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EXTENDED REPORT

Effect of secukinumab on clinical and radiographic outcomes in ankylosing spondylitis: 2-year results from the randomised phase III MEASURE 1 study

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ABSTRACT

Objective To evaluate the effect of secukinumab, an interleukin-17A inhibitor, on clinical signs and symptoms and radiographic changes through 2 years in patients with ankylosing spondylitis (AS).

Methods In the phase III MEASURE 1 study, patients were randomised to receive intravenous secukinumab 10 mg/kg (at baseline, week 2 and week 4) followed by subcutaneous secukinumab 150 mg (intravenous 150 mg; n=125) or 75 mg (intravenous 75 mg; n=124) every four weeks, or matched placebo (n=122). Placebo-treated patients were re-randomised to subcutaneous secukinumab 150 or 75 mg from week 16. Clinical efficacy assessments included Assessment of SpondyloArthritis international Society 20 (ASAS20) response rates through week 104. Radiographic changes at week 104 were assessed using the modified Stoke Ankylosing Spondylitis Spine Score (mSASSS).

Results 97 (77.6%) and 103 (83.1%) patients in the intravenous 150 mg and intravenous 75 mg groups, respectively, completed week 104. In the full analysis set (intent-to-treat), ASAS20 response rates at week 104 were 73.7% and 68.0% in the intravenous 150 mg and intravenous 75 mg groups, respectively. Among patients with evaluable X-rays who were originally randomised to secukinumab (n=168), mean change in mSASSS from baseline to week 104 was 0.30 ± 2.53 . Serious adverse events were reported in 12.2% and 13.4% of patients in the 150 mg and 75 mg groups, respectively.

Conclusions Secukinumab improved AS signs and symptoms through 2 years of therapy, with no unexpected safety findings. Data from this study suggest a low mean progression of spinal radiographic changes, which will need to be confirmed in longer-term controlled studies.

Trial registration number NCT01358175.

INTRODUCTION

Ankylosing spondylitis (AS), a chronic inflammatory disease primarily affecting the axial skeleton, can be associated with progressive irreversible structural damage, resulting in functional deterioration.^{1–3} Long-term treatment goals are to maximise quality of life through control of signs and symptoms, prevention of structural damage and preservation of physical function.⁴

Tumour necrosis factor (TNF) inhibitors are the recommended pharmacotherapy for patients with

high disease activity despite treatment with non-steroidal anti-inflammatory drugs (NSAIDs),^{4–5} based on their proven efficacy in improving signs, symptoms and physical function.^{6–10} However, up to 40% of patients do not respond to or cannot tolerate TNF inhibitors,¹¹ and loss of efficacy can occur over time.¹² Moreover, their effect on spinal osteoproliferative changes, a major component of structural damage in AS, is unclear.^{13–16}

The pro-inflammatory cytokine interleukin-17A (IL-17A) is implicated in various pathophysiological features of spondyloarthritis, including inflammation and pathogenic bone remodelling.^{17–29} In placebo-controlled phase III studies, secukinumab, a fully human anti-IL-17A monoclonal antibody, significantly improved the signs and symptoms of psoriasis,³⁰ psoriatic arthritis (PsA),³¹ and AS.³² Here, we present an update on the efficacy and safety of secukinumab in patients with AS during the non-controlled continuation phase of MEASURE 1 (NCT01358175) through 2 years. Results of exploratory radiographic endpoints at 2 years are also presented.

METHODS

Study design and patients

Study design and patient eligibility criteria have been described previously.³² Briefly, patients were ≥ 18 years of age, with AS fulfilling the modified New York Criteria, and active disease as defined by a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score of ≥ 4 ³³ and a spinal pain score of ≥ 4 cm on a visual analogue scale (0–10 cm), despite treatment with maximal tolerated doses of NSAIDs. Patients who previously received one anti-TNF agent could enrol if they had an inadequate response or had stopped treatment for safety or tolerability reasons (anti-TNF-IR). Patients could continue on stable doses of sulfasalazine, methotrexate, prednisone and NSAIDs. Key exclusion criteria are detailed in the online supplementary materials.

