

Received Date : 28-Jun-2016

Revised Date : 02-Mar-2017

Accepted Date : 15-Mar-2017

Article type : Original Article

Efficacy and Safety of Ustekinumab in Japanese Patients with Severe Atopic Dermatitis: A Randomised, Double-Blind, Placebo-Controlled, Phase 2 Study

H. Saeki¹, K. Kabashima², Y. Tokura³, Y. Murata⁴, A. Shiraishi⁴, R. Tamamura⁴,
B. Randazzo⁵, K. Imanaka^{4*}

¹Department of Dermatology, Nippon Medical School, Japan; ²Department of Dermatology, Kyoto University Graduate School of Medicine, Kyoto, Japan; ³Department of Dermatology, Hamamatsu University School of Medicine, Hamamatsu, Japan; ⁴Janssen Pharmaceutical K.K., Tokyo, Japan; ⁵Immunology, Janssen Research & Development, LLC, Spring House, PA, USA.

***Corresponding Author**

Dr. Keiichiro Imanaka
Janssen Pharmaceutical K.K.,
Tokyo, Japan
Telephone: +81 80 8443 9373
Fax: +81 3 4411 5086
Email: kimanaka@its.jnj.com

Running Title: Ustekinumab in patients with severe atopic dermatitis

Funding sources: This study was funded by Janssen Pharmaceutical K.K., Tokyo, Japan.

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/bjd.15493

This article is protected by copyright. All rights reserved.

Conflicts of interest: Yoko Murata, Ayako Shiraishi, Ryo Tamamura and Keiichiro Imanaka are employees of Janssen Pharmaceutical K.K, Japan. Bruce Randazzo is an employee of Janssen Research & Development, LLC, USA. Hidehisa Saeki is a consultant for Janssen Pharmaceutical K.K, Japan. Kenji Kabashima and Yoshiki Tokura declare no conflict of interest.

Authors' contributions: Drs. Saeki, Kabashima, Tokura were involved in conception and design of the study, acquisition of data, interpretation of data and critical revision of the manuscript. Drs. Imanaka, Tamamura, Murata, Randazzo were involved in conception and design of the study, interpretation of data and drafting the manuscript. Dr. Shiraishi was involved in analysis of data, interpretation of data and critical revision of the manuscript. All authors contributed to the development of the manuscript and approved the final manuscript for submission. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

What is already known about this topic?

- There are reports suggesting the involvement of Th17 cells in the pathogenesis of atopic dermatitis (AD)
- Several case studies have reported therapeutic benefits of ustekinumab in patients with severe AD, while few studies have failed to show the benefits.

What does this study add?

- Ustekinumab 45 mg and 90 mg did not demonstrate meaningful efficacy in Japanese patients with severe AD.
- Ustekinumab treatment was generally well-tolerated in Japanese patients with severe AD.

Summary

Background: Ustekinumab, a fully human monoclonal antibody against interleukin-12/23, may be potentially effective for severe atopic dermatitis (AD) treatment.

Objectives: To evaluate efficacy and safety of ustekinumab 45 mg and 90 mg in severe AD patients.

Methods: In this placebo-controlled, randomised, phase 2 study, adult Japanese patients (aged 20–65 years) with severe or very severe AD entered a 12-week double-blind treatment period to receive (1:1:1) ustekinumab 45 mg, 90 mg or placebo subcutaneous injections at weeks 0 and 4; follow-up until week 24. Primary efficacy endpoint was percent change from baseline in Eczema Area and Severity Index (EASI) score at week 12. Major secondary efficacy endpoints: proportion of patients achieving EASI-50, EASI-75, Investigator's Global Assessment score 0-1, change from baseline Atopic Dermatitis Itch Scale and Dermatology Life Quality Index, all at week 12.

Results: 79 patients were randomised (ustekinumab 45 mg: n=24, 90 mg: n=28, placebo: n=27). Ustekinumab treatment showed nonsignificant improvement in least-square mean change from baseline EASI score at week 12 (45 mg: –38.2%, 95% confidence interval [CI] –21.02; 19.51, $p<0.94$ and 90 mg: –39.8%, 95% CI, –21.84; 17.14, $p<0.81$) versus placebo (–37.5%). Nonsignificant improvement in major secondary efficacy endpoints was also observed in both ustekinumab groups versus placebo. The most common (>2 patients) treatment-emergent adverse events were nasopharyngitis (similar incidence among all groups); and worsened AD (higher in placebo vs ustekinumab groups).

Conclusion: Ustekinumab at 45 mg and 90 mg did not demonstrate meaningful efficacy in Japanese patients with severe AD. The treatment was generally well-tolerated.

Key words: atopic dermatitis, interleukin-12, interleukin-23, ustekinumab

Introduction

Atopic dermatitis (AD), is a common, chronic or chronically relapsing inflammatory skin disease, which is characterised by pruritus, eczematous lesions and xerosis (dry skin) that has a worldwide prevalence of 15–20% in children and 1–3% in adults.¹⁻⁴ In Japan, AD is the second most common skin disease observed in dermatology clinics⁵ and the lifetime prevalence rate of AD in all ages was found to be 3.3%.⁶

AD is believed to be driven through type 2 helper T-cell (Th2)-mediated immune response. During the chronic phase of the disease, a switch towards Th1-mediated immune response occurs and interleukin (IL)-12 promotes the differentiation of Th1 cells.⁷⁻¹¹ Besides Th1/Th2 cell responses, evidences suggest the involvement of Th17 cells in the pathogenesis of AD.¹²⁻

¹⁴ The key factors that promote Th17 differentiation are transforming growth factor- β 1 and IL-6, while IL-23 stimulates proliferation and survival.¹⁵ Th17 are associated with production of various inflammatory cytokines, including IL-17A, IL-17F, IL-21 and IL-22. Therefore, down regulation of IL-23 and IL-12 appear to be a potential target for the treatment of AD.¹²

Ustekinumab, a fully human immunoglobulin (Ig) G1 monoclonal antibody that binds to the shared p40 subunit of IL-12 and IL-23, is approved for the treatment of moderate-to-severe plaque psoriasis.^{16,17} Ustekinumab regulates Th1 and Th17 pathway by blocking IL-12 and IL-23, and therefore could be a good potential therapeutic option for patients with AD. Case studies are reported for the potential effect of ustekinumab in patients with severe refractory AD and who had inadequate response with prior treatments.^{18,19} Patients who received ustekinumab 45 mg reported substantial improvement in the disease condition, especially pruritus. Based on these case studies, this phase 2 study was conducted to demonstrate proof-of-concept for ustekinumab in the treatment of AD.

