Efficacy and safety of ustekinumab in Japanese patients with severe atopic dermatitis: a randomized, double-blind, placebo-controlled, phase II study

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Summary

Background Ustekinumab, a fully human monoclonal antibody against interleukin-12/23, may potentially be effective for severe atopic dermatitis (AD) treatment. Objectives To evaluate efficacy and safety of ustekinumab 45 mg and 90 mg in patients with severe AD.

Methods In this randomized, placebo-controlled, phase II study, Japanese patients (aged 20–65 years) with severe or very severe AD entered a 12-week double-blind treatment period during which they received (1 : 1 : 1) ustekinumab 45 mg, 90 mg or placebo subcutaneous injections at weeks 0 and 4, with follow-up until week 24. The primary efficacy end point was percentage change from baseline in Eczema Area and Severity Index (EASI) score at week 12. Major secondary efficacy end points included the 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.

Results A total of 79 patients were randomized [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 to 19.51; P < 0.94 and 90 mg: −39.8%, 95% CI −21.84 to 17.14; P < 0.81] vs. placebo (−37.5%). A nonsignificant improvement in major secondary efficacy end points was observed in both ustekinumab groups vs. placebo. The most common treatment-emergent adverse events were nasopharyngitis and worsened AD (higher in placebo vs. ustekinumab groups).

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

What’s already known about this topic?

- There are reports suggesting the involvement of T helper 17 cells in the pathogenesis of atopic dermatitis (AD).
- Several case studies have reported therapeutic benefits of ustekinumab in patients with severe AD, while a 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.
Atopic dermatitis (AD) is a common, chronic or chronically relapsing inflammatory skin disease, which is characterized by pruritus, eczematous lesions and xerosis (dry skin) and 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 for all age groups was found to be 3.3%.6 AD is believed to be driven through T helper (Th)2-cell-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.2,7–11 Besides Th1/Th2 cell responses, evidence suggests the involvement of Th17 cells in the pathogenesis of AD.12–14 The key factors that promote Th17 differentiation are transforming growth factor-β1 and IL-6, while IL-23 stimulates proliferation and survival.15 Th17 cells are associated with the production of various inflammatory cytokines, including IL-17A, IL-17F, IL-21 and IL-22. Therefore, downregulation of IL-23 and IL-12 appears to be a potential target for the treatment of AD.12

Ustekinumab, a fully human IgG1 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 the 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 have reported the potential effect of ustekinumab in patients with severe refractory AD and those who had inadequate response to 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 II study was conducted to demonstrate proof of concept for ustekinumab in the treatment of AD.

Patients and methods

Patients

Adult Japanese patients (20–65 years of age) were eligible if they had severe or very severe active AD (Rajka and Langeland index score of 8–9, Eczema Area and Severity Index (EASI) ≥ 12 and Investigator’s Global Assessment (IGA) score of 4 or 5], including a chronic or chronically relapsing course with the 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.10 We also included patients who had an inadequate response to, or were not willing to use, topical corticosteroids, topical calcineurin inhibitors and/or phototherapy.

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

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 (Clinical Trial Registration: NCT01945086).

Study design

This phase II, randomized, 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 randomized (1 : 1 : 1) to receive ustekinumab 45 mg, 90 mg or placebo by subcutaneous injection at week 0 and week 4. The study randomization, based on a computer-generated randomization 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 for those of strongest potency), topical calcineurin inhibitors, emollients, antileukotriene therapies, or topical or oral herbal preparations, but the dosage was required to be stable for at least 4 weeks prior to randomization. The dosage 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 following the reduction or discontinuation of these therapies; however, restart or a dosage 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, based 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 the 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 Dermatology Life Quality Index (DLQI), 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 end points