Between 9 November 2011 and 21 January 2013, eligible patients were randomly assigned (1:1:1) to one of two secukinumab arms or placebo (randomisation procedures are described in the online supplementary materials). Patients randomised to secukinumab received a 10 mg/kg intravenous infusion at baseline and weeks 2 and 4,

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followed by subcutaneous injections of 150 mg (secukinumab intravenous 150 mg) or 75 mg (intravenous 75 mg) every four weeks from week 8; patients in the placebo group were treated using the same intravenous-to-subcutaneous schedule. Placebo-treated patients were randomly reassigned (1:1) to receive secukinumab 150 or 75 mg subcutaneous every four weeks from week 16 (non-responders) or week 24 (responders), with response based on Assessment of SpondyloArthritis international Society 20 (ASAS20) response criteria.³

Procedures and end points

Disease activity and efficacy assessments^{3 34 35} were conducted at baseline and throughout the study, with key assessments at weeks 16 and 52 (as previously reported),³² and week 104; further details are provided in the online supplementary materials.

Lateral view radiographs of the cervical and lumbar spine were obtained at baseline and week 104. Images were digitised centrally and patient identifiers and temporal indicators removed to ensure blinding. Radiographs were scored using the modified Stoke Ankylosing Spondylitis Spine Score (mSASSS) method (total score range: 0–72; see online supplementary materials for further details).^{36 37} Scoring was conducted by two central, independent readers, blinded with regard to treatment group and temporal sequence, who both read each film; statistical analyses used the mean score from the two readers. The top 5% of cases with the highest between-reader differences for change in radiographic score were identified for adjudication, with the two readers performing a third consensus read. Data from X-ray completers (patients with X-rays at both baseline and week 104) are presented as mean change from baseline to week 104.

Safety analyses assessed adverse events (AEs), serious AEs and routine laboratory values. Biochemical investigations were classified according to the Common Terminology Criteria for Adverse Events (V4.03).³⁸ Blood samples were collected at baseline through week 104 for assessment of secukinumab immunogenicity using a MesoScale Discovery bridging immunoassay.³⁹

Statistical analysis

Clinical efficacy analyses at week 104 were carried out on data from patients originally randomised to secukinumab. Statistical analyses for binary variables up to week 104 used multiple imputation to account for missing data, while mixed-effect model repeated measures, with missing data assumed missing at random, were used for continuous variables (except high-sensitivity C-reactive protein (hsCRP) was reported as observed). Data are also reported 'as observed' among patients with evaluable data. Radiographic analyses were assessed in X-ray completers who were initially randomised to secukinumab treatment, and in X-ray completers who switched from placebo to secukinumab at week 16 or 24 (placebo switchers). In each population, data were pooled between treatment groups.

RESULTS

Patients

Of 371 patients originally randomised to treatment, 97/125 (77.6%) patients in the secukinumab intravenous 150 mg group, 103/124 (83.1%) in the intravenous 75 mg group and 90/122 (73.8%) in the placebo group (no placebo given beyond week 24) completed week 104. AEs (6.4% of patients), lack of efficacy (4.4%) and patient/guardian decision (5.8%) were the main reasons for discontinuation among secukinumab-treated patients (see online supplementary figure S1).

Demographic and baseline characteristics have been reported previously.³² Mean time since diagnosis in the three randomised

groups was 6.5–8.3 years, mean total BASDAI scores were 6.1–6.5 and median hsCRP levels were 7.4–9.2 mg/L. Approximately 73% of patients were anti-TNF-naïve.

Concomitant medications through 104 weeks were very similar to 52 weeks and baseline, and included sulfasalazine (35.0%), methotrexate (15.8%), systemic glucocorticoids (19.7%) and NSAIDs (93.6%).

Clinical efficacy

Among patients who continued on secukinumab treatment, ASAS20 and ASAS40 response rates similar to those achieved at weeks 16 and 52³² were observed at week 104 (figure 1A, B). ASAS20/40 response rates at week 104 (with multiple imputation of missing values) were 73.7/55.7%, respectively, in the secukinumab intravenous 150 mg group and 68.0/48.5% in the intravenous 75 mg group (table 1). Response rates using observed data are reported in table 1. Improvements consistent with those reported previously at weeks 16 and 52³² were also observed in total BASDAI score (figure 1C) and all other secondary end points at week 104 (table 1).

In prespecified subgroup analyses, ASAS20 and ASAS40 response rates in both anti-TNF-naïve and anti-TNF-IR patients were higher with secukinumab than placebo at week 16 (see online supplementary figure S2). Observed data showed that 59/69 (85.5%) and 47/65 (72.3%) anti-TNF-naïve patients in the secukinumab intravenous 150 mg and intravenous 75 mg groups, respectively, achieved an ASAS20 response at week 104; an ASAS40 response was achieved by 48/69 (69.6%) and 34/65 (52.3%) patients, respectively. In anti-TNF-IR patients, 10/18 (55.6%) and 15/21 (71.4%) patients achieved an ASAS20 response in the intravenous 150 mg and intravenous 75 mg groups, respectively, while 8/18 (44.4%) and 12/21 (57.1%) patients achieved an ASAS40 response.

