

ORIGINAL ARTICLE

Twenty-four-week interim analysis from a phase 3 open-label trial of adalimumab in Japanese patients with moderate to severe hidradenitis suppurativa

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ABSTRACT

Hidradenitis suppurativa (HS) is a chronic skin disease characterized by recurrent painful inflamed nodules/abscesses and draining fistulas that negatively impact quality of life. Adalimumab, a monoclonal antibody against tumor necrosis factor- α , has been approved in the EU, USA and Japan for the treatment of moderate to severe HS. This is an interim analysis of an ongoing phase 3, multicenter, open-label, single-arm study of the safety and efficacy of adalimumab weekly dosing in Japanese patients with moderate to severe HS. Fifteen patients received adalimumab 160 mg at week 0, 80 mg at week 2 and 40 mg every week thereafter starting at week 4. The fulfillment of Hidradenitis Suppurativa Clinical Response was assessed under adalimumab treatment; clinical response was assessed by skin pain, total abscess and inflammatory nodule count and modified Sartorius score; and quality of life and safety were assessed. At week 12, 86.7% of patients achieved clinical response, with improvements at week 12 across the primary and secondary end points generally sustained through week 24. Adalimumab weekly dosing was generally safe and well tolerated with no new safety findings through week 24. These results suggest that adalimumab is effective and well tolerated in Japanese patients with moderate to severe HS.

Key words: adalimumab, hidradenitis, hidradenitis suppurativa, Japan, skin diseases.

INTRODUCTION

Hidradenitis suppurativa (HS), also known as acne inversa, is a chronic, inflammatory, recurrent, debilitating skin disease involving the terminal hair follicle. The disease usually presents after puberty with painful, deep-seated, inflamed lesions in the apocrine gland-bearing areas of the body, most commonly the axillary, inguinal and anogenital regions (Dessau definition), all of which negatively affect patients' quality of life (QOL).^{1,2} Prevalence of HS varies between Eastern and Western countries,^{3–6} and the clinical manifestations of HS are heterogeneous.⁷ Clinical studies from Western countries found that HS is 2–5-times more common in women than in men, with skin lesions more commonly occurring in inguinal and axillary folds and anogenital regions.^{8,9} In contrast, a 2014 survey of 100 patients with HS from 44 hospitals in Japan found a 2.2-times

higher prevalence in men, with the most commonly affected anatomical locations being the buttocks, axillae and genital area.⁴ Similarly, a national epidemiological study of 300 patients with HS across 58 hospitals in Japan found a 2.7-times higher prevalence in men, with more severe lesions found in the axillae. These disparities suggest that Japanese HS patient backgrounds may differ from those of HS patients in Western countries.⁶

Treatment options to reduce the extent and progression of HS include oral or topical antibiotics, surgical removal of lesions, or incision and drainage of abscesses.¹⁰ HS treatment is often graduated to reflect disease extent based on Hurley's staging criteria and progress of disease activity.^{11,12}

Hidradenitis suppurativa pathophysiology involves follicular occlusion and inflammatory cell infiltration. Tumor necrosis factor- α (TNF- α), which activates inflammatory cells such as

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neutrophils and lymphocytes and induces pro-inflammatory cytokines, may play a pathogenic role. Adalimumab (ADA; Humira® [AbbVie, North Chicago, IL, USA]) is a human monoclonal antibody that binds to TNF- α with high affinity and specificity, neutralizes TNF biologic function and attenuates inflammatory and immune responses. Previous trials of ADA in adults with HS have been performed primarily in Western populations, with relatively few Asian patients enrolled (14 patients in the combined phase 3 PIONEER trials and two in the phase 2 trial).^{13,14} Based on findings from those trials, ADA was approved for the treatment of adult HS in the EU and USA in 2015.^{15,16} In Japan, ADA is approved for the treatment of rheumatoid arthritis, plaque psoriasis, arthritic psoriasis, generalized pustular psoriasis, Crohn's disease, ankylosing spondylitis, juvenile idiopathic arthritis, ulcerative colitis, intestinal Behçet's disease, uveitis and HS. Herein, we report the results through week 24 of a phase 3 study investigating the efficacy and safety of ADA weekly dosing in Japanese patients with moderate to severe HS.

METHODS

Patients

Eligible patients were men and non-pregnant women aged 18 years or older with diagnosed HS who had had stable disease for 2 months or more at baseline, lesions in two or more anatomical areas (one of which was Hurley stage II or III) and a total abscess and inflammatory nodule (AN) count of three or more at baseline. Patients were excluded from the study if they were of child-bearing potential and not using contraception; had received prior ADA treatment or other anti-TNF therapy; participated in an ADA trial; or received topical therapies for HS or oral concomitant analgesics (including opioids) for HS-related pain 14 days or less prior to the baseline visit. Patients who received antibiotic treatment or systemic non-biologic therapies (other than permitted oral antibiotics, doxycycline or minocycline) for HS 28 days or less prior to the baseline visit were also excluded. See Table S1 for a detailed list of inclusion and exclusion criteria.

Study design and treatment

This was a 24-week interim analysis of data collected during an ongoing phase 3, multicenter, open-label, single-arm study in Japanese patients with moderate to severe HS (clinicaltrials.gov, NCT02904902). The study was designed and conducted in accordance with Good Clinical Practice as defined by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, the Declaration of Helsinki and all other applicable regulations. An independent ethics committee/institutional review board approved the protocol and informed consent documents. Patients provided written informed consent.

The study included a 35-day screening period, open-label treatment period and a phone call follow up 70 days after the last study drug dose (Fig. 1). All patients received s.c. injections of ADA 160 mg at week 0 and 80 mg at week 2, followed by 40 mg every week (ADAew) starting at week 4. The

treatment period was expected to extend to 99 weeks or more, until HS indication approval or marketing application withdrawal in Japan.

Assessments

Efficacy

The primary efficacy end point was the proportion of patients achieving Hidradenitis Suppurativa Clinical Response (HiSCR) at week 12, which was defined as 50% or more reduction from baseline in total AN count with no increase in abscess or draining fistula count. Three secondary end points were assessed. First, the proportion of patients achieving AN count zero, one or two was assessed at week 12. Second, the proportion of patients achieving at their worst a 30% or more reduction and 1-unit or more reduction from baseline in Patient Global Assessment for Skin Pain Numerical Rating Scale (NRS30). The NRS30 was based on a 24-h recall of the worst skin pain due to HS using an 11-point scale of 0 (no skin pain) to 10 (skin pain as bad as you can imagine). NRS30 was assessed at week 2 among patients with NRS of 3 or more at baseline. Third, the mean change in modified Sartorius scores was assessed from baseline to week 12.

Change from baseline in HS QOL rating (0, worst possible; 10, best possible) was assessed at weeks 4, 12 and 24. To determine the impact of skin problems on patient QOL, the change from baseline in Dermatology Life Quality Index (DLQI) score was assessed at weeks 4, 12 and 24. A decrease in DLQI score indicated improved health-related QOL. Change from baseline in patient satisfaction with medication effectiveness and global satisfaction were assessed using the Treatment Satisfaction Questionnaire – Medication (TSQM) at weeks 12 and 24. TSQM scores range 0–100, with higher scores indicating greater satisfaction.

Safety

Treatment-emergent adverse event (AE) frequency, relationship and severity were assessed for safety and tolerability of ADA. Vital sign measurements and clinical laboratory test results, which included hematology, blood chemistry and urinalysis, were also monitored. AEs reported on or after the first study drug dose and up to 70 days after the last dose were recorded.

Statistical analysis

Because of the limited number of HS patients in Japan, this study was designed to enroll approximately 15 patients for feasibility purposes. Based on a 25% response rate with no medication and 60% clinical response rate at week 12 (based on experience from PIONEER I and PIONEER II),¹³ a sample size of 13 patients was expected to provide 80.1% statistical power to detect a clinical response using a one-sample χ^2 -test (one-sided, $\alpha = 0.025$).