The primary efficacy end point was the percentage change in EASI from baseline at week 12. The major secondary efficacy end points were evaluated at week 12 and included the 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), the proportion of patients with an IGA score of 0 (clear) or 1 (almost clear) at week 12, the proportion of patients achieving ≥ 2-point decrease in IGA at week 12, the change from baseline of DLQI at week 12 and the change from baseline in ADIS at week 12. Additional secondary end points were those evaluated at week 24 and included the percentage change in EASI from baseline through week 24, the proportion of patients achieving EASI 50 and EASI 75, IGA score of 0 (clear) or 1 (almost clear), the proportion of patients achieving ≥ 2-point decrease 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 immunocomplex were assessed at weeks 0, 4 and 12, and thymus- and activation-regulated chemokine (TARC) was assessed throughout week 24. Serum concentrations of cytokines such as IL-17A, IL-17F and IL-23 were analysed using ultrasensitive immunoassay system (Singulex Inc., Alameda, CA, U.S.A.) at weeks 0, 4 and 12 to were analysed using an ultrasensitive immunoassay system. Total IgE, eosinophil cationic protein (ECP) and immunocomplex 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 ultrasensitive immunoassay system (Singulex Inc., Alameda, CA, U.S.A.) at weeks 0, 4 and 12 to were analysed using an ultrasensitive immunoassay system. The DNA samples extracted from whole blood samples (10 mL) collected from all randomized patients on day 1 were analysed via quantitative polymerase chain reaction 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, a sample size of 72 patients (24 patients per treatment group) was calculated to provide 90% power to detect a difference of ≥ 30% in the primary end point, i.e. percentage change in EASI from baseline at week 12 in both the ustekinumab groups vs. placebo group, with an assumption of 28% SD at 0.05 significance level (two-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 an ultrasensitive immunoassay system) were analysed to compare the change from baseline at week 12 using the Mann–Whitney U-test. Data for 20 protein variants were log2 transformed and analysed using a nonparametric Mann–Whitney U-test. All tests were performed at a 0.05 significance level. Statistical comparisons were performed for primary or major secondary efficacy end points at week 12 only. Descriptive statistics were performed for the additional secondary efficacy end points through week 24 (change in serum biomarkers, clinical laboratory test and vital signs). Missing data were imputed using last observation carried forward. The full analysis set (for efficacy analyses) was based on all randomized patients who received at least one administration of the study treatment and had at least one assessment of EASI after treatment administration. The safety analysis set included all patients who received at least one administration of study treatment. Further details regarding inclusion/exclusion criteria, sample size determination and prohibited treatments are available in Appendix S1 (see Supporting Information).

Results

Of 95 patients with severe and very severe AD who were screened, 79 were randomized to ustekinumab 45 mg (n = 24), 90 mg (n = 28) or placebo (n = 27) (Fig. 1). A total of three patients discontinued the study following withdrawal of consent (n = 1 patient each, placebo and ustekinumab 90 mg) and TEAE (n = 1 patient, ustekinumab 90 mg). One patient receiving ustekinumab 45 mg discontinued treatment as a result of a TEAE, but still 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: 56% (29 of 52)] had received prior systemic corticosteroid or ciclosporin therapy for AD.
than those in the placebo group [48% (13 of 27)]. Prior exposure to medications for AD other than systemic corticosteroids was well balanced across the treatment groups (Table 1). A total of nine patients (11%) used potent topical corticosteroids as concomitant medication; three patients (4%) used moderately potent corticosteroids, five patients (6%) used mild topical corticosteroids, and one patient received topical tacrolimus in the ustekinumab 90 mg group (Table S2; see Supporting Information).

**Primary and major secondary efficacy end points**

The mean percentage change from baseline in EASI score at week 12 (primary efficacy end point) was numerically greater; however, this was not significant for the ustekinumab 45-mg group [least square (LS) mean –38.2%, 95% confidence interval (CI) –21.02–19.51; P < 0.94] and 90-mg group (LS mean –39.8%, 95% CI –21.84–17.14; P < 0.81) vs. 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 vs. placebo (Table 2). None of the patients achieved an IGA score of 0 (clear) or 1 (almost clear) at week 12. A total of seven patients in each group achieved ≥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 was numerically greater only for ustekinumab 90 mg vs. 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 greater with 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 end points**

The mean percentage improvement from baseline in EASI was greater with ustekinumab 90 mg vs. placebo and the improvement was maintained from week 12 (41% vs. 38%) to week 24 (46% vs. 36%). However, improvement with ustekinumab 45 mg was comparable with placebo from week 12 (39%) to 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 vs. placebo (Fig. 2b, c). The mean percentage change from baseline in EASI sign score showed a greater response with ustekinumab 90 mg (Table S1; see Supporting Information). Four patients achieved an IGA score of 1 (almost clear) and none of the patients achieved an IGA score of 0 (clear) at the end of the study. At week 24, four patients (17%) receiving ustekinumab 45 mg and six patients (22%) in the 90-mg group achieved ≥2-point decrease in IGA from baseline vs. three patients (12%) in the placebo group (Fig. 2d).
Table 1 Patient demographics and baseline characteristics (full analysis set)