Radiographic findings

Of the 97 patients in the secukinumab intravenous 150 mg group and 103 patients in the intravenous 75 mg group who completed week 104, 86 (88.7%) and 82 (79.6%), respectively, had evaluable X-rays at baseline and week 104 (X-ray completers) meeting predefined statistical analysis windows. Baseline characteristics of the X-ray completer cohort were similar between dose groups (table 2) and to those previously reported in the overall population.³² Overall, 104 (61.9%) X-ray completers had syndesmophytes at baseline and 105 (62.5%) had hsCRP >5 mg/L. Baseline characteristics of the 89 placebo-switcher X-ray completers (see online supplementary table S1) were similar to those originally randomised to secukinumab.

Figure 2 shows the cumulative probability plot for change from baseline in mSASSS at week 104 among X-ray completers randomised to secukinumab at baseline. The change in mSASSS (mean±SD) over 104 weeks was 0.30±2.53 in the pooled secukinumab group, 0.30±1.94 in the intravenous 150 mg group and 0.31±3.04 in the intravenous 75 mg group (table 3). Changes among placebo switchers were 0.54±2.45 (pooled), 0.44±2.09 (150 mg) and 0.64±2.79 (75 mg) (see online supplementary table S2 and figure S3). The smallest detectable change (SDC) was 1.838 and 2.814 at an 80% and 95% level of agreement, respectively. As defined by SDC at the 80% level of agreement, a large proportion of patients (>80%) had no spinal radiographic progression. The Bland-Altman plot in online supplementary figure S4 shows the level of agreement between the two readers; variability was observed, particularly when an mSASSS change of >0 was recorded. The intraclass