The primary and secondary efficacy outcomes through the first 24 weeks were analyzed using the full analysis set (FAS) population, defined as all patients who received one or more dose of study drug and had one or more post-treatment

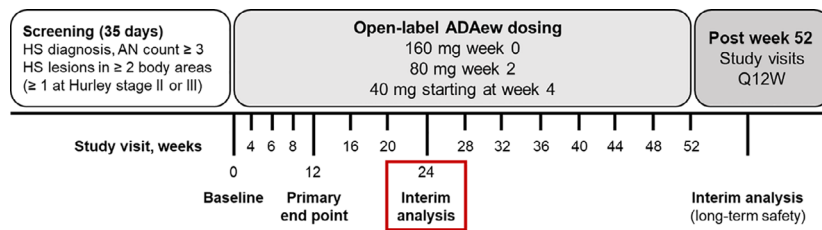


Figure 1. Study design. Twenty-four-week interim analysis (red box) of safety and efficacy of ADAew in Japanese patients with moderate to severe HS. ADA, adalimumab; AN, total abscess and inflammatory nodule; ew, every-week dosing; HS, hidradenitis suppurativa; Q12W, every 12 weeks.

efficacy assessment. Statistical analysis (two-tailed, $\alpha = 0.05$) was performed using SAS statistical software (SAS Institute, Cary, NC, USA). Missing data were handled by non-responder imputation for categorical efficacy variables and last observation carried forward method for continuous efficacy variables. The safety population was defined as all patients who received one or more dose of study drug. Demographics and baseline characteristics were summarized using descriptive statistics. Efficacy data were reported as the number and proportion of patients achieving HiSCR, AN count and NRS30 end points, using a 95% confidence interval (CI) for comparison with non-responders. Modified Sartorius score data are reported as mean (standard deviation [SD]) change from baseline. Safety data are reported as the number and proportion of patients experiencing an AE.

RESULTS

Patients

A total of 15 patients were enrolled and treated in this study across eight study sites in Japan. One patient was discontinued from the study for withdrawal of consent due to an AE of cellulitis. The majority of patients were male ($n = 13$, 86.7%), current tobacco users ($n = 12$, 80%), had no family history of HS ($n = 14$, 93.3%) and received no prior surgery for HS ($n = 9$, 60%) (Table 1). A total of eight patients received prior antibiotic treatment for HS, the most frequently reported being minocycline ($n = 5$), and six patients received prior non-antibiotic treatment for HS, the most frequently reported being corticosteroids ($n = 3$). The median age was 44 years, and median body mass index (BMI) was 26.5 kg/m². Overall, patients had substantial HS disease at baseline with a median HS duration of 11.7 years. Sixty percent of patients had Hurley stage II and 40% had Hurley stage III disease. The median (range) AN count was nine (3–21). In patients with baseline lesion counts of zero or more, lesions more commonly occurred in the following anatomical regions: left buttock ($n = 12$, 80.0%), right buttock ($n = 11$, 73.3%), right inguocrural fold ($n = 11$, 73.3%), left inguocrural fold ($n = 10$, 66.7%) and right axilla ($n = 10$, 66.7%). The anatomical regions with the fewest lesions included: perianal region ($n = 4$, 26.7%), perineum ($n = 4$, 26.7%), left sub/inframammary area ($n = 3$, 20.0%) and right sub/inframammary area ($n = 2$, 13.3%).

Table 1. Baseline demographics and characteristics

Characteristic	ADAew ($N = 15$)
Sex, n (%)	
Female	2 (13.3)
Male	13 (86.7)
Race, Asian, n (%)	15 (100)
BMI, kg/m ² , n (%)	
Normal (<25)	7 (46.7)
Overweight (25 to <30)	4 (26.7)
Obese (30 to <40)	2 (13.3)
Morbidly obese (≥ 40)	2 (13.3)
Tobacco use, n (%)	
Current	12 (80)
Former	1 (6.7)
Never	2 (13.3)
Hurley stage, n (%)	
II	9 (60)
III	6 (40)
HS family history, n (%)	
Yes	1 (6.7)
No	14 (93.3)
Prior HS medication, n (%)	
Antibiotic	8 (53.3)
Other	
Topical	5 (33.3)
Systemic	1 (6.7)
Prior HS surgery, n (%)	
Yes	6 (40)
No	9 (60)
Age, years, median (range)	44 (26–52)
BMI, kg/m ² , median (range)	26.5 (18.1–50.6)
Lesion count, median (range)	
Abscess	2 (0–13)
Draining fistula	2 (0–15)
Non-draining fistula	7 (0–19)
Inflammatory nodule	6 (1–21)
Hypertrophic scar	6 (0–35)
Modified Sartorius score, [†] median (range)	111 (72–286)
Duration of HS, years, median (range)	11.7 (0.9–33.1)
DLQI score, [‡] (median, range)	6 (0–15)
C-reactive protein, mg/L, (median, range)	3.1 (0.2–41.2)
HS pain at worst, NRS (median, range) [§]	4 (0–5.6)