|                          | Ustekinumab 45 mg (n = 24) | Ustekinumab 90 mg (n = 28) | Placebo (n = 27) |
|--------------------------|-----------------------------|-----------------------------|------------------|
| Median age, years (range)| 38.5 (25–57)                | 34.0 (20–50)                | 30.0 (20–57)     |
| Male sex, 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 (%)|                          |                             |                  |
| Severe⁴                  | 16 (67)                     | 22 (79)                     | 20 (74)          |
| Very severe⁵             | 8 (33)                      | 6 (21)                      | 7 (26)           |
| EASI score, mean (SD)    | 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⁻¹), median (range) | 7455.0 (275–16000) | 5575.0 (311–16000) | 3860.0 (57–16000) |
| TARC (pg mL⁻¹), median (range) | 2286.5 (402–1370) | 1904.5 (306–20640) | 1922.0 (218–7139) |
| ECP (µg L⁻¹), median (range) | 19.8 (3-146-0)     | 15.9 (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 corticosteroids⁶ |                            |                             |                  |
| Very strong              | 23 (96)                     | 26 (93)                     | 27 (100)         |
| Strong, medium, weak     | 22 (92)                     | 26 (93)                     | 26 (96)          |
| Strongest                | 17 (71)                     | 12 (45)                     | 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; TARC, thymus and activation-regulated chemokine. ⁴Severe, ≥ 30% of skin involvement by severe eruption; ⁵Very severe, ≥30% of skin involvement by severe eruption; ⁶Severe eruption, primarily erythema, papules, erosion, infiltration and lichenification; ⁷Potency of topical corticosteroids were classified based on guidelines for management of AD (Saeki H et al., 2009).²⁰

Table 2 Primary and major secondary efficacy assessments at week 12 (last observation carried forward, full analysis set)

|                          | Ustekinumab 45 mg (n = 24) | P-value (vs. placebo)⁷ | Ustekinumab 90 mg (n = 28) | P-value (vs. placebo)⁷ | Placebo (n = 27) |
|--------------------------|-----------------------------|------------------------|-----------------------------|------------------------|------------------|
| Percentage change in EASI score | –38.2 (7.40) | 0.94 | –39.8 (6.86) | 0.81 | –37.5 (6.98) |
| EASI 50 responders, n (%) | 9 (38)         | 1.00 | 10 (36)      | 0.79 | 11 (41)       |
| EASI 75 responders, n (%) | 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 diary score      | –1.4 (0.62)    | 0.73 | –2.8 (0.57)  | 0.18 | –1.7 (0.58)   |
| Evening diary 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) |

Data are least square 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. ⁷Analysed using Fisher’s exact test.

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

Biomarkers
A total of nine of 79 patients (11%) had filaggrin gene mutations; four in the ustekinumab 45-mg group [S2554X (two patients), R501X and K4022X (one patient each)], one in the ustekinumab 90-mg group (R501X and 3321delA) and four in the placebo group [S2554X (two patients), 3321delA and K4022X (one patient each)] (Table S3; see Supporting Information).

Treatment with ustekinumab 45 mg showed a reduction in median serum total IgE (–285 IU mL⁻¹) from baseline at week 12, while no reduction was observed following treatment with ustekinumab 90 mg or placebo. The reduction in median ECP level at week 12 was similar for the ustekinumab 90-mg group (–3.80 µg mL⁻¹) and placebo group (–3.70 µg mL⁻¹), and was higher than in the ustekinumab 45-mg group (–2.45 µg mL⁻¹). The reduction in baseline median TARC levels from week 2 to 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

| No. of patients | 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 | 27 | 26 |
| Placebo         | 27 | 27 | 27 | 27 | 27 | 26 | 26 | 26 |

Fig 2. Efficacy end points through week 24 (full analysis set). (a) Percentage change from baseline in Eczema Area and Severity Index (EASI) score. (b) The proportion of patients achieving EASI 50. (c) The proportion of patients achieving EASI 75. (d) The proportion of patients with ≥ 2-point decrease in Investigator’s Global Assessment (IGA) score. 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.
Ustekinumab dosage groups (45 mg – 263.5 pg mL⁻¹ and 90 mg – 208.0 pg mL⁻¹), while it was increased in the placebo group (+19.5 pg mL⁻¹). No consistent trend was observed in the reduction of median TARC levels in any treatment group through week 24 (Fig. 3).

Treatment with ustekinumab 45 mg and 90 mg significantly increased serum concentration of IL-12 p40 (> 5.9-fold change) and IL-12 p70 (> 1.8-fold change) at week 4 and week 12 (Fig. S1; see Supporting Information). The concentration of IL-17A marginally increased (17 – 51%) with the treatment from baseline at week 4 and week 12. However, serum concentration of IFN-γ slightly decreased from baseline to week 4 and week 12 (Fig. S1; see Supporting Information). No difference between treatment groups was observed in serum concentrations of other cytokines at both 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; see Supporting Information), and also when compared with patients without mutations (Figs S1 and S2; see Supporting Information).