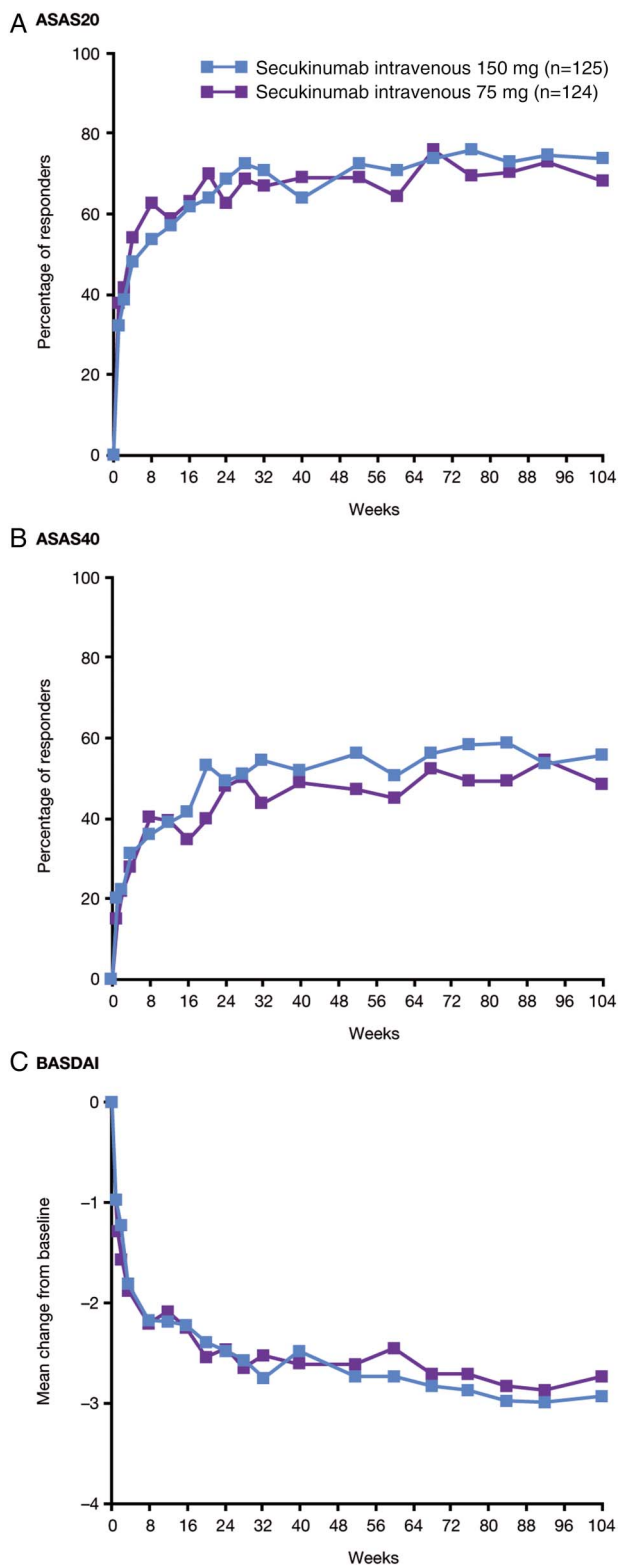


Figure 1 Summary of selected clinical efficacy end points through week 104 for patients randomised to secukinumab at baseline. Assessment of SpondyloArthritis international Society response criteria (ASAS20) (A) and ASAS40 (B) response rates, and mean change in total Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score (C) over time to week 104 is shown. Multiple imputation applied to handle missing data for ASAS20 and ASAS40, mixed-effects model repeated measures used for BASDAI. Patients received a 10 mg/kg loading dose of secukinumab at baseline and weeks 2 and 4, before receiving indicated dose of secukinumab subcutaneously every four weeks from week 8.

correlation coefficient (ICC) score for agreement between readers was 0.570 for change in mSASSS.

Baseline mSASSS was higher among patients with known predictors of radiographic progression compared with those without (table 3). Mean mSASSS change at week 104 among X-ray completers randomised to secukinumab was higher in males than females, in those with baseline syndesmophytes versus those without, in patients with elevated versus normal baseline hsCRP levels and in smokers versus non-smokers (table 3). Among the X-ray completers who had no syndesmophytes at baseline and who were randomised to secukinumab, 61/64 (95.3%), remained free from syndesmophytes at week 104. Of the 104 X-ray completers with syndesmophytes at baseline, approximately 70% did not develop additional syndesmophytes through week 104 (see online supplementary table S3).

Safety

The most common AEs with secukinumab were nasopharyngitis, diarrhoea, headache, upper respiratory tract infections and pharyngitis (table 4). Discontinuations due to AEs were infrequent. The incidence of serious AEs was low, and similar between the two secukinumab groups (table 4; see online supplementary table S4).

One death was reported among secukinumab-treated patients throughout the study; on day 706, a patient in the intravenous 75 mg group with a history of arterial hypertension and smoking died due to acute respiratory failure secondary to cardiac failure and pulmonary fibrosis. No suicides or suicidality-related AEs were reported among secukinumab-treated patients.

Candida infections were reported in four secukinumab-treated patients (0.7 cases per 100 patient-years of secukinumab exposure); two oral candidiasis (one in each dose group), one cutaneous *Candida* infection (150 mg group) and one genital candidiasis (75 mg group). All four events were considered mild and non-serious, resolved spontaneously or with standard anti-fungal therapy, and did not result in study discontinuation. Herpes viral infections — mainly oral herpes and herpes zoster infections — were reported by 8.3% of patients in the 150 mg group and 2.2% in the 75 mg group. All cases were non-serious. One led to treatment discontinuation (herpes zoster infection in the 150 mg group).

Grade 3 neutropenia occurred at a single visit in each of three patients receiving secukinumab 75 mg and one receiving secukinumab 150 mg. Grade 4 neutropenia was reported in one patient (75 mg group) at a single visit. None of these events led to treatment interruption or discontinuation. One grade 3 case was associated with a non-serious upper respiratory tract infection.

Crohn's disease was reported as a non-serious AE in four patients in the 75 mg group (of whom two had a history of Crohn's disease and one a history of a polyp and colon adenoma) and one patient in the 150 mg group, equivalent to 0.8 cases per 100 patient-years of secukinumab exposure. Two patients (one in each group; one with a history of Crohn's disease) discontinued because of an AE of Crohn's disease. A history of uveitis was reported in 62 (16.7%) patients at baseline. An AE of uveitis was reported in 12 patients (seven with history of uveitis) on secukinumab, equivalent to 2.0 cases per 100 patient-years of secukinumab exposure. One was a serious AE (150 mg group); this resolved and did not require discontinuation of study treatment. Nineteen (5.1%) patients had a history of psoriasis. Five patients reported an AE of psoriasis during the study (two on 75 mg, three on 150 mg),

Table 1 Summary of efficacy data at week 104 among patients randomised to secukinumab at baseline