[†]Range 0 to no upper limit. [‡]Range 0–30. [§]Range 0–10. ADA, adalimumab; BMI, body mass index; DLQI, Dermatology Life Quality Index; ew, every-week dosing; HS, hidradenitis suppurativa; NRS, Numerical Rating Scale.

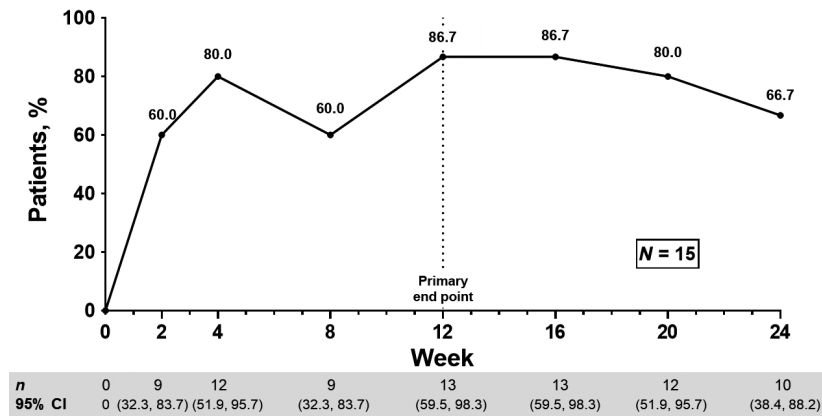


Figure 2. Achievement of HiSCR over 24 weeks (*n* = 15). ADA, adalimumab; CI, confidence interval; HiSCR, Hidradenitis Suppurativa Clinical Response.

Efficacy

The primary end point was the proportion of patients achieving HiSCR at week 12. Overall, the majority of patients (86.7%) achieved HiSCR at week 12 (Fig. 2). At week 2, 60% of patients had achieved HiSCR and this remained generally constant from weeks 4 through 20. At week 24, 66.7% of patients achieved HiSCR. The primary end point findings were supported by improvement in secondary end points of AN count and modified Sartorius scores. The majority of patients (73.3%) achieved a count of zero, one or two at week 12 (Fig. 3).

From baseline, the rate of achieving a count of zero, one or two increased to 26.7% by week 2, peaked by week 16 at 86.7% and was achieved by 53.3% of patients at week 24. Among patients with baseline skin pain NRS of 3 or more (*n* = 9), one-third achieved NRS30 by week 2, and more than half achieved and sustained NRS30 from weeks 4 through 24 (Fig. 4). This rate was generally maintained through week 24. The mean (SD) change from baseline in the modified Sartorius score was -16.7 (15.1) at week 2, indicating improvement in severity of HS symptoms with ADAew treatment (Fig. 5). The decrease in modified Sartorius

score continued through week 24, indicating sustained improvement over time.

The ADAew regimen improved health-related QOL through week 24 as assessed by DLQI. Mean DLQI at baseline was 5.5. The mean (SD) change from baseline in DLQI was -2.2 (3.4) at 4 weeks and -0.5 (5.3) at 24 weeks (Table 2). Mean baseline TSQM effectiveness and global satisfaction scores were 34.8 and 40.0, respectively. At week 12, the mean (SD) change from baseline in TSQM assessment of medication effectiveness and global satisfaction was 30.4 (29.5) and 24.3 (19.4), respectively. Increased patient satisfaction with medication effectiveness and global satisfaction were sustained through week 24. Similarly, mean HS QOL rating increased from 3.8 at baseline to 6.0 at week 4, and continued to improve to 6.1 at week 12 and 6.5 at week 24.