In the set of cytokines measured using the Singulex ultra-sensitive immunoassay platform, a significant increase from baseline in the ratios of IL-23 levels at week 4 and week 12 was observed with ustekinumab 90 mg vs. placebo (P = 0.016 using the Mann–Whitney U-test test) (Fig. S3; see Supporting Information). At week 12 in the ustekinumab 90-mg group, in seven 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 week 12 vs. baseline was similar across the treatment groups.

Safety

The proportion of patients with any TEAEs in the ustekinumab 45-mg group was 18 of 24 patients (75%), 16 of 28 patients (57%) in the 90-mg group and 20 of 27 patients (74%) in the placebo group. The most frequent TEAEs observed (occurring in more than two patients in any group) were nasopharyngitis, with similar incidence in ustekinumab groups [45-mg group: six of 24 (25%); 90-mg group: six of 28 (21%)] and placebo group [seven of 27 (26%)], and worsened AD, which was comparatively greater in patients in the placebo group [eight of 27 (30%)] compared with the ustekinumab groups [45-mg group: four of 24 (17%); 90-mg group: three of 28 (11%)] (Table 3). One patient in the ustekinumab 45-mg group experienced a nonserious TEAE of erysipelas of mild severity on day 27 and discontinued treatment. Following treatment with topical nadifloxacin on day 29, the event resolved 6 days after onset (day 32). One patient in the ustekinumab 90-mg group discontinued study participation because of worsened AD. There were no reports of injection site reactions, new malignancy, or active tuberculosis during the study. Furthermore, no deaths, serious TEAEs or 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 a 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 patients from Japan with severe AD. At the end of this 24-week study, the proportion of patients achieving ≥ 2-point 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 the assessment of itch reduction is a prime factor for evaluating the efficacy of drugs for AD treatment. Eczema-related itching during morning and evening (ADIS) for the ustekinumab-treatment groups was comparable with the placebo group. However, the impact of itching on sleep at night (ADIS) was numerically improved with ustekinumab 90 mg. In four published case reports, an overall improvement in severe refractory AD, particularly for pruritus, has been observed following treatment with ustekinumab 45 mg. However, the assessment methods in these case reports differed from those used in our study (visual analogue scale for pruritus and the Scoring Atopic Dermatitis index). In two cases, ustekinumab 45 mg showed an inadequate response in patients with AD who were refractory to usual topical and systemic therapies. Similarly, in a recent phase II study, treatment with ustekinumab showed nonsignificant improvement in clinical response compared with placebo, which corroborated the findings of the present study.

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 II study, where a higher than expected placebo effect was attributed to the use of background topical corticosteroids.

The rate of TEAEs for ustekinumab treatment was comparable with placebo. The safety findings for ustekinumab were consistent with previous psoriasis studies of ustekinumab, including a study in Japanese patients with moderate-to-severe plaque-type psoriasis. The filaggrin gene polymorphism was observed in nine of 79 patients (11%), with the 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 because of the small number of patients who had a filaggrin mutation. Similar results were observed in another study conducted in Japanese patients with AD, in which eight of 143 patients (5.6%) were identified as having filaggrin mutations, including S2554X in two patients (1.4%) and 3321delA in six patients (4.2%). 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 a result of stabilization with ustekinumab. Exploratory biomarkers (IL-17A, IL-17F and IL-23) were evaluated in order to understand their relevance in relation to the mechanism of Th17 signalling and IL-23. For IL-23, one sample showed high variability in serum concentration as a result of stabilization with ustekinumab. The analysis did not indicate a 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 patients with psoriasis, does not appear to be a feature in patients with AD, at least at the time points (12 weeks) evaluated in this study. There are also studies that postulate a low expression of IL-17A and IL-17F in AD, suggesting a different disease mechanism from psoriasis. Future studies targeting IL-17 will be helpful to gain a better understanding of its role in AD. In order to understand further the role of IL-12/23 inhibition in the treatment of severe AD, skin biopsy samples were collected from patients in the study who consented and a microarray analysis was carried out. The results of the skin biopsies performed in this study will be published as a separate report.

Possible limitations of this 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.

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Author contributions

H.S., K.K. and Y.T. were involved in conception and design of the study, acquisition of data, interpretation of data and critical revision of the manuscript. K.I., R.T., Y.M. and B.R. were involved in conception and design of the study, interpretation of data and drafting the manuscript. A.S. 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.

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