Methods

Patients

Adult Japanese patients (20–65 years of age) were eligible if they had severe or very severe active AD (Rajka-Langeland score of 8–9; Eczema Area and Severity Index [EASI] ≥ 12 and Investigator's Global Assessment [IGA] 4 or 5), including chronic or chronically relapsing course with presence of pruritus and eczematous changes in a typical distribution; had an onset before the age of 13 years and were diagnosed as per the criteria defined by the Japanese Dermatological Association.²⁰ Patients who had inadequate response to or were not willing to use topical corticosteroids, topical calcineurin inhibitors and/or phototherapy were also included.

Patients were ineligible if they had any other skin conditions that could interfere with the assessment of AD, history of any malignancy (except for basal cell and squamous cell carcinoma), serious infections or herpes zoster within 2 months from screening, or prior treatment with biologic agents targeting IL-12 or IL-23 (like ustekinumab, briakinumab, guselkumab or MK-322, etc), or any other marketed biologic agents within 3 months, or an experimental biologic therapy within 6 months from randomisation.

All patients who participated in the study provided written informed consent. The study was approved by institutional review boards and was conducted in accordance with the Declaration of Helsinki, International Conference on Harmonization and Good Clinical Practice guidelines.

Study design

This phase 2, randomised, double-blind, placebo-controlled, parallel-group study was conducted at 15 outpatient dermatology clinics in Japan between September 2013 and December 2014. The study consisted of a screening period (up to 42 days), a double-blind treatment period (week 0–12) and a follow-up period (week 12–24). Eligible patients were randomised (1:1:1) to receive ustekinumab 45 mg, 90 mg or placebo by subcutaneous injection at weeks 0 and 4. The study randomisation, based on a computer-generated randomisation schedule, was balanced using permuted blocks. All patients, investigators and the study sponsor were blinded to treatment allocation and the blinding was maintained until all patients completed the study and the database was locked. Patients were allowed to use the following medications during the study: topical corticosteroids (except of strongest potency), topical calcineurin inhibitors, emollients, antileukotriene therapies, or topical or oral herbal preparations, but the dosage had to be stable for at least 4 weeks prior to randomisation. The dose and dosing regimen of topical corticosteroids or topical calcineurin inhibitors could be reduced or discontinued after week 4 if the patient's skin condition improved and the investigator deemed it appropriate that AD was unlikely to worsen by reduction or discontinuation of these therapies; however restart or a dose increase of these therapies was not allowed until week 12 following their reduction or discontinuation.

Efficacy and safety evaluations

The efficacy parameters were evaluated through week 24. The severity of AD was assessed using EASI.²¹ Four body regions (head and neck, trunk, upper limbs and lower limbs) were assessed separately for erythema, infiltration/papulation, excoriation, and lichenification. The IGA, on a 6-point scale (0 = “clear” to 5 = “very severe disease”), was performed to measure AD severity based on morphology without referring back to the baseline state. The eczema-

related itching was assessed using Atopic Dermatitis Itch Scale (ADIS; 11-point scale: 0=“no itching at all” to 10=“worst possible itching”) as rated by patients daily during morning and evening. The DLQI (dermatology life quality index) a 10-item questionnaire was used to evaluate the impact of the disease on patients’ quality of life. Safety evaluations, including treatment-emergent adverse events (TEAEs), laboratory investigations, electrocardiogram, vital signs, physical examination, injection site reactions, and tuberculosis evaluation, were performed throughout the study. Serum samples were assessed for ustekinumab levels and for antibodies to ustekinumab at weeks 0, 12, and 24 using an electrochemiluminescence immunoassay method.

Study endpoints

The primary efficacy endpoint was the percentage change in EASI from baseline at week 12. The major secondary efficacy endpoints were evaluated at week 12 and included, proportion of patients achieving at least 50% improvement from baseline in EASI (EASI-50) and at least 75% of improvement from baseline in EASI (EASI-75), proportion of patients with an IGA score of 0 (clear) or 1 (almost clear) at week 12, proportion of patients achieving ≥ 2 points decreases in IGA at week 12, change from baseline of DLQI at week 12 and change from baseline in ADIS at week 12. Additional secondary endpoints were those evaluated at week 24 and included percentage change in EASI from baseline through week 24, proportion of patients achieving EASI-50 and EASI-75, IGA score of 0 (clear) or 1 (almost clear), proportion of patients achieving ≥ 2 points decreases in IGA at week 24, and changes from baseline in ADIS through week 24.

Biomarker evaluations

Pharmacodynamic response was assessed by evaluating change from baseline in the serum biomarkers. Total IgE, eosinophil cationic protein (ECP) and immunochemistry were assessed at weeks 0, 4 and 12, and thymus and activation-regulated chemokine (TARC) was assessed through week 24. Serum concentrations of cytokines such as IL-17A, IL-17F and IL-23 were analysed using an ultra-sensitive immunoassay system (Singulex, Inc., Alameda, CA) at weeks 0, 4 and 12 to evaluate its relevance to the biology of Th17 signalling. Additionally, 20 protein analytes (IL-1 α , IL-1B, IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, IL-12p40, IL-12p70, IL-13, IL-15, IL-16, IL-17A, granulocyte-macrophage colony-stimulating factor [GM-CSF], interferons [IFN]- γ , tumor necrosis factor [TNF]- α , TNF- β , and vascular endothelial growth factor [VEGF]) were measured at weeks 0, 4 and 12 using a Meso-Scale Discovery (MSD, Gaithersburg, MD) platform.