Efficacy end point	Imputed		Observed	
	Secukinumab intravenous 150 mg (n=125)	Secukinumab intravenous 75 mg (n=124)	Secukinumab intravenous 150 mg	Secukinumab intravenous 75 mg
ASAS20 response	73.7%	68.0%	69/87 (79.3%)	62/86 (72.1%)
ASAS40 response	55.7%	48.5%	56/87 (64.4%)	46/86 (53.5%)
hsCRP, median change from baseline (min, max) (mg/L)	N/A	N/A	-4.20 (-143.6, 50.0) (n=88)	-2.7 (-97.5, 30.2) (n=87)
ASAS5/6 response	57.9%	52.2%	56/87 (64.4%)	49/86 (57.0%)
BASDAI, mean change from baseline	-2.93 (0.18)	-2.75 (0.18)	-3.41 (2.12) (n=87)	-3.04 (1.81) (n=86)
SF-36 PCS score, mean change from baseline	6.88 (0.68)	6.36 (0.69)	8.06 (8.08) (n=87)	7.41 (6.83) (n=85)
ASQoL score, mean change from baseline	-4.38 (0.45)	-4.34 (0.45)	-4.82 (4.83) (n=86)	-4.58 (4.44) (n=85)
ASAS partial remission	25.6%	19.3%	28/87 (32.2%)	20/86 (23.3%)

Binary variables are reported using multiple imputation (percentage of responders) to account for missing data and as observed data (n/m (%), where n=number of patients with response and m=number of patients with evaluable data). For continuous variables, mean change from baseline is reported as least-square mean change (SE) where mixed-effects model repeated measures analysis was performed and as observed data (SD). Patients received a 10 mg/kg loading dose of secukinumab at baseline and weeks 2 and 4, before receiving indicated dose of secukinumab subcutaneously every four weeks from week 8.

ASAS, Assessment of SpondyloArthritis international Society response criteria; ASQoL, Ankylosing Spondylitis Quality of Life; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; hsCRP, high-sensitivity C-reactive protein; N/A, not available; SF-36 PCS, Short Form-36 physical component summary.

Table 2 Baseline characteristics of the X-ray completer cohort randomised to secukinumab at baseline

Characteristic	Secukinumab intravenous 150 mg (n=86)	Secukinumab intravenous 75 mg (n=82)
Age, mean (SD) years	39.6 (12.0)	42.4 (13.1)
Male gender, n (%)	63 (73.3)	60 (73.2)
Weight, mean (SD) kg	75.2 (16.4)	78.4 (19.3)
Time since AS diagnosis, mean (SD) years	6.6 (7.0)	7.8 (8.9)
HLA-B27 positive, n (%)	64 (74.4)	72 (87.8)
Current smoker, n (%)	25 (29.1)	17 (20.7)
Anti-TNF-naive, n (%)	60 (69.8)	62 (75.6)
Medication use at baseline, n (%)		
Methotrexate	14 (16.3)	12 (14.6)
Sulfasalazine	27 (31.4)	32 (39.0)
Glucocorticoids	13 (15.1)	10 (12.2)
hsCRP, median (min, max), mg/L	7.8 (0.2, 147.7)	9.7 (0.4, 100.0)
Elevated hsCRP >5 mg/L, n (%)	55 (64.0)	50 (61.0)
Total BASDAI, mean (SD)	6.2 (1.6)	6.0 (1.5)
BASFI, mean (SD)	5.6 (2.2)	5.4 (2.0)
BASMI (linear), mean (SD)	3.9 (1.8)	4.2 (1.7)
mSASSS, mean (SD)	9.6 (16.6)	10.8 (16.7)
Syndesmophyte present, n (%)	51 (59.3)	53 (64.6)
Total back pain, mean (SD)	63.9 (17.2)	63.3 (18.6)
Patient's global assessment of disease activity, mean (SD)	64.6 (17.7)	60.5 (18.6)

Data are n (%), mean (SD), or median (minimum–maximum).

AS, ankylosing spondylitis; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; BASMI, Bath Ankylosing Spondylitis Metrology Index; HLA, human leucocyte antigen; hsCRP, high-sensitivity C-reactive protein; mSASSS, modified Stoke Ankylosing Spondylitis Spine Score; TNF, tumour necrosis factor.

three of which were described as worsening or exacerbation of psoriasis. No psoriasis AEs were considered serious or required treatment interruption or discontinuation.

Four secukinumab-treated patients (two in each dose group) had cardiovascular events adjudicated as meeting major adverse cardiac event (MACE) criteria: three myocardial infarctions and one ischaemic stroke (see online supplementary table S5). None of these events led to treatment discontinuation. The incidence of MACE was 0.6 per 100 patient-years of secukinumab exposure.