Safety

All treatment-emergent AEs are summarized in Table 3. Overall, 11 patients reported one or more AE, six of whom reported an AE that was deemed possibly related to the study drug. All AEs were mild or moderate in severity. No severe AEs were

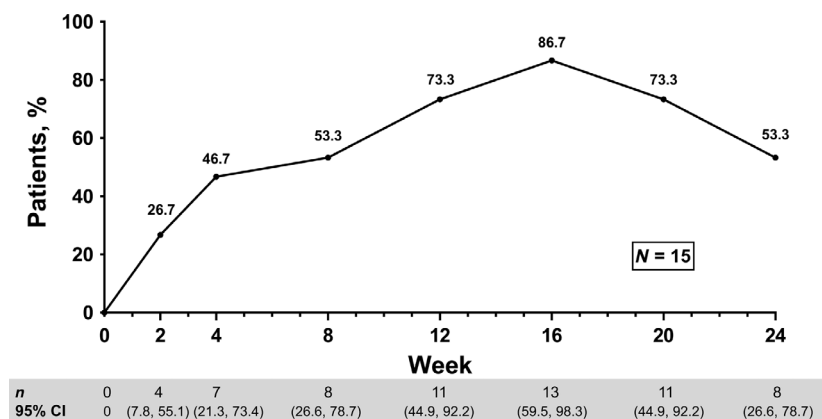


Figure 3. Achievement of total AN count of zero, one or two at each visit over 24 weeks (*n* = 15). AN, abscess and inflammatory nodule; CI, confidence interval; ew, every-week dosing; HiSCR, Hidradenitis Suppurativa Clinical Response.

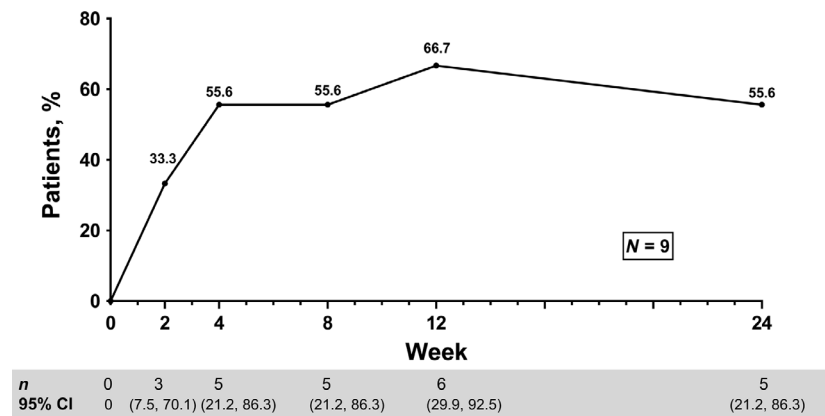


Figure 4. Achievement of skin pain NRS30 among patients with baseline NRS of 3 or more (at worst) over 24 weeks ($n = 9$). CI, confidence interval; NRS30, 30% or more reduction and 1-unit or more reduction from baseline in Patient Global Assessment for Skin Pain Numerical Rating Scale.

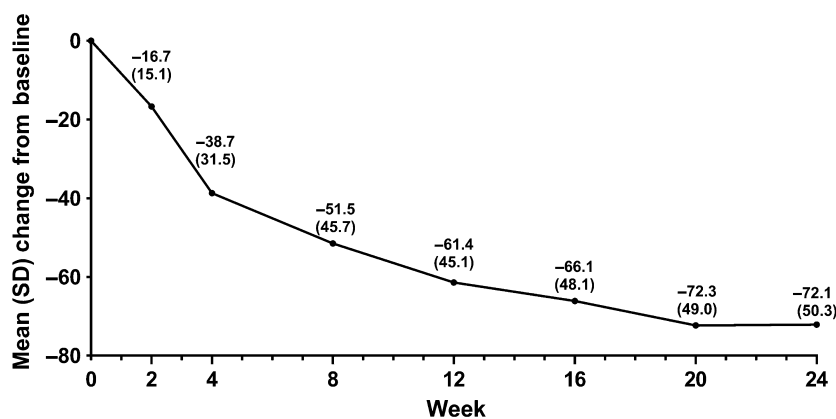


Figure 5. Improvement in modified Sartorius scores from baseline over 24 weeks ($n = 15$). SD, standard deviation.