The DNA samples extracted from whole blood samples (10 mL) collected from all randomised patients on day 1 were analyzed via quantitative PCR Taqman assays for single-nucleotide polymorphism (R501X, 3321delA, S1695X, Q1701X, S2554X, S2889X, S3296X, and K4022X); and the relationship between ustekinumab response in severe AD and filaggrin variants was evaluated.

Statistical analysis

Based on a prior study conducted in Japanese patients with moderate AD,²² a sample size of 72 patients (24 patients per treatment group) was calculated to provide 90% power to detect a difference of $\geq 30\%$ point in the primary endpoint, i.e., percentage change in EASI from baseline at week 12 in both the ustekinumab groups vs placebo group, with an assumption of 28% standard deviation at 0.05 significance level (2-sided).

The continuous variables were analysed using the ANCOVA model, with treatment as a factor and baseline value as a covariate. The binary variables were analysed using Fisher's exact test. The biomarkers (measured using ultra-sensitive immunoassay system) were analysed to compare the change from baseline at week 12 using Mann-Whitney test. Data of 20 protein variants were log2 transformed and analysed using a nonparametric Mann-Whitney test. All tests were performed at a 0.05 significance level. Statistical comparisons were performed for primary or major secondary efficacy endpoints at week 12 only. Descriptive statistics were performed for the additional secondary efficacy endpoints through week 24; change in serum biomarkers, clinical laboratory test, and vital signs. Missing data were imputed using last observation carried forward (LOCF). Full analysis set (for efficacy analyses) were based on all randomised patients who received ≥ 1 administration of study treatment and had at least one assessment of EASI after treatment administration. Safety analysis set included all patients who received ≥ 1 administration of study treatment.

Results

Of 95 patients with severe and very severe AD who were screened, 79 were randomised to ustekinumab 45 mg (n=24), 90 mg (n=28) or placebo (n=27; Fig. 1). Total 3 patients discontinued the study due to withdrawal of consent (n=1 patient each, placebo and ustekinumab 90 mg) and TEAE (n=1 patient, ustekinumab 90 mg). One patient in ustekinumab 45 mg discontinued treatment due to TEAE, but completed the study. The demographics and baseline characteristics were generally comparable across the treatment groups, except for IgE levels (Table 1). A higher proportion of patients in both ustekinumab groups (combined: 55.8% [29/52]) had received prior systemic corticosteroid or cyclosporine therapy for AD than those in the placebo group (48.1% [13/27]). Prior exposure to medications for AD other than systemic corticosteroids was well balanced across the

treatment groups (Table 1). A total of 9 (11.4%) patients used potent topical corticosteroids as concomitant medication, 3 (3.8%) patients used moderately potent corticosteroids, 5 (6.3%) patients used mild topical corticosteroids, and one patient received tacrolimus topical in ustekinumab 90 mg group (Table S2).

Primary and major secondary efficacy endpoints

The mean percentage change from baseline in EASI score at week 12 (primary efficacy endpoint) was numerically greater, however not significant for the ustekinumab 45 mg (least square [LS] mean, -38.2%, 95% confidence interval [CI], -21.02; 19.51, $p < 0.94$) and 90 mg (LS mean, -39.8%, 95% CI, -21.84; 17.14, $p < 0.81$) groups versus placebo (-37.5%; Table 2).

The difference in proportion of EASI-50 and EASI-75 responders at week 12 was not significant for ustekinumab groups versus placebo (Table 2). None of the patients achieved an IGA score of 0 (clear) or 1 (almost clear) at week 12. A total of 7 patients in each group achieved a ≥ 2 point decrease in IGA from baseline at week 12 (Table 2).

The LS mean change from baseline at week 12 in ADIS (morning and evening) score was not significant, but numerically greater with only ustekinumab 90 mg versus placebo (Table 2).

The ADIS impact of itching on sleep at night was numerically reduced with ustekinumab 90 mg when compared with placebo at week 12 (mean change, -0.4 vs -0.2), whereas no improvement was observed with ustekinumab 45 mg (mean change, -0.05). The LS mean reduction from baseline in DLQI total score at week 12 was numerically greater in the ustekinumab 45 mg (-1.7) and 90 mg (-1.6) groups, but not significant when compared with the placebo group (-0.7).

Additional secondary efficacy endpoints

The mean percentage improvement from baseline in EASI was greater with ustekinumab 90 mg versus placebo and the improvement was maintained from week 12 (41% vs 38%) through week 24 (46% vs 36%). However, improvement with ustekinumab 45 mg was comparable with placebo from week 12 (39%) through week 24 (39%; Fig. 2a). The proportion of EASI-50 and EASI-75 responders at week 24 was higher with ustekinumab 45 mg and 90 mg versus placebo (Fig. 2b, 2c). Mean percent change from baseline in EASI sign score showed a greater response with ustekinumab 90 mg (Table S1). Four patients achieved an IGA score of 1 (almost clear) and none of the patients achieved an IGA score of 0 (clear) at end of the study. At week 24, 4 (17%) patients in ustekinumab 45 mg and 6 (22%) patients in 90 mg group achieved ≥ 2 point decrease in IGA from baseline versus 3 (12%) patients in placebo (Fig. 2d).

Of 51 patients who had at least one evaluable sample obtained after ustekinumab (45 or 90 mg) administration, 3 (6%) tested positive for antibodies to ustekinumab. The titre was 1:400 in 1 patient in the 45-mg group at week 24; 1:50 and 1:1600 in 1 patient in the 45 mg group at week 12 and week 24, respectively; and 1:100 in 1 patient in the 90 mg group at week 24.