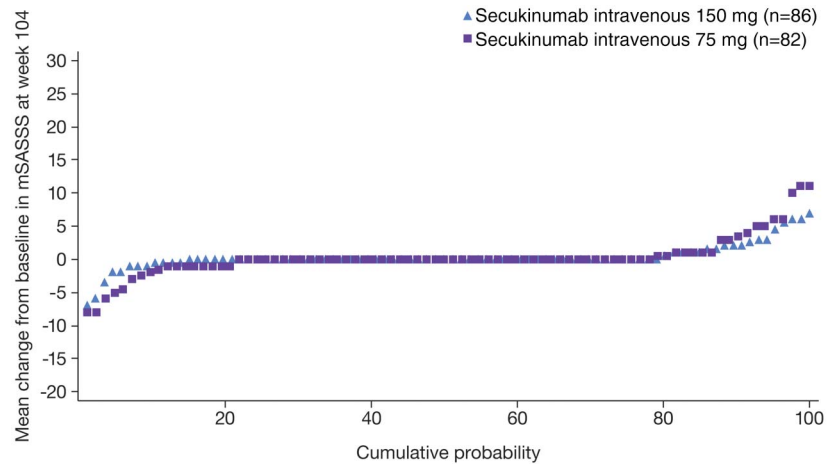
Four cases of malignant/unspecified tumours were reported (0.6 per 100 patient-years of secukinumab exposure), all before week 52, and have been described previously.³²

Treatment-emergent anti-secukinumab antibodies were detected through week 104 in two patients in the secukinumab 150 mg group; no neutralising antibodies were detected and neither patient experienced a loss of ASAS20 response.

DISCUSSION

This analysis demonstrates that secukinumab improves the clinical signs and symptoms of AS through 2 years of continued therapy. Secukinumab was effective in both anti-TNF-naive and anti-TNF-IR patients, although absolute response rates were generally higher in anti-TNF-naive patients. In contrast to the anti-TNF-naive subgroup, ASAS20 and ASAS40 response rates were highest with secukinumab intravenous 75 mg in anti-TNF-IR patients. However, these results should be viewed in the context of the relatively small number of anti-TNF-IR patients, particularly at week 104, and the heterogeneity of this subpopulation, which comprised patients who failed anti-TNF treatment for any one of several reasons, including lack of primary or secondary efficacy, or intolerance. Overall, given the lack of therapeutic alternatives, these findings indicate that secukinumab may address an unmet clinical need in

Figure 2 Cumulative probability plot for change from baseline in the modified Stoke Ankylosing Spondylitis Spine Score (mSASSS) at week 104 in X-ray completers randomised at baseline to secukinumab (observed data). X-ray completers are those patients with X-rays at both baseline and at week 104. Patients received a 10 mg/kg loading dose of secukinumab at baseline and weeks 2 and 4, before receiving indicated dose of secukinumab subcutaneously every four weeks from week 8.



anti-TNF-IR patients, as well as providing a high level of efficacy as first-line therapy in anti-TNF-naïve patients.

Prevention of structural damage is a long-term treatment goal in AS. The effect of anti-TNFs on radiographic progression in AS is unclear. mSASSS changes of 0.8–0.9 over 2 years have been reported with TNF inhibitors in AS clinical trials compared with 0.9–1.3 in respective matched biologic-naïve historical control cohorts from the Outcomes in AS International Study (OASIS).^{14–16} Authors concluded that the results do not provide evidence that anti-TNF therapy inhibits radiographic progression over 2 years. More recent studies have suggested that longer-term (approximately 8 years) treatment with an anti-TNF or earlier treatment initiation may be required to demonstrate an effect on radiographic progression.^{40–41} In the present study, the mean change in mSASSS through 2 years of secukinumab therapy was 0.30 (SD 2.53) overall, and 0.38–0.52 among patients with known predictors of radiographic progression at baseline, such as syndesmophytes or elevated CRP.⁴² Comparisons between these findings and those reported in the aforementioned studies and historical cohorts cannot be made because of differences in study designs and populations. Data from OASIS are from a period when treatment options were limited, and early TNF inhibitor trials are likely to have had more severe disease than those enrolled in MEASURE 1 and other recent placebo-controlled trials. Indeed, patients with evidence of radiographic progression are now more likely to be prescribed an approved TNF inhibitor than enter a clinical trial in which they might be randomised to placebo, and the anti-TNF trials included patients with longer disease duration (~10–11 years vs ~7 years in X-ray completers)^{8–14–16} and more severe radiographic disease at baseline (mSASSS ~16–20^{13–16} vs ~10) than in our study. Agreement between readers in mSASSS change was modest, with an ICC within the expected range of those reported from other studies.^{13–15–43} The Bland-Altman plot indicates that there is inter-reader variability, particularly where changes in mSASSS have occurred. The low overall rate of progression seen with secukinumab requires further exploration in long-term controlled studies before definite conclusions can be reached on whether anti-IL-17A therapy is effective in inhibiting mSASSS progression in patients with AS. Comparing radiographic changes associated with secukinumab with the historical cohorts, matched in terms of baseline disease, is also a possible area of future research.

