Efficacy and safety of secukinumab in Japanese patients with active ankylosing spondylitis: 24-week results from an open-label phase 3 study (MEASURE 2-J)

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ABSTRACT
Objective: Secukinumab, a fully human monoclonal antibody that neutralizes interleukin-17A, improved the signs and symptoms of ankylosing spondylitis (AS) in three Phase 3 global studies (MEASURE 1, 2, and 3). Here, we describe the efficacy and safety results through Week 24 of a study of secukinumab in Japanese patients with active AS.

Methods: In this multicenter, open-label, single arm, 52-week study, 30 AS patients self-administered secukinumab 150 mg subcutaneously at baseline, Weeks 1, 2, 3, and 4, and every 4 weeks thereafter. The primary efficacy endpoint was ASAS 20 response at Week 16. Overall safety and tolerability were assessed beyond Week 24 up to the data reporting cut-off date.

Results: The ASAS 20 response rate was 70% (21/30) at Week 16, which was sustained to Week 24. Secukinumab was effective in various clinical outcomes including patient’s global assessment of disease activity, spinal pain, nocturnal pain, physical function, spinal mobility, and CRP level. Comparable ASAS 20 and 40 responses were observed regardless of previous anti-TNF therapy. Secukinumab was well-tolerated with a safety profile consistent with previous reports.

Conclusion: Secukinumab 150 mg provided sustained improvement in the signs and symptoms of Japanese AS patients through 24 weeks, with no new or unexpected safety signals.

Introduction
Ankylosing spondylitis (AS) is a chronic inflammatory disease characterized by new bone formation resulting in progressive, irreversible structural damage of mainly the axial skeleton and the sacroiliac joints. AS is associated with significant disability and, thus, constitutes a major burden to patients [1,2]. In addition to axial involvement, a lesser proportion of patients experience involvement of the peripheral joints, which leads to functional impairment and reduced quality of life (QoL) [3]. Genetics is a crucial factor for the development of AS, and a high proportion of AS patients are human leukocyte antigen-B27 (HLA-B27) positive [4]. The mean AS prevalence per 10,000 is estimated to be 23.8 in Europe. However, it is substantially lower in the Japanese population (0.7), consistent with the lower frequency of HLA-B27 in the Japanese general population (0.5% or less), compared with Europeans (4–13%) and other Asian populations such as the Chinese (4–8%) or South Koreans (2.3–3%) [5–9].

The Assessment of SpondyloArthritis International Society/European League Against Rheumatism/American College of Rheumatology (ASAS/EULAR/ACR) treatment recommendations cite non-steroidal anti-inflammatory drugs (NSAIDs) as the first-line treatment for patients with active, predominantly axial manifestations of spondyloarthritis (SpA) [10]. Tumor necrosis factor (TNF) inhibitors are added as the first-line biologic therapy for AS [11], and adalimumab and infliximab are approved for the treatment of AS in Japan [12,13]. However, up to 40% of patients experience an inadequate response (primary or secondary treatment failure), intolerance, relapse of disease upon discontinuation, or unacceptable safety concerns with anti-TNF therapy; thus, there remains an unmet medical need for novel treatments with a different mechanism of action [14,15].

The interleukin (IL)-23/IL-17 axis is implicated in the pathogenic mechanism of AS [16]. Secukinumab, a fully human anti-IL-17A monoclonal antibody, has demonstrated significant improvement in the signs and symptoms of active AS in phase 3 global studies with reported responses sustained over 4 years in MEASURE 1 (NCT01358175), 3 years in MEASURE 2 (NCT01649375) and 2 years in MEASURE 3 (NCT02008916) [17–20].

Although there seems to be a minimal difference between the Japanese and non-Japanese populations in terms of
pharmacokinetics of monoclonal antibodies [21], genetic, environmental, and/or cultural dissimilarities among different populations may contribute to individual and ethnic variations in clinical responses [22]. Therefore, it is of clinical importance to conduct a local study in the Japanese population. Here, we present the efficacy results up to Week 24 and safety data up to the data cut-off date of 30-Aug-2017 (including Week 24 data and beyond) from MEASURE 2-J (NCT02750592), the first study to assess the efficacy of IL-17A inhibition in Japanese patients with active AS.