Biomarkers

A total of 9/79 (11.4%) patients had filaggrin gene mutations: 4 in the ustekinumab 45 mg group (S2554X [2 patients], R501X and K4022X [1 patient each]), 1 in the ustekinumab 90 mg group (R501X and 3321delA) and 4 in the placebo group (S2554X [2 patients], 3321delA and K4022X [1 patient each]), Table S3.

Treatment with ustekinumab 45 mg showed a reduction in median serum total IgE (–285 IU/mL) from baseline at week 12, while no reduction was observed with ustekinumab 90 mg treatment and placebo. The reduction in median ECP level at week 12 was similar between ustekinumab 90 mg (–3.80 µg/mL) and placebo (–3.70 µg/mL) groups, and was higher than ustekinumab 45 mg group (–2.45 µg/mL). The reduction in baseline median TARC levels from week 2 till week 20 was highly variable in all the treatment groups (Fig. 3). However, at week 24, a greater reduction in the median TARC levels was observed in both the ustekinumab dose groups (45 mg, –263.5 pg/mL and 90 mg, –208.0 pg/mL), while it was increased in the placebo group (+19.5 pg/mL). No consistent trend was observed in median TARC levels reduction in any treatment group through week 24 (Fig. 3).

The ustekinumab 45 and 90 mg treatment significantly increased serum concentration of IL-12 p40 (>5.9 fold change) and IL-12 p70 (>1.8 fold change) at week 4 and 12 (Fig. S1).

Concentration of IL-17A marginally increased (17%–51%) with the treatment from baseline at week 4 and 12. However, serum concentration of IFN-γ slightly decreased from baseline to week 4 and 12 (Fig. S1). No difference was observed in serum concentrations of other cytokines between treatment groups at both the time points. In patients with filaggrin mutations, although the number affected was small, there was no difference observed in cytokine levels in response to treatment at both week 4 and week 12 (Table S3); and also when compared with patients without mutations (Fig. S1 and S2).

In the set of cytokines measured using the Singulex ultra-sensitive immunoassay platform, a significant increase in ratios of IL-23 level at week 4 and 12 from baseline was observed with ustekinumab 90 mg versus placebo ($p=0.016$ by Mann-Whitney test; Fig. S3). At week 12 in ustekinumab 90 mg group, in 7 of 27 samples, the increase in IL-23 level was >1.5-fold

higher than the baseline level, but one sample showed a large increase (9.2-fold at week 12 and 1.6-fold at week 4). The ratio of IL-17A and IL-17F levels at week 4 and 12 versus baseline was similar across the treatment groups.

Safety

The proportion of patients with any TEAEs with ustekinumab 45 mg was 18/24 (75%) patients, 90 mg was 16/28 (57%) patients and with placebo was 20/27 (74%) patients. The most frequent TEAEs (occurring in >2 patients in any group) observed were: nasopharyngitis, with similar incidence in ustekinumab groups (45 mg: 6/24 [25%], 90 mg: 6/28 [21%]) and placebo group (7/27 [26%] patients); and worsened AD, which was comparatively greater in patients in placebo group (8/27 [30%]) compared with ustekinumab groups (45 mg: 4/24 [17%] and 90 mg: 3/28 [11%]), Table 3. One patient in the ustekinumab 45 mg group experienced a non-serious TEAE of erysipelas of mild severity on day 27 and discontinued treatment. On treatment with topical nadifloxacin on day 29, the event resolved 6 days after onset (day 32). One patient in the ustekinumab 90 mg discontinued study participation due to worsened AD. There were no reports of injection-site reactions, new malignancy, or active tuberculosis during the study. Furthermore, no deaths, serious TEAEs and no clinically relevant changes in vital signs and laboratory investigations were observed.

Discussion

In this study, ustekinumab treatment (45 mg and 90 mg) did not show clinically meaningful difference compared with placebo based on primary (change in EASI score) and major secondary efficacy outcomes (achievement of EASI-50, EASI-75, IGA score 0-1, change from baseline ADIS and DLQI, at week 12) in severe AD patients from Japan. At end of this

24-week study, the proportion of patients achieving ≥ 2 points decrease in IGA was numerically higher with ustekinumab than placebo. Ustekinumab was generally well-tolerated in patients with severe AD.

Pruritus or itching is one of the most common symptoms of AD and hence assessment of itch reduction is a prime factor for evaluating the efficacy of drugs for AD treatment. The eczema-related itching during morning and evening (ADIS) with ustekinumab treatment was comparable with placebo. However, the ADIS impact of itching on sleep at night was numerically improved with ustekinumab 90 mg. In four published case reports, ustekinumab 45 mg has shown overall improvement in severe refractory AD, particularly pruritus.^{18,19,23,24} However, the assessments differed from our study (Visual Analogue Scale for pruritus and the Scoring Atopic Dermatitis [SCORAD] index). In two cases, ustekinumab 45 mg showed an inadequate response in AD patients who were refractory to usual topical and systemic therapies.²⁵ Similarly, in a recent phase 2 study, treatment with ustekinumab showed nonsignificant improvement in clinical response compared with placebo, which corroborated the findings of the present study.²⁶

A confounding high placebo effect was observed in the present study, which might be due to the psychological effect of receiving injections and an improved compliance to concomitant medications. Similar results were observed in a recent phase 2 study, where higher than expected placebo effect was attributed to the use of background topical corticosteroids.²⁶

The rate of TEAEs with ustekinumab treatment was comparable with placebo. The safety findings of ustekinumab were consistent with previous psoriasis studies of ustekinumab, including a study in Japanese patients with moderate-to-severe plaque-type psoriasis.^{17,27,28}