Secukinumab showed an acceptable safety profile over 622.5 patient-years of exposure, with no new safety signals or unexpected safety findings compared with the first 52 weeks³²

or with the safety profile reported in PsA and psoriasis.^{30–31} The incidence of AEs was higher with 150 mg than with 75 mg, driven primarily by non-serious infections. Serious infections were infrequent in both secukinumab groups. *Candida* infections, a known risk with IL-17 inhibitors given the role of IL-17 in mucosal defence,⁴⁴ were infrequent, mild and clinically manageable with antifungals. No dose dependence was observed for other safety risks. All four patients who reported MACE events on secukinumab treatment had pre-existing cardiovascular risk factors. The incidence of MACE in our study (0.6 per 100 patient-years) is consistent with reported data in AS.⁴⁵

Spondyloarthritis is often associated with extra-articular manifestations such as uveitis, psoriasis and inflammatory bowel disease.² Patients with previous or stable presentation of these conditions could enrol in MEASURE 1. The incidence of extra-articular manifestations reported as AEs in our study was low and consistent with expected rates in AS. IL-17A has been reported to have either a pathogenic or a protective role in Crohn's disease.^{46–47} The incidence of Crohn's disease in the present study (0.8 per 100 patient-years of secukinumab exposure) compares with reported rates of 0.2–1.3 per 100 patient-years for TNF inhibitors in the AS population.⁴⁸

Limitations of this analysis include the lack of comparator group beyond week 16, limiting interpretation of long-term findings to a comparison between secukinumab doses and to longitudinal evaluation. Despite the use of accepted statistical methods to account for missing data during the continuation period of the study, there remains a possible bias from the fact that patients who stay on study are those who do well on study treatment. Nevertheless, retention rates were high throughout the study and only 4.4% of patients withdrew because of lack of efficacy during the 2-year period. The slow nature of radiographic disease progression in AS means long follow-up periods are required to show measurable changes. This prohibits the inclusion of a placebo comparator and can introduce confounding effects of concomitant treatment with other drugs that influence radiographic progression.⁴⁹ Although blinded to treatment groups and sequence, readers were aware that all patients received secukinumab, possibly introducing an observational bias.

In conclusion, these longitudinal results from MEASURE 1 demonstrate that secukinumab provides similar levels of improvement in the clinical signs and symptoms of AS at 2 years as those previously reported during the short-term placebo-controlled period and provide the first uncontrolled

Clinical and epidemiological research

Table 3 mSASSS in the X-ray completer cohort randomised to secukinumab at baseline

Variable	Secukinumab intravenous 150 mg	Secukinumab intravenous 75 mg	Secukinumab pooled
Overall population			
Patients (n)	86	82	168
Baseline	9.63 (16.63)	10.84 (16.69)	10.22 (16.62)
Change at week 104	0.30 (1.94)	0.31 (3.04)	0.30 (2.53)
Patients with syndesmophytes at baseline			
Patients (n)	51	53	104
Baseline	16.12 (19.09)	16.69 (18.32)	16.41 (18.61)
Change at week 104	0.49 (2.50)	0.45 (3.77)	0.47 (3.20)
Patients without syndesmophytes at baseline			
Patients (n)	35	29	64
Baseline	0.17 (0.56)	0.16 (0.40)	0.16 (0.49)
Change at week 104	0.01 (0.19)	0.03 (0.33)	0.02 (0.26)
Elevated hsCRP			
Patients (n)	55	50	105
Baseline	11.57 (17.69)	14.22 (19.16)	12.83 (18.36)
Change at week 104	0.48 (2.25)	0.46 (3.08)	0.47 (2.66)
Normal hsCRP			
Patients (n)	31	32	63
Baseline	6.18 (14.19)	5.56 (10.04)	5.87 (12.16)
Change at week 104	-0.03 (1.16)	0.06 (3.00)	0.02 (2.27)
Male			
Patients (n)	63	60	123
Baseline	11.91 (18.57)	13.70 (18.44)	12.78 (18.45)
Change at week 104	0.19 (2.01)	0.58 (3.44)	0.38 (2.79)
Female			
Patients (n)	23	22	45
Baseline	3.39 (6.44)	3.05 (5.68)	3.22 (6.02)
Change at week 104	0.59 (1.73)	-0.46 (1.23)	0.08 (1.58)
Smokers (at baseline)			
Patients (n)	25	17	42
Baseline	13.10 (19.45)	10.88 (9.20)	12.20 (16.00)
Change at week 104	-0.18 (1.71)	1.56 (4.00)	0.52 (2.95)
Non-smokers (at baseline)			
Patients (n)	61	65	126
Baseline	8.21 (15.28)	10.83 (18.21)	9.56 (16.84)
Change at week 104	0.49 (2.00)	-0.02 (2.67)	0.23 (2.38)

n indicates number of patients with evaluable paired X-ray data at both baseline and week 104 (X-ray completers). Data shown as mean (SD). mSASSS ranges from 0 to 72, with higher scores indicating greater radiographic damage. Patients received 10 mg/kg secukinumab at baseline and weeks 2 and 4, before receiving indicated dose of secukinumab subcutaneously every four weeks from week 8. hsCRP, high-sensitivity C-reactive protein; mSASSS, modified Stoke Ankylosing Spondylitis Spine Score.

data on spinal radiographic progression in patients with AS under treatment with an IL-17A inhibitor. Long-term controlled studies are needed to evaluate whether secukinumab inhibits the progression of structural manifestations of AS.

Table 4 Incidence of treatment-emergent adverse events (AEs) during the entire treatment period through to week 104

Variable	Any secukinumab 150 mg (n=181)*	Any secukinumab 75 mg (n=179)*	Any secukinumab pooled (n=360)*
Exposure to study treatment (days) [†]	621.3 (187.5)	642.0 (180.9)	631.6 (184.3)
Number of patients with event (%)			
Any AE	157 (86.7)	144 (80.4)	301 (83.6)
Serious AE [‡]	22 (12.2)	24 (13.4)	46 (12.8)
Any AE leading to discontinuation [§]	17 (9.4)	8 (4.5)	25 (6.9)
Infection or infestation [¶]	110 (60.8)	100 (55.9)	210 (58.3)
Common AEs (seen in >5% of patients on secukinumab), n (%)			
Nasopharyngitis	44 (24.3)	35 (19.6)	79 (21.9)
Diarrhoea	25 (13.8)	22 (12.3)	47 (13.1)
Headache	22 (12.2)	20 (11.2)	42 (11.7)
Upper respiratory tract infection	17 (9.4)	21 (11.7)	38 (10.6)
Pharyngitis	21 (11.6)	12 (6.7)	33 (9.2)
Dyslipidaemia	14 (7.7)	16 (8.9)	30 (8.3)
Influenza	17 (9.4)	13 (7.3)	30 (8.3)
Oropharyngeal pain	16 (8.8)	13 (7.3)	29 (8.1)
Arthralgia	13 (7.2)	11 (6.1)	24 (6.7)
Back pain	13 (7.2)	7 (3.9)	20 (5.6)
Leucopenia	8 (4.4)	12 (6.7)	20 (5.6)
Cough	10 (5.5)	9 (5.0)	19 (5.3)
Nausea	10 (5.5)	9 (5.0)	19 (5.3)
AEs of special interest, n (exposure-adjusted incidence rate per 100 patient-years)			
<i>Candida</i> infections	2 (0.7)	2 (0.6)	4 (0.7)
Serious infections	3 (1.0)	3 (1.0)	6 (1.0)
Crohn's disease	1 (0.3)	4 (1.3)	5 (0.8)
Major adverse cardiac events (adjudicated)	2 (0.7)	2 (0.6)	4 (0.6)
Malignancy	3 (1.0)	1 (0.3)	4 (0.6)
Neutropenia (preferred term)	9 (3.1)	14 (4.8)	23 (3.9)

*Includes patients randomised to secukinumab at baseline and patients who were randomised to placebo who switched to secukinumab at weeks 16 or 24.

[†]Reported as mean (SD).

[‡]Serious AEs also include deaths.

[§]Up to week 104; an additional two patients discontinued secukinumab due to any AEs after week 104.

[¶]System organ class category.

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Effect of secukinumab on clinical and radiographic outcomes in ankylosing spondylitis: 2-year results from the randomised phase III MEASURE 1 study

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