reported. The most commonly reported AEs were nasopharyngitis and cellulitis. A total of two serious AEs were reported, both cellulitis, and were considered to have a reasonable possibility of being related to the study drug. One patient discontinued from the study by withdrawing consent due to an AE of cellulitis. Additional related AEs included nasopharyngitis, erythema, folliculitis, lymphocyte count increase, erythema, pruritus, skin exfoliation, dental caries and toothache. There were no reports of opportunistic infection, oral candidiasis, tuberculosis, malignancy, allergic reaction or death through week 24. Results of subgroup analyses showed a similar safety profile by smoking status, BMI and hemoglobin A1c. No clinically meaningful changes in vital sign measurements or mean laboratory values and urinalysis were observed.

DISCUSSION

The results of this 24-week interim analysis demonstrated that ADAew treatment was effective, safe and well tolerated in Japanese patients with moderate to severe HS. The majority of patients achieved a clinically relevant reduction in objective

disease activity as demonstrated by a reduction in HiSCR at week 12 (primary end point) (Fig. S1). The clinical response was supported by improvements at week 12 in skin pain due to HS, total AN count and modified Sartorius score (secondary end points), and translated to improvements in overall patient QOL, as measured by HS QOL, DLQI and TSQM. Improvements demonstrated at week 12 were generally sustained through week 24. The observed safety profile of ADAew treatment in this study was consistent with safety profiles in other ADA clinical trials.^{13,17} Importantly, no new safety concerns were identified in this analysis. Because this Japanese study is still ongoing, an evaluation of the 52-week long-term safety, efficacy and tolerability of ADAew in Japanese patients with moderate to severe HS is forthcoming.

Racial differences in HS rates have been previously reported.¹⁸ Classically, HS was thought to occur more frequently in people of African descent than those of European ancestry.¹⁹ More recent epidemiological studies have shown that the majority of HS patients are white;²⁰ however, these findings are dependent on how and where data are collected and may reflect the racial demographics of the areas in which

Table 2. Change from baseline in patient quality of life and treatment satisfaction in Japanese patients treated with weekly adalimumab ($n = 15$)

Variable	Mean	SD
DLQI [†]		
Week 4	-2.2	3.4
Week 12	-1.6	5.0
Week 24	-0.5	5.3
TSQM		
Effectiveness [‡]		
Week 12	30.4	29.5
Week 24	25.9	34.9
Global satisfaction [§]		
Week 12	24.3	19.4
Week 24	29.5	17.1
HS QOL [¶]		
Week 4	2.2	3.3
Week 12	2.3	3.2
Week 24	2.7	3.7

[†]Mean DLQI at baseline was 5.5. [‡]Mean TSQM effectiveness score at baseline was 34.8. [§]Mean TSQM global satisfaction score at baseline was 40.0. [¶]Mean HS QOL rating at baseline was 3.8. ADA, adalimumab; DLQI, Dermatology Life Quality Index; HS, hidradenitis suppurativa; QOL, quality of life; SD, standard deviation; TSQM, Treatment Satisfaction Questionnaire – Medication.

the studies are conducted.^{18,21} Relatively few studies have investigated HS epidemiology in Asian populations.^{3–6} Using the Korean National Health Insurance database, the prevalence of HS in South Korea is estimated to be 0.06%.³ Differences in HS epidemiology between races may be the result of genetic mutations or variation in patients' genetic backgrounds.^{22,23} Therefore, future studies on the safety and efficacy of weekly ADA treatment in Korean and other Asian patients with HS are warranted.

Although this single-arm, open-label study was conducted in a limited number of patients without a placebo or active comparator treatment arm, the results provide an adequate characterization of the efficacy and safety profile of ADA in the Asian population. The proportion of patients with a clinical response to ADA at week 12 and the mean change from baseline in TSQM at week 12 was higher in the current study than what was reported in the global PIONEER trials.¹³ Differences in the study populations might have contributed to the difference in the observed treatment effect of ADA and QOL assessments between studies. In the current study, lesions were predominantly located in the buttock area. In addition, the current study was conducted mainly in men with an average BMI of 26.5 kg/m². Conversely, most patients in the PIONEER trials were women with an average BMI of 33 kg/m².

Adalimumab is the only European Medicines Agency- and US Food and Drug Administration-approved treatment for moderate to severe HS. ADA is now registered in Japan for treatment of HS. The results presented here are consistent with findings in previous ADA clinical trials in Western countries and demonstrate that weekly ADA is a safe and effective treatment for HS in Japanese patients.

Table 3. Treatment-emergent adverse events in Japanese patients treated with weekly adalimumab

	Patients, n (%) ($n = 15$)	
	AE	AE possibly related to study drug
Overall		
Any AE	11 (73.3)	6 (40.0)
Mild	8 (53.3)	—
Moderate	3 (20.0)	—
Severe	0 (0)	—
Any serious AE	2 (13.3)	2 (13.3)
Cellulitis	2 (13.3)	2 (13.3)
AE leading to discontinuation	1 (6.7)	1 (6.7)
Cellulitis	1 (6.7)	1 (6.7)
Preferred term		
Nasopharyngitis	3 (20.0)	2 (13.3)
Cellulitis	2 (13.3)	2 (13.3)
Dental caries	2 (13.3)	1 (6.7)
Toothache	2 (13.3)	1 (6.7)
Asthenopia	1 (6.7)	—
Diarrhea	1 (6.7)	—
Erythema	1 (6.7)	1 (6.7)
Erythrasma	1 (6.7)	1 (6.7)
Folliculitis	1 (6.7)	1 (6.7)
Headache	1 (6.7)	—
Lymphocyte count increased	1 (6.7)	1 (6.7)
Neutropenia	1 (6.7)	—
Post-traumatic neck syndrome	1 (6.7)	—
Pruritus	1 (6.7)	1 (6.7)
Pyrexia	1 (6.7)	—
Sinusitis	1 (6.7)	—
Skin exfoliation	1 (6.7)	1 (6.7)
Skin infection	1 (6.7)	—

AE, adverse event.

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trials-data-and-information-sharing/data-and-information-sharing-with-qualified-researchers.html.

CONFLICT OF INTEREST: A. M. has received research grants, consulting fees and/or speaker's fees from AbbVie, Eli Lilly Japan, Janssen Pharmaceutical, Kyowa Hakko Kirin, Leo Pharma, Maruho, Mitsubishi-Tanabe Pharma and Novartis. K. O. has received research grants from AbbVie. S. I. has served as paid speaker for and/or participated in clinical trials sponsored by companies that manufacture drugs used for the treatment of psoriasis, including AbbVie, Mitsubishi-Tanabe Pharma, Janssen Pharmaceutical, Novartis, Eli Lilly Japan, Kyowa Hakko Kirin, Leo Pharma, Maruho, Celgene, Torii Pharmaceutical and Taiho Pharmaceutical. K. T. has served as paid speaker for and/or participated in clinical trials sponsored by companies that manufacture drugs used for the treatment of psoriasis, including AbbVie, Mitsubishi-Tanabe Pharma, Janssen Pharmaceutical, Novartis, Eli Lilly Japan, Kyowa Hakko Kirin, Leo Pharma and Maruho. Y. O. has received funds for research/research grants/speaker fees from Novartis, Eli Lilly Japan, Shiseido, Celgene, Torii Pharmaceutical, Kaken Pharmaceutical, Mitsubishi-Tanabe Pharma, Maruho, Kyowa Hakko Kirin, Janssen Pharmaceutical, AbbVie, Eisai and Celgene. N. H. has received consultant fees from AbbVie and honoraria from Maruho. T. T. has received research funds from Maruho and honoraria for speaker, consultancy and advisory board membership from AbbVie, Boehringer Ingelheim, Celgene, Janssen, Kyowa Hakko Kirin, Leo Pharma, Lilly, Mitsubishi Tanabe Pharma, Novartis and Sanofi. N. M. was an AbbVie employee at the time of the study. S. K., Y. Z. and M. Y. are full-time employees of AbbVie and may own stock/options. No other authors have conflicts of interest to declare.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Figures S1. Representative images of improved inflammatory nodules/abscesses/fistulas in the right axilla of a Japanese HS patient treated with ADAew for 24 weeks. ADA, adalimumab; ew, every-week dosing.

Table S1. Inclusion and exclusion criteria