Methods

Study design

MEASURE 2-J is an ongoing, multicenter, open-label, single arm, 52-week study assessing the use of subcutaneous (s.c.) secukinumab self-administration with pre-filled syringes in patients with active AS. The study is being conducted at 10 centers in Japan. After 4–10 weeks of screening, approximately 30 patients were planned to enter the treatment period and receive secukinumab 150 mg s.c. once weekly for 4 weeks (at baseline, Weeks 1, 2, 3, and 4) and every 4 weeks thereafter up to Week 48. Rescue medication was not allowed until Week 16; however, patients who were deemed not to be benefiting from study treatment were allowed to discontinue from the study at any time. The study design is shown in Supplemental Figure S1.

Patients

Patients included were aged ≥18 years with active AS fulfilling the modified New York criteria with a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score of ≥4 (scores range from 0–10, with higher scores indicating more severe disease activity) and a spinal pain score of ≥4 cm on a 10 cm visual analog scale (VAS; with higher numbers indicating greater disease activity) at baseline, despite current or previous treatment with the highest recommended doses of NSAIDs. Patients using NSAIDs as part of their AS therapy were included if they had received a stable dose for at least 2 weeks before baseline. Patients treated with an anti-TNF agent (not >1) could enroll if they had an inadequate response after at least 3 months of treatment or had stopped anti-TNF therapy at any point due to tolerability reasons (anti-TNF-inadequate responders [IRs]), and had an appropriate washout period prior to baseline. Concomitant use of systemic corticosteroids (≤10 mg/day prednisone or equivalent) was allowed if the dose was stable for at least 2 weeks before baseline. Patients taking methotrexate (≤25 mg/week) and sulfasalazine (≤3 g/day) were allowed if the dose was stable for at least 4 weeks before baseline.

Key exclusion criteria included evidence of an ongoing infectious or malignant process on chest x-ray or magnetic resonance imaging (MRI) obtained within 3 months of screening, evidence of tuberculosis infection, total spinal ankylosis, human immunodeficiency virus or hepatitis B or C positivity at screening or baseline, active systemic infection within 2 weeks before baseline, and previous treatment with cell-depleting therapies or biologic agents other than anti-TNF agents.

The study was conducted in accordance with Good Clinical Practice and the principles of the Declaration of Helsinki and was approved by the institutional review board or independent ethics committee of each study site. Informed consent was obtained from each patient in writing before any study assessment was performed.

Outcome measures

The primary efficacy endpoint was the proportion of patients achieving an ASAS 20 response at Week 16. Secondary outcome measures at Week 16 included the proportion of patients with an ASAS 40 response, the proportion of patients achieving a BASDAI 50 response, change from baseline in high sensitivity C-reactive protein (hsCRP) level, the proportion of patients achieving an ASAS5/6 response, change from baseline in total BASDAI score, physical component summary (PCS) score on the 36-item Short-Form Health Survey (SF-36), and Ankylosing Spondylitis quality of life (ASQoL), and the proportion of patients with an ASAS partial remission response.

Exploratory endpoints included assessments of change from baseline in Ankylosing Spondylitis Disease Activity Score (ASDAS)-CRP, patient’s global assessment of disease activity, total spinal pain, nocturnal back pain, Bath Ankylosing Spondylitis Functional Index (BASFI), spinal mobility assessed by the Bath Ankylosing Spondylitis Metrology Index (BASMI) linear score, proportion of patients achieving ASDAS-CRP inactive disease, and subgroup analyses (ASAS 20 and ASAS 40 responses) by inadequate response (IR) or intolerance to previous anti-TNF use (anti-TNF-naïve vs anti-TNF-IR) and body weight.

The overall safety and tolerability of secukinumab was assessed separately for the initial (up to Week 16) treatment period and the entire safety reporting period. In this interim analysis, the data reporting cut-off date (30-Aug-2017) was the date when the last patient had completed the Week 24 visit or discontinued study treatment earlier. Therefore, safety results of the entire safety reporting period include data beyond Week 24. Safety assessments included the evaluation of all adverse events (AEs) and serious AEs (SAEs) including injection site reactions and anti-secukinumab antibody development (immunogenicity). Samples positive for anti-secukinumab antibodies were further analyzed for their neutralizing potential by an enzyme-linked immunosorbent assay [23]. Blood sampling for immunogenicity analysis was done before study drug administration at baseline, pre-dose at Weeks 16, 24, 52, and at the Week 60 follow-up visit.

Statistical analysis

Considering the lower AS prevalence in Japan (0.0065%) [6], and the past AS clinical studies conducted in Japan [12,13], it was considered feasible to enroll approximately 30 patients in this study. Assuming an ASAS 20 response rate of 60% at Week 16 [24], the estimated lower limit of
the 95% confidence interval (CI) for the ASAS 20 response rate in this sample of 30 Japanese patients treated with secukinumab 150 mg s.c. was approximately 42.5%, which was above the upper limit of the 95% CI for the response rate of the placebo control group in the MEASURE 2 study (ASAS 20 response: 28.4%, 95% CI: 18.1–38.7%) [24].

Evaluations of efficacy were performed on the full analysis set, which comprised all patients who entered into the treatment periods (Supplemental Figure S1). The primary and other binary efficacy variables up to Week 24 were evaluated using non-responder imputation. Missing values, including those due to discontinuation of study treatment, were imputed as failures to achieve the given response (non-responses). Missing values for continuous efficacy variables were not imputed and are reported as observed.

The safety set included all patients who took at least one dose of study treatment during the treatment period. Safety endpoints were summarized descriptively.

### Results

#### Patients

A total of 37 patients were screened, and 30 patients (81.1%) were deemed eligible and entered the treatment period. Demographics and baseline disease characteristics are summarized in Table 1. The majority (90.0%) of patients were <65 years of age with mean age of 44.0 years; mean time since diagnosis of AS was 4.6 years. Two-thirds of the patients were male. The mean body mass index (BMI), baseline BASDAI, and hsCRP level were 23.49 kg/m², 6.9, and 12.06 mg/L, respectively. Almost half of the patients were HLA-B27 positive (46.7%), and just over one-quarter (26.7%) were TNF-IR. Of the 30 patients, 28 (93.3%) completed 24 weeks of treatment. Two patients discontinued the study up to Week 24: one due to an SAE of drug eruption and the other due to a lack of efficacy (Figure 1). Two more patients discontinued after Week 24, one due to an AE of cervical cancer and the other due to an AE of periostitis.

#### Efficacy

Secukinumab 150 mg showed a rapid onset of action in Japanese patients with AS. The proportion of patients with

| Characteristic | Secukinumab 150 mg (N = 30) |
|---------------|----------------------------|
| Age in years, mean (SD) | 44.0 (13.52) |
| Male, n (%) | 20 (66.7) |
| Body weight in kg, mean (SD) | 64.7 (14.5) |
| Body mass index in kg/m², mean (SD) | 23.5 (4.13) |
| Body weight stratification, n (%) | |
| <70 kg | 21 (70.0) |
| 70–90 kg | 7 (23.3) |
| >90 kg | 2 (6.7) |
| Time since diagnosis of AS in years, mean (SD) | 4.6 (7.7) |
| HLA-B27 positive, n (%) | 14 (46.7) |
| Current smoker at baseline, n (%) | 7 (23.3) |
| No previous anti-TNF therapy, n (%) | 22 (73.3) |
| Medication use — no. (%) | |
| Methotrexate (11.2 ± 5.2 mg/week) | 7 (23.3) |
| Sulfasalazine (1.2 ± 0.5 g/day) | 6 (20.0) |
| Corticosteroid (2.5 ± 0.5 mg/day) | 3 (10.0) |
| Patients’ global assessment of disease activity, 0–100 mm VAS, mean (SD) | 72.8 (13.5) |
| Total spinal pain, 0–100 mm VAS, mean (SD) | 71.1 (13.5) |
| Nocturnal back pain, 0–100 mm VAS, mean (SD) | 68.2 (14.0) |
| hsCRP, mg/L- mean (SD) | 12.06 (14.39) |
| BASDAI total score, mean (SD) | 6.9 (1.6) |
| BASFI total score, mean (SD) | 5.6 (2.2) |
| BASMI (linear), mean (SD) | 5.0 (1.6) |
| ASQoL, mean (SD) | 11.5 (3.7) |
| SF-36 PCS, mean (SD) | 36.5 (6.4) |

ASQoL: Ankylosing Spondylitis quality of life; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; BASMI: Bath Ankylosing Spondylitis Metrology Index; HLA: human leukocyte antigen; hsCRP: high-sensitivity C-reactive protein; N: total number of patients in the treatment group; SD: standard deviation; SF-36 PCS: 36-Item Short-Form Health Survey Physical Component Summary score; TNF: tumor necrosis factor; VAS: visual analog scale.

Figure 1. Patient disposition up to Week 24. NSAID: non-steroidal anti-inflammatory drug; s.c.: subcutaneous.
ASAS 20/40 responses was 23.3%/10.0% at Week 1, 53.3%/33.3% at Week 4, and 70.0%/46.7% at Week 16. The ASAS 20 response was sustained (70%) and ASAS 40 response was increased to 56.7% at Week 24 (Figure 2). In the subgroup of anti-TNF-naïve subjects (n = 22), ASAS20/40 response rates at Week 16 were 68.2%/40.9%; corresponding rates in anti-TNF-IR subjects (n = 8) were 75.0%/62.5%. ASAS 20/40 responses in patients with body weight < 70 kg (n = 21), 70-90 kg (n = 7), and >90 kg (n = 2) were 76.2%/52.4%, 42.9%/28.6%, and 100%/50%, respectively. Clinical responses at Week 16 across endpoints are presented in Table 2. These responses were sustained through Week 24.

The mean change (standard deviation [SD]) from baseline in ASDAS-CRP at Week 16 was /C0 1.7 (1.0). The proportion of patients with a clinically important change (≥1.1 units), major improvement (≥2.0 units), and inactive disease (<1.3) in ASDAS-CRP at Week 16 was 63.3% (19/30), 33.3% (10/30), and 26.7% (8/30), respectively. Secukinumab treatment also improved (decreased) scores of patient’s global assessment of disease activity and back pain, with a rapid reduction of VAS scores within the first 4 weeks of treatment; these effects were sustained through Week 24 (Figure 3). The mean changes (SD) from baseline in patient’s global assessment of disease activity, total spinal pain, and nocturnal back pain VAS scores at Week 16 were −34.7 (25.9), −35.4 (27.4), and −33.4 (27.3), respectively. Improvements in physical function (based on BASFI, BASMI, and SF-36 PCS) and QoL (based on ASQoL) were also observed with secukinumab at Week 16, with improvements sustained or further improved by Week 24 (Figure 4).

Safety

The overall incidence of AEs up to Week 16 was 76.7%. The commonly reported AEs (≥10%) by primary system organ class were infections and infestations, gastrointestinal disorders, skin and subcutaneous tissue disorders, and general disorders and administration site conditions. Viral upper respiratory tract infection, stomatitis, and influenza were the frequently reported treatment-emergent AEs (≥10%) by preferred term during the first 16 weeks of treatment. The incidence of AEs and SAEs is shown in Table 3. The safety results for the entire period collected by the last patient’s Week 24 visit were analyzed. Across the period, the median duration of secukinumab exposure was 310.0 days, and the cumulative exposure was 25.5 patient-years. A total of 3 (10.0%) patients experienced 4 SAEs during the entire safety reporting period. The events were drug eruption, adenocarcinoma of the cervix, and 2 episodes of coronary artery occlusion in 1 patient. The episode of drug eruption started on Day 63 with local itching and eventual generalized skin lesions with multiple areas of patchy hair loss on the entire head. It was suspected to be related to study treatment by the investigator, and treatment was

Table 2. Clinical responses with secukinumab across endpoints in the overall population at week 16.

| Variable | Secukinumab 150 mg | N = 30 |
|----------|--------------------|-------|
| ASAS 20; n/N (%)a | 21/30 (70.0) |
| ASAS 40; n/N (%)a | 14/30 (46.7) |
| BASDAI 50; n/N (%)a | 11/30 (36.7) |
| hsCRP; geometric mean of post-baseline/baselineb | 0.247 |
| ASAS 5/6; n/N (%)a | 14/30 (46.7) |
| BASDAI: mean change from baselineb | −3.088 |
| SF-36 PCS: mean change from baselineb | 6.306 |
| ASQoL: mean change from baselineb | −3.4 |
| ASAS partial remission; n/N (%)a | 6/30 (20.0) |
| ASDAS-CRP: mean change from baselineb | −1.740 |
| ASDAS-CRP inactive disease; n/N (%)a | 8/30 (26.7) |

aData reported as non-responder imputation; bData reported as observed. Number of evaluable patients for hsCRP, BASDAI, SF-36 PCS, ASDAS-CRP were 28 and 27 for ASQoL. ASAS: Assessment of SpondyloArthritis International Society; ASDAS: Ankylosing Spondylitis Disease Activity Score; ASQoL: Ankylosing Spondylitis quality of life; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; hsCRP: high-sensitivity C-reactive protein; N: total number of patients in the treatment group; SF-36 PCS: 36-item Short-Form Health Survey Physical Component Summary score.

The mean change (standard deviation [SD]) from baseline in ASDAS-CRP at Week 16 was −1.7 (1.0). The proportion of patients with a clinically important change (≥1.1 units), major improvement (≥2.0 units), and inactive disease (<1.3) in ASDAS-CRP at Week 16 was 63.3% (19/30), 33.3% (10/30), and 26.7% (8/30), respectively. Secukinumab treatment also improved (decreased) scores of patient’s global assessment of disease activity and back pain, with a rapid reduction of VAS scores within the first 4 weeks of treatment; these effects were sustained through Week 24 (Figure 3). The mean changes (SD) from baseline in patient’s global assessment of disease activity, total spinal pain, and nocturnal back pain VAS scores at Week 16 were −34.7 (25.9), −35.4 (27.4), and −33.4 (27.3), respectively. Improvements in physical function (based on BASFI, BASMI, and SF-36 PCS) and QoL (based on ASQoL) were also observed with secukinumab at Week 16, with improvements sustained or further improved by Week 24 (Figure 4).
permanently discontinued on Day 85, followed by supportive treatment with topical corticosteroids and anti-histamines until near resolution on Day 281. Adenocarcinoma of the cervix was confirmed on Day 191 by the result of a Papanicolaou smear test. The event was suspected to be related to study treatment by the investigator and led to treatment discontinuation on Day 261. In addition, 1 patient discontinued study treatment due to an AE of periostitis of the mandible diagnosed on Day 165, which resolved on Day 189 after treatment with antibiotics. The case was moderate in severity and secukinumab was discontinued on Day 196. Incidence rates of treatment-emergent AEs by system organ class and preferred term over the entire safety reporting period are shown in Table 4.

Candida infection (high-level term) was reported in 2 patients: one reported as vulvovaginal candidiasis and one reported as Candida infection. These events were mild in severity, and the vulvovaginal candidiasis case was considered to be related to study treatment. One patient who had a diagnosis of irritable bowel syndrome before study entry was clinically diagnosed with colitis that was ongoing at the data reporting cut-off date (Table 4) and was later reported as ulcerative colitis (UC) suspected to be related to study treatment. Neutropenia and malignant or unspecified tumors were reported in 2 (6.7%) and 1 (3.3%) patients during the entire safety reporting period, respectively. No administration and immune reactions, major adverse cardiac events, or Crohn’s disease events were reported. Treatment-emergent anti-secukinumab antibodies (i.e. positive post-treatment but negative at baseline) were detected in 4 samples obtained from 3 patients; two samples from 1 patient were positive at Week 16 and Week 60, and samples from the other 2 patients were positive at Week 24. Neutralizing antibodies were not detected in any of these patient, and anti-drug antibodies were not associated with a loss of efficacy, alterations in PK profiles, or immunogenicity-related AEs. There were no deaths reported.

**Discussion**

While the efficacy and safety of secukinumab in AS have been documented previously [18–20,24,25], this is the first study demonstrating the efficacy, safety, and tolerability of secukinumab in Japanese AS patients, despite current or
previous NSAID and/or anti-TNF therapy. Overall, secukinumab rapidly reduced the signs and symptoms of Japanese patients with AS consisting of 26.7% anti-TNF-IR patients.

