



# A Pooled Analysis Reporting the Efficacy and Safety of Secukinumab in Male and Female Patients with Ankylosing Spondylitis

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## ABSTRACT

**Introduction:** Despite of higher disease burden, lower efficacy to biologics has been reported in female compared to male patients with ankylosing spondylitis (AS). The aim of this study was to evaluate the efficacy and safety of secukinumab by sex in patients with active AS from five phase 3 studies (MEASURE 1–5) through 52 weeks.

**Methods:** Baseline demographics, disease characteristics and efficacy outcomes at Weeks 16 and 52 were summarized for males versus

females. Baseline predictor analysis used multi-variable logistic regression for binary outcome measures or generalized linear model for continuous outcome measures to assess the impact of sex as one of the independent variables on selected efficacy outcomes at Week 52.

**Results:** Overall, 1031 males and 396 females were included in this analysis. Smoking status, hs-CRP, prior exposure to TNF inhibitors, BASMI occiput-to-wall and tragus-to-wall distance (cm) were higher in males, whereas MASES was higher in females. Efficacy outcomes i.e., ASAS40 responses and BASDAI change from baseline at Weeks 16 and 52 were generally comparable between males and females. Response rates were found to be significantly higher in male patients when compared with

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female patients only for ASDAS-CRP inactive disease (ID) at Week 52.

**Conclusion:** Comparable efficacy and safety outcomes were observed between male and female patients with active AS treated with secukinumab over 52 weeks. Further, sex was not an independent predictor of treatment response to secukinumab as assessed by ASAS40 responder rates and BASDAI change from baseline; association of ASDAS-CRP ID responder rates with sex warrants further exploration.

**Trial registration:** ClinicalTrials.gov; NCT01358175, NCT01649375, NCT02008916, NCT02159053, and NCT02896127.

**Keywords:** Ankylosing spondylitis; Interleukins; Sex; Biologics; Axial spondyloarthritis; Secukinumab; DMARDs; TNF inhibitors; Quality of life; Spondyloarthropathies

### Key Summary Points

#### Why carry out this study?

The relative efficacy of the treatment of AS may differ between males and females, hence a better understanding of the sex-attributable differences in response to biologic therapy is important.

This is the first post hoc analysis from a large, pooled dataset of patients with AS, reporting the efficacy and safety of an IL-17 inhibitor by sex.

#### What was learned from the study?

High retention rates for both males and females were observed in this pooled dataset in contrast to previous studies with TNF inhibitors.

Secukinumab demonstrated comparable improvements in the assessed outcome measures across males and females through Week 52, except for ASDAS-CRP ID response rates.

## INTRODUCTION

Ankylosing spondylitis (AS) is a chronic inflammatory disease of the axial skeleton and the sacroiliac joints [1, 2], historically seen as a predominantly male condition [3]. However, a steady decline in the male–female ratio has been reported among patients with AS, with increasing rates of diagnosis among women over 36 years (1980–2016) [4]. Recent studies have shown that female patients with AS report higher disease activity and functional impairment [5] with a reduced quality of life [6] and are likely to have higher disease burden than males [7–9]. In terms of AS phenotype, notable differences have been reported between male and female patients [10]; males present with more severe spinal radiographic changes [11] and less peripheral arthritis [12, 13].

It is generally recognized that the relative efficacy of the treatment of AS may differ between males and females, hence a better understanding of the sex-attributable differences in response to biologic therapy is important. However, data on the variability of treatment response to biologics with respect to sex in AS are limited. Previous analysis after tumor necrosis factor inhibitors (TNFi) suