

The limitations of our pilot studies are the small number of patients, the lack of a placebo group and its open label design. Because of the small size of these trials, some of the crucial effects could not reach the significance. Notably, changes in IgE level after hUCB-MSC administration were not significant. Next large 2b/3 phases are planned to make up for current limitations with the large number of patients (planned as 276) and placebo arm. Moreover, further studies are under way to be designed to correlate our previous mechanistic findings with clinical efficacy because the underlying mechanisms of hUCB-MSC efficacy against AD might involve other subsets of immune responses including various helper T cell subtypes as well as mast cell regulation.

### References


### Conclusion

In conclusion, this study is the first-in-class clinical trial demonstrating that adults with moderate to severe AD responded to stem cell treatment using hUCB-MSCs, regardless of HLA match, without noteworthy adverse events.

### Acknowledgments

Funding/Support This study was sponsored by Kangstem Biotech.

### Role of the Funder/Sponsor

The sponsor of the study had no role in the analysis or interpretation of the data. The sponsor made some contributions toward the study design and the decisions without interfering with data interpretation.

### Conflicts of Interest Disclosures

K-HR and K-SK belong to Kangstem Biotech, a biotechnology company in the area of stem cell therapeutics. The other authors declare that they have no conflicts of interest.

### Author Contributions


Figure 1. Flowchart of Phase I and IIA trials
MSCs indicates mesenchymal stem cells

Tae-Yoon Kim, Figure 1
Figure 2. Changes in disease severity and efficacy end points by hUCB-MSC treatment
(A) Comparison of the symptoms of the participants before and after treatment. (B) Percent change in EASI score compared to baseline was measured. (C) Proportion of participants who had 50% improvement in EASI score (EASI-50) was measured. (D) Percent change in IGA score compared to baseline was assessed. * P<0.05, ** P<0.01, *** P<0.001. Results are shown as mean ± SE.
Figure 3. Change in SCORAD index by hUCB-MSC treatment
(A-E) Percent changes in SCORAD score and sub-category score were measured. Percent changes in (A) extent criteria, (B) intensity criteria, (C) pruritus score, (D) insomnia score, and (E) total SCORAD score were assessed. (F) Proportion of participants who had 50% improvement in SCORAD score (SCORAD-50) was measured. * P<0.05, ** P<0.01, *** P<0.001. Results are shown as mean ± SE.
Figure 4. Changes in biomarkers by hUCB-MSC treatment
(A) Total IgE level in serum was measured at screening and last visits. (B) Percent change in blood eosinophil count was calculated. * P<0.05, ** P<0.01. Results are shown as mean ± SE.
Table 1. Demographic and clinical characteristics of the participants at baseline. *

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Dosage 2.5 x 10^7 MSC</th>
<th>Dosage 5.0 x 10^7 MSC</th>
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<tr>
<td>number</td>
<td>14</td>
<td>11</td>
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<tr>
<td>age-yr</td>
<td>29.07 ± 2.03</td>
<td>28.03 ± 1.07</td>
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<tr>
<td>male number (%)</td>
<td>64.29</td>
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<tr>
<td>EASI score†</td>
<td>20.54 ± 3.97</td>
<td>19.60 ± 2.30</td>
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<tr>
<td>IGA score‡</td>
<td>3.786 ± 0.16</td>
<td>3.909 ± 0.21</td>
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<tr>
<td>SCORAD score¶</td>
<td>61.17 ± 4.11</td>
<td>65.48 ± 3.37</td>
</tr>
<tr>
<td>Pruritus score¶</td>
<td>7.00 ± 0.54</td>
<td>6.18 ± 0.89</td>
</tr>
</tbody>
</table>

* Values are mean ± SE.
† Scores on the Eczema Area and Severity Index (EASI) range from 0 to 72, with higher scores indicating greater severity.
‡ The investigator’s global assessment of the severity of atopic dermatitis was scored on a scale of 0 (clear) to 5 (very severe).
¶ SCORAD scores range from 0 to 103, with higher scores indicating greater severity.
∥ Scores on the pruritus score range from 0 (no itch) to 10 (worse imaginable itch).
### Table 2. Efficacy End Points.*

<table>
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<tr>
<th>End point</th>
<th>Dosage</th>
<th>2.5 x 10^7 MSC</th>
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<tr>
<td>number</td>
<td>14</td>
<td>11</td>
<td>25</td>
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</tr>
</tbody>
</table>

≥ EASI-50
- number of patients (%)†
  - Week 2 0 (0) 1 (9) 1 (4)
  - Week 6 4 (29) 5 (46) 9 (35)
  - Week 12 5 (36) 6 (55) 11 (44)

Change in EASI score (%)
  - Week 2 -16.45 ± 4.42 † † -27.55 ± 4.74 † † -21.33 ± 3.36 † †
  - Week 6 -17.57 ± 10.52 † † -40.34 ± 6.75 † † -27.59 ± 6.87 † †
  - Week 12 -25.81 ± 11.27 † † -55.02 ± 5.83 † † -38.66 ± 7.31 † †

Change in IGA score (%)
  - Week 2 -8.93 ± 3.32 † † -13.64 ± 5.18 † † -11.00 ± 2.92 † †
  - Week 6 -15.95 ± 4.77 † † -18.48 ± 5.00 † † -17.07 ± 3.40 † †
  - Week 12 -18.69 ± 5.03 † † -33.03 ± 6.61 † † -25.00 ± 4.22 † †

≥ SCORAD-50
- number of patients (%)†
  - Week 2 0 (0) 1 (9) 1 (4)
  - Week 6 1 (7) 4 (36) 5 (20)
  - Week 12 3 (21) 5 (45) 8 (32)

Change in SCORAD score (%)
  - Week 2 -22.03 ± 3.84 † † -33.06 ± 4.21 † † -26.89 ± 2.99 † †
  - Week 6 -22.43 ± 5.43 † † -38.11 ± 5.35 † † -29.33 ± 4.09 † †
  - Week 12 -28.04 ± 6.20 † † -49.97 ± 4.33 † † -37.80 ± 4.33 † †

Change in pruritus score (%)
  - Week 2 -31.25 ± 7.02 † † -47.42 ± 11.83 † † -38.37 ± 6.58 † †
  - Week 6 -27.10 ± 9.94 † † -51.03 ± 8.56 † † -37.83 ± 7.02 † †
  - Week 12 -33.47 ± 11.15 † † -57.55 ± 7.41 † † -44.07 ± 7.33 † †

Change in insomnia score (%)
  - Week 2 -39.44 ± 9.23 † † -65.44 ± 8.91 † † -50.98 ± 6.88 † †
  - Week 6 -25.30 ± 20.54 † † -61.28 ± 10.87 † † -41.13 ± 12.78 † †
  - Week 12 -36.63 ± 21.43 † † -65.28 ± 10.79 † † -49.23 ± 13.01 † †

* Values are mean ± SE.
† EASI-50 and SCORAD-50 represent reduction of 50% in the EASI score and SCORAD score, respectively.
† P<0.05 for the comparison with baseline
†† P<0.001 for the comparison with baseline
### Table 3. Adverse Events

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<tr>
<td>Any adverse event – no. of patients (%)</td>
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<tr>
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<tr>
<td>General disorders and administration site conditions</td>
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<td>Gastrointestinal disorders</td>
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<td>Serious adverse event – no. of patients</td>
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<td>Study discontinuation due to adverse event – no. of patients</td>
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<tr>
<td>Skin infection – no. of patients (%)</td>
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