Other than ethnicity, the demographics of this study population, including age, gender, and proportion of anti-TNF naïve patients, were comparable to that in global secukinumab studies in AS (MEASURE 1, 2, and 3), except for a lower frequency of HLA-B27 (46.7% vs 70%) and lighter body weight (64.7 kg vs 82.3 kg [18–20,24,25]. In the current study, 16 patients were HLA-B27-negative, of which four had a history or concomitant skin diseases (1 psoriasis and 2 palmoplantar pustulosis at baseline and 1 history of palmoplantar pustulosis). Indeed, psoriasis can be seen in nearly 10% of AS patients [26], and Jadon et al. [27] reported that 24.4% of AS patients fulfilling modified New York Criteria for AS also met the Classification of Psoriatic Arthritis criteria. An additional clinical study of Japanese AS patients showed similar results in terms of HLA-B27 positivity (48.8%) [12], suggesting that these relatively lower rates in AS are likely related to the low HLA-B27 prevalence in the Japanese general population. Of note, a previous study has shown that HLA-B39 was positive in HLA-B27-negative AS patients [28]. Although HLA types other than B27 were not investigated in this study, it is possible that HLA-B27-negative patients in this study may have been positive for other AS-related HLA phenotypes.

In this study population, improvement in the primary and all secondary endpoints was seen with treatment with secukinumab 150 mg at Week 16; continued treatment efficacy was observed throughout the 24-week observation period. In addition to the positive effects on disease activity and pain, parallel improvements in physical function (BASFI, SF-36 PCS), spinal mobility (BASM1), and QoL (ASQoL) further support the efficacy of secukinumab in Japanese AS patients. Slightly higher ASAS 20/40 responses were observed in the current study compared with an earlier global study of secukinumab in AS (70.0%/46.7% in MEASURE 2-J vs 61.1%/36.1% in MEASURE 2) [24]. A similar tendency toward higher efficacy was observed in Asian patients who participated in the global secukinumab AS studies [29]. It has been reported that obesity negatively affects the outcome of axial SpA patients treated with anti-TNF agents [30] and secukinumab clearance and volume of distribution vary with body weight [31]; therefore, in addition to the design of open-label study, the overall lighter patient weights in MEASURE 2-J could have contributed to the positive treatment outcome. In this study, ASAS responses were higher in the subgroup of patients with body weight less than 70kg than in the 70-90 kg subgroup. The responses were also higher in patients weighing >90 kg; however, given the low number of patients weighing >90 kg (2 patients), these results are difficult to interpret.

In a subgroup analysis by lack of response to previous anti-TNF use, clinical responses in this study were confirmed with secukinumab in both anti-TNF-naïve and anti-TNF-IR populations, with the response rates in anti-TNF-IR patients being higher in MEASURE 2-J than those observed in the global secukinumab AS studies. However, considering the small sample size (n = 8) of the anti-TNF-IR subgroup in the present study, conclusions regarding differences in efficacy rates by prior response to TNF-inhibitor therapy cannot be drawn.

Table 3. Safety profile up to week 16 and over the entire safety-reporting period.

| Variables                                      | Up to Week 16 | Entire safety-reporting period |
|------------------------------------------------|---------------|-------------------------------|
| Exposure to study treatment, days, median      |               | 310.0                         |
| Any AE                                         | 23 (76.7)     | 25 (83.3)                     |
| Deaths                                         | 0             | 0                             |
| Any SAE                                        | 1 (3.3)       | 3 (10.0)                      |
| Discontinuation due to AE                      | 1 (3.3)       | 3 (10.0)                      |
| Common adverse events                          |               |                               |
| Upper respiratory tract infection              | 7 (23.3)      | 12 (40.0)                     |
| Stomatitis                                     | 4 (13.3)      | 5 (16.7)                      |
| Influenza                                      | 3 (10.0)      | 4 (13.3)                      |
| Bronchitis                                     | 1 (3.3)       | 2 (6.7)                       |
| Gastroenteritis                                | 2 (6.7)       | 2 (6.7)                       |
| Infected dermal cyst                           | 1 (3.3)       | 2 (6.7)                       |
| Leukopenia                                     | 2 (6.7)       | 2 (6.7)                       |
| Pyrexia                                        | 2 (6.7)       | 2 (6.7)                       |
| Rhinorhoea                                     | 1 (3.3)       | 2 (6.7)                       |
| Selected AEs of interest                       |               |                               |
| Hypersensitivity                               | 3 (10.0)      | 7 (23.3)                      |
| Neutropenia                                    | 2 (6.7)       | 2 (6.7)                       |
| Crohn’s disease                                | 0             | 0                             |
| Major adverse cardiac events                   | 0             | 0                             |
| Cardio-cerebrovascular-related events          | 0             | 1 (3.3)                       |
| Administration and immune reactions            | 0             | 0                             |
| Immunogenicity                                 | 1 (3.3)       | 3 (10.0)                      |
| Malignant or unspecified tumors                | 0             | 1 (3.3)                       |

Data are number (%). Safety results of the entire safety reporting period include data beyond Week 24 reported up to the date of the last patient’s Week 24 study visit. A subject with multiple occurrences of an AE is counted only once in this AE category. *The most common AEs are reported as the preferred terms and occurred at an incidence of at least 5% during the entire safety reporting period. AE: adverse event; SAE: serious AE.
Table 4. Absolute and relative frequencies for treatment-emergent AEs possibly related to study treatment, by primary system organ class and preferred term – entire treatment period.

| Primary system organ                        | Secukinumab 150 mg class and Preferred term |
|---------------------------------------------|---------------------------------------------|
| Number of patients with at least one AE     | Secukinumab 150 mg (N = 30)                  |
| Blood and lymphatic system disorders        | 2 (6.7)                                     |
| Cardiac disorders                           | 2 (6.7)                                     |
| Ear and labyrinth disorders                 | 1 (3.3)                                     |
| Gastrointestinal disorders                  | 11 (36.7)                                   |
| General disorders and administration site conditions | 4 (13.3)                                 |
| Immune system disorders                     | 1 (3.3)                                     |
| Infections and infestations                 | 19 (63.3)                                   |
| Injuries, poisoning and procedural complications | 4 (13.3)                                 |
| Musculoskeletal and connective tissue disorders | 2 (6.7)                                    |
| Neoplasms benign, malignant and unspecified (including cysts and polyps) | 1 (3.3)                                     |
| Nervous system disorders                    | 3 (10.0)                                    |
| Renal and urinary disorders                 | 1 (3.3)                                     |
| Respiratory, thoracic and mediastinal disorders | 4 (13.3)                                 |

There were no new or unexpected safety signals reported in this study, and the safety profile was consistent with earlier reports of secukinumab [18,19,24,25,32,33], with no deaths reported over the entire safety reporting period and no patterns seen in reported SAEs. Mild *Candida* infection was reported in 2 patients, and 1 (3.3%) ulcerative colitis (UC) case was reported. Stolwijk et al. [34] demonstrated that patients with AS are at 3.3-fold higher risk of developing inflammatory bowel disease (IBD) compared with the general population, and IBD has been reported in 4–16% of AS patients [34–36]. Therefore, the possibility cannot be excluded that the UC case observed in this study could have been related to the patient’s underlying AS. Despite a possible role of IL-17 in the barrier integrity of the gut [37] and the known association of IBD with AS, a pooled safety data of secukinumab treatment in AS showed a low incidence of Crohn’s disease and UC (exposure-adjusted incidence rates of 0.5 and 0.2 per 100 patient-years, respectively) [38]. Nonetheless, the risk of IBD associated with anti-IL-17 treatment remains to be elucidated.

In the current study, detection of anti-secukinumab antibodies was higher than that seen in previous global secukinumab AS studies [18–20,24,25]; however, this percentage may not be representative of the underlying population rate, due to the small sample size of this study.

Limitations of this study include its non-randomized, single-arm, open-label study design, limited sample size, lack of long-term data, and absence of imaging assessments.

In summary, secukinumab provided sustained improvement over 24 weeks in the signs and symptoms of AS in Japanese patients, with improved physical function, QoL, and objective markers of inflammation, regardless of previous treatment with anti-TNF agents.

**Author Contributors**

Brian O. Porter, Sibylle Haemmerle, Ayako Fujishige, Shuhei Kaneko, and Shigeto Kobayashi were involved in the study design. Mitsumasa Kishimoto and Atsuo Taniguchi enrolled subjects into the study. All authors contributed to the analysis and interpretation of the data.
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Conflict of interest

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