The filaggrin gene polymorphism was observed in 9 of 79 (11.4%) patients, with most commonly reported variants being S2554X (n = 4) and 3321delA (n = 2). However, it was difficult to explore the relationship between ustekinumab response and filaggrin variants due to the small number of patients who had filaggrin mutation. Similar results were observed in another study conducted in Japanese patients with AD, in which 8 of 143 (5.3%) were identified with filaggrin mutations, including S2554X in 2 patients (1.4%) and 3321delA in 6 patients (4.2%).²⁹ No consistent trend in changes of the Th2 biomarkers, TARC, ECP and IgE were observed over the study period; hence, no correlation could be demonstrated with the severity measures of AD. The IL-12p40 and p70 serum biomarker levels were elevated after ustekinumab treatment, likely due to stabilisation with ustekinumab. Exploratory biomarkers (IL-17A, IL-17F, and IL-23) were evaluated to understand the relevance with the mechanism of Th17 signalling and IL-23. For IL-23, one sample showed high variability in serum concentration as a result of stabilisation with ustekinumab. The analysis did not indicate treatment-dependent effect on IL-17A and IL-17F levels. In addition, interpretation of IL-17F was challenging, as the changes from baseline could not be determined for samples that were at or below the lower limit of quantitation. The reduction in circulating levels of IL-17A and IL-17F cytokines, as seen in psoriasis patients, does not appear to be a feature in patients with AD, at least in the time points (12 weeks) evaluated in this study. There are also studies that postulate low expression of IL-17A and IL-17F in AD, suggesting a different disease mechanism from psoriasis.^{30,31} Future studies of targeting IL-17 will be helpful to better understand its role in AD. In order to further understand the role of IL-12/23 inhibition in the treatment of severe AD, skin biopsy samples from patients who consented in the study were collected and microarray analysis has been carried out. The results of skin biopsy performed in this study will be published as a separate report.

Possible limitations of the study include small sample size, short treatment duration and frequency of ustekinumab dosing (administered only twice during the study). In addition, the permitted use of concomitant topical steroids probably contributed to the high rates of response in the placebo group.

In conclusion, the present proof-of-concept study did not show a clinically meaningful efficacy improvement after treatment with ustekinumab 45 mg and 90 mg in patients with severe AD. No new safety signals were observed in the study and ustekinumab treatment was well-tolerated.

Acknowledgments: The authors thank the study participants without whom this study would never have been accomplished and also thank the investigators for their participation in the study. Authors also acknowledge Samuel DePrimo and Stanley Belkowski (Janssen Research & Development, LLC, USA) for providing biomarker analysis. The authors also thank Dr. Takayuki Ota for his contribution to this manuscript. Writing assistance was provided by Ramji Narayanan, ISMPP CMPP™ (SIRO Clinpharm Pvt. Ltd., Thane, India), funded by Janssen Pharmaceutical K.K., Japan and publication support was provided by Kenichiro Tsutsumi (Janssen Pharmaceutical K.K., Japan).

References

- 1 Leung DY, Bieber T. Atopic dermatitis. *Lancet* 2003; **361**: 151-60.
- 2 Akdis CA, Akdis M, Bieber T *et al.* Diagnosis and treatment of atopic dermatitis in children and adults: European Academy of Allergology and Clinical Immunology/American Academy of Allergy, Asthma and Immunology/PRACTALL Consensus Report. *Allergy* 2006; **61**: 969-87.

- 3 Nutten S. Atopic dermatitis: global epidemiology and risk factors. *Ann Nutr Metab*
2015; **66 Suppl 1**: 8-16.
- 4 Kabashima K. New concept of the pathogenesis of atopic dermatitis: interplay among
the barrier, allergy, and pruritus as a trinity. *J Dermatol Sci* 2013; **70**: 3-11.
- 5 Furue M, Chiba T, Takeuchi S. Current status of atopic dermatitis in Japan. *Asia Pac*
Allergy 2011; **1**: 64-72.
- 6 Muto T, Hsieh SD, Sakurai Y *et al*. Prevalence of atopic dermatitis in Japanese adults.
Br J Dermatol 2003; **148**: 117-21.
- 7 Grewe M, Walther S, Gyufko K *et al*. Analysis of the cytokine pattern expressed in
situ in inhalant allergen patch test reactions of atopic dermatitis patients. *J Invest*
Dermatol 1995; **105**: 407-10.
- 8 Leung DY, Boguniewicz M, Howell MD *et al*. New insights into atopic dermatitis. *J*
Clin Invest 2004; **113**: 651-7.
- 9 Nomura T, Kabashima K, Miyachi Y. The panoply of alphabetaT cells in the skin. *J*
Dermatol Sci 2014; **76**: 3-9.
- 10 Nakajima S, Kitoh A, Egawa G *et al*. IL-17A as an inducer for Th2 immune responses
in murine atopic dermatitis models. *J Invest Dermatol* 2014; **134**: 2122-30.
- 11 Noda S, Suarez-Farinas M, Ungar B *et al*. The Asian atopic dermatitis phenotype
combines features of atopic dermatitis and psoriasis with increased TH17
polarization. *J Allergy Clin Immunol* 2015; **136**: 1254-64.
- 12 Kikly K, Liu L, Na S *et al*. The IL-23/Th(17) axis: therapeutic targets for autoimmune
inflammation. *Curr Opin Immunol* 2006; **18**: 670-5.
- 13 Weaver CT, Hatton RD, Mangan PR *et al*. IL-17 family cytokines and the expanding
diversity of effector T cell lineages. *Annu Rev Immunol* 2007; **25**: 821-52.
- 14 Koga C, Kabashima K, Shiraishi N *et al*. Possible pathogenic role of Th17 cells for

- atopic dermatitis. *J Invest Dermatol* 2008; **128**: 2625-30.
- 15 Palmer MT, Weaver CT. Autoimmunity: increasing suspects in the CD4+ T cell lineup. *Nat Immunol* 2010; **11**: 36-40.
- 16 Dauden E, Santiago-et-Sanchez-Mateos D, Sotomayor-Lopez E *et al*. Ustekinumab: effective in a patient with severe recalcitrant generalized pustular psoriasis. *Br J Dermatol* 2010; **163**: 1346-7.
- 17 Leonardi CL, Kimball AB, Papp KA *et al*. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 76-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 1). *Lancet* 2008; **371**: 1665-74.
- 18 Puya R, Alvarez-Lopez M, Velez A *et al*. Treatment of severe refractory adult atopic dermatitis with ustekinumab. *Int J Dermatol* 2012; **51**: 115-6.
- 19 Fernandez-Anton Martinez MC, Alfageme Roldan F, Ciudad Blanco C *et al*. Ustekinumab in the treatment of severe atopic dermatitis: a preliminary report of our experience with 4 patients. *Actas Dermosifiliogr* 2014; **105**: 312-3.
- 20 Saeki H, Furue M, Furukawa F *et al*. Guidelines for management of atopic dermatitis. *J Dermatol* 2009; **36**: 563-77.
- 21 Hanifin JM, Thurston M, Omoto M *et al*. The eczema area and severity index (EASI): assessment of reliability in atopic dermatitis. EASI Evaluator Group. *Exp Dermatol* 2001; **10**: 11-8.
- 22 Murata Y, Song M, Kikuchi H *et al*. Phase 2a, randomized, double-blind, placebo-controlled, multicenter, parallel-group study of a H4 R-antagonist (JNJ-39758979) in Japanese adults with moderate atopic dermatitis. *J Dermatol* 2015; **42**: 129-39.
- 23 Shroff A, Guttman-Yassky E. Successful use of ustekinumab therapy in refractory severe atopic dermatitis. *JAAD Case Rep* 2015; **1**: 25-6.

- 24 Agusti-Mejias A, Messeguer F, Garcia R *et al.* Severe refractory atopic dermatitis in
an adolescent patient successfully treated with ustekinumab. *Ann Dermatol* 2013; **25**:
368-70.
- 25 Samorano LP, Hanifin JM, Simpson EL *et al.* Inadequate response to ustekinumab in
atopic dermatitis - a report of two patients. *J Eur Acad Dermatol Venereol* 2016; **30**:
522-3.
- 26 Khattri S, Brunner PM, Garcet S *et al.* Efficacy and safety of ustekinumab treatment
in adults with moderate-to-severe atopic dermatitis. *Exp Dermatol* 2016.
- 27 Igarashi A, Kato T, Kato M *et al.* Efficacy and safety of ustekinumab in Japanese
patients with moderate-to-severe plaque-type psoriasis: long-term results from a phase
2/3 clinical trial. *J Dermatol* 2012; **39**: 242-52.
- 28 Papp KA, Langley RG, Lebwohl M *et al.* Efficacy and safety of ustekinumab, a
human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 52-week
results from a randomised, double-blind, placebo-controlled trial (PHOENIX 2).
Lancet 2008; **371**: 1675-84.
- 29 Nomura T, Sandilands A, Akiyama M *et al.* Unique mutations in the filaggrin gene in
Japanese patients with ichthyosis vulgaris and atopic dermatitis. *J Allergy Clin*
Immunol 2007; **119**: 434-40.
- 30 Nograles KE, Suarez-Farinas M, Shemer A *et al.* Atopic dermatitis keratinocytes
exhibit normal T(H)17 cytokine responses. *J Allergy Clin Immunol* 2010; **125**: 744-6,
6 e1-6 e2.
- 31 Guttman-Yassky E, Lowes MA, Fuentes-Duculan J *et al.* Low expression of the IL-
23/Th17 pathway in atopic dermatitis compared to psoriasis. *J Immunol* 2008; **181**:
7420-7.

Supporting Information

Table S1. Percent change from baseline in EASI sign score through week 24 (Full analysis set)

Table S2. Summary of topical concomitant medication

Table S3. Response to treatment in patients with filaggrin mutation

Figure S1. Serum concentration of cytokines in response to treatment. (a) IL-12p40 (b) IL-12p70 (c) IL-17A (d) IFN γ

Figure S2. Serum concentration of cytokines in response to treatment in patients with filaggrin mutation. (a) IL-12p40 (b) IL-12p70 (c) IL-17A (d) IFN γ

Figure S3. Mean change from baseline in plasma levels of cytokines. (a) IL-17A (b) IL-17F (c) IL-23

Appendix. Supplementary Methods

Figure Legends

Figure 1. Patient disposition. *One patient in ustekinumab 90 mg group withdrew from study participation before week 4 treatment administration. †One patient in ustekinumab 45 mg discontinued the study treatment due to adverse event; however, the patient completed the study participation.

Figure 2. Efficacy endpoints through week 24 (Full analysis set) (a) Percentage change from baseline in EASI Score (b) Proportion of patients achieving EASI-50 (c) Proportion of patients achieving EASI-75 (d) Proportion of patients with IGA Score ≥ 2 points decrease. EASI, Eczema Area and Severity Index; EASI-50, Patients achieving at least 50% improvement from baseline in EASI score; EASI-75, Patients achieving at least 75% improvement from baseline in EASI score; IGA, Investigator's Global Assessment.

Figure 3. Reduction in median thymus and activation-regulated chemokine (TARC) levels through week 24 (Safety analysis set). TARC, Thymus and activation-regulated chemokine.

Table 1. Patient demographics and baseline characteristics (Full analysis set)

	Ustekinumab 45 mg (n=24)	Ustekinumab 90 mg (n=28)	Placebo (n=27)
Age (years), median (range)	38.5 (25–57)	34.0 (20–50)	30.0 (20–57)
Gender (men), n (%)	17 (71)	19 (68)	19 (70)
BMI (kg/m ²), mean (SD)	23.2 (3.50)	23.0 (3.81)	24.2 (5.86)
Duration of AD (years), mean (SD)	33.8 (9.02)	28.9 (9.50)	29.5 (10.17)
Age of onset of AD, n (%)			
<3 years	13 (54)	15 (54)	16 (59)
≥3 to <6 years	5 (21)	4 (14)	7 (26)
≥6 years	6 (25)	9 (32)	4 (15)
Measures of severity, n (%)			
Severe*	16 (67)	22 (79)	20 (74)
Very severe†	8 (33)	6 (21)	7 (26)
EASI score	38.0 (10.84)	36.5 (12.60)	37.4 (12.19)
<30, n (%)	5 (21)	9 (32)	8 (30)
≥30, n (%)	19 (79)	19 (68)	19 (70)
Baseline EASI score, mean (SD)	38.0 (10.84)	36.5 (12.60)	37.4 (12.19)
IGA, n (%)			
Severe (Score = 4)	21 (88)	24 (86)	22 (82)
Very severe (Score = 5)	3 (13)	4 (14)	5 (19)
ADIS (weekly average), mean (SD)			
Morning diary score	10.0 (4.62)	8.7 (3.75)	9.0 (3.78)
Evening diary score	11.2 (4.37)	9.5 (3.70)	10.4 (3.57)
IgE (IU/mL), median (range)	7455.0 (275–16000)	5575.0 (311–16000)	3860.0 (57–16000)
TARC (pg/mL), median (range)	2286.5 (402–11370)	1904.5 (306–20640)	1922.0 (218–7139)
ECP (µg/L), median (range)	19.8 (3.4–146.0)	15.9 (3.3–103.0)	19.4 (2.0–63.5)
Prior medication for AD, n (%)			
Systemic corticosteroids or cyclosporin	16 (67)	13 (46)	13 (48)
Topical corticosteroids ^{‡ 20}			
Very strong	23 (96)	26 (93)	27 (100)
Strong, medium, weak	22 (92)	26 (93)	26 (96)
Strongest	17 (71)	12 (43)	13 (48)
Topical calcineurin inhibitors	21 (88)	24 (86)	19 (70)
Phototherapy	6 (25)	9 (32)	7 (26)

AD, Atopic dermatitis; ADIS, Atopic Dermatitis Itch Scale by patient diary; BMI, Body mass index; EASI, Eczema Area and Severity Index; ECP, Eosinophil cationic protein; IGA, Investigator's Global Assessment; IgE, Immunoglobulin E; TARC, Thymus and activation-regulated chemokine.

*Severe: ≥10% but <30% skin involvement by severe eruption; †Very severe: ≥30% of body involvement by severe eruption; Severe eruption: primarily erythema, papules, erosion, infiltration and lichenification; ‡Potency of topical corticosteroids were classified based on guidelines for management of atopic dermatitis (Saeki H et al, 2009).

Table 2. Primary and major secondary efficacy assessments at week 12 (LOCF; full analysis set)

	Ustekinumab 45 mg (n=24)	P value (vs placebo)*	Ustekinumab 90 mg (n=28)	P value (vs placebo)*	Placebo (n=27)
Percentage change in EASI score	−38.2 (7.40)	0.94	−39.8 (6.86)	0.81	−37.5 (6.98)
No. of EASI-50 responders (%)	9 (38)	1.00	10 (36)	0.79	11 (41)
No. of EASI-75 responders (%)	2 (8)	0.67	5 (18)	1.00	4 (15)
IGA ≥2 points decrease	7 (29)	1.00	7 (25)	1.00	7 (26)
Change in ADIS (weekly average)					
Morning dairy score	−1.4 (0.62)	0.73	−2.8 (0.57)	0.18	−1.7 (0.58)
Evening dairy score	−1.6 (0.71)	0.67	−2.4 (0.64)	0.67	−2.0 (0.65)
DLQI	−1.7 (0.73)	0.304	−1.6 (0.68)	0.337	−0.7 (0.69)

*Analyzed using Fisher's exact test.

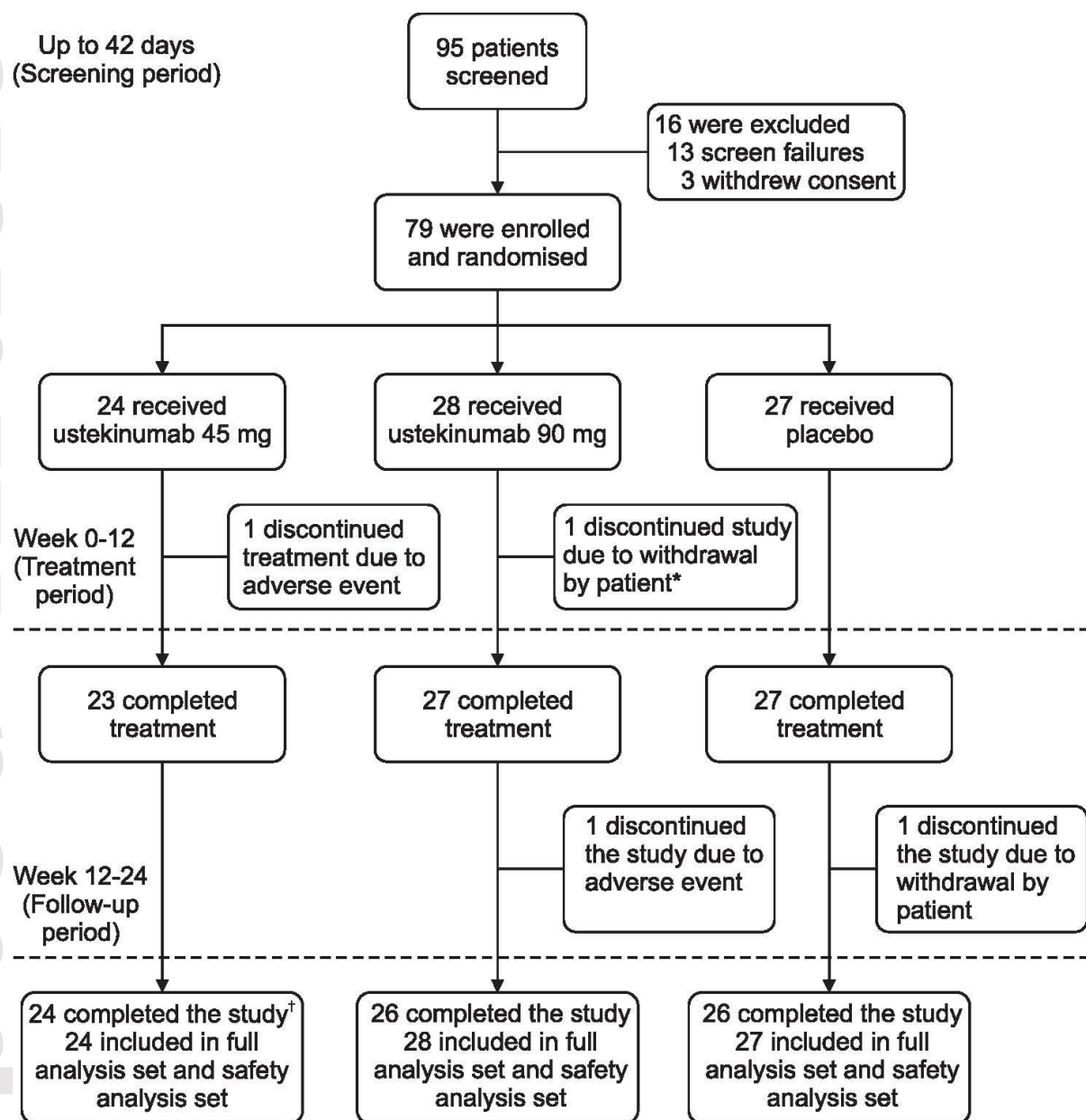
Data are LS mean (SE) unless otherwise specified. ADIS, Atopic Dermatitis Itch Scale; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; EASI-50, Patients achieving at least 50% improvement from baseline in EASI score; EASI-75, Patients achieving at least 75% improvement from baseline in EASI score; IGA, Investigator's Global Assessment; LOCF, Last observation carried forward.

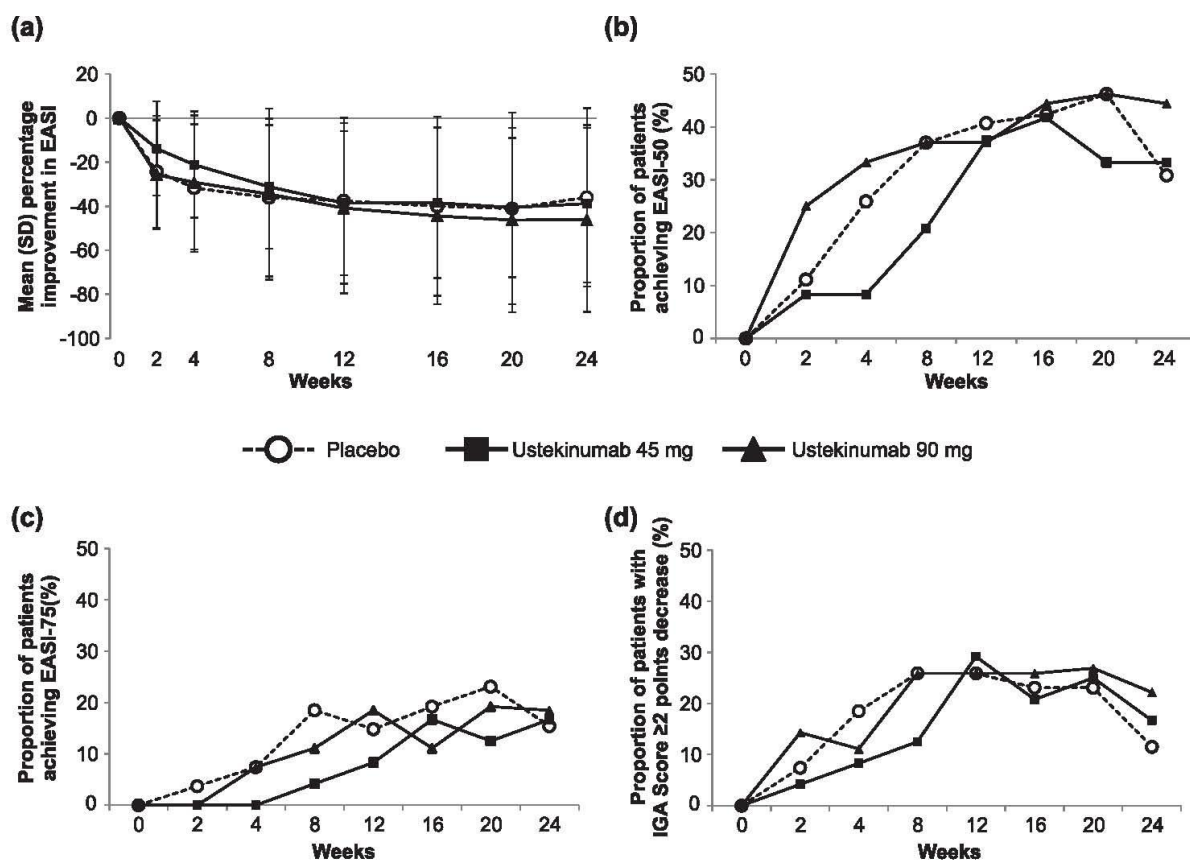
Table 3. Summary of adverse events (Safety analysis set)

N (%)	Ustekinumab 45 mg (N = 24)	Ustekinumab 90 mg (N = 28)	Placebo (N = 27)
Any TEAEs	18 (75.0)	16 (57.1)	20 (74.1)
Treatment-related TEAEs	6 (25.0)	7 (25.0)	4 (14.8)
Most Common TEAEs (>2 patients in any group)			
Nasopharyngitis	6 (25.0)	6 (21.4)	7 (25.9)
Worsened AD	4 (16.7)	3 (10.7)	8 (29.6)

AD, atopic dermatitis; TEAEs, treatment emergent adverse events.

Up to 42 days
(Screening period)





No. of patients	Weeks							
	0	2	4	8	12	16	20	24
Ustekinumab 45 mg	24	24	24	24	24	24	24	24
Ustekinumab 90 mg	28	28	27	27	27	27	26	27
Placebo	27	27	27	27	27	26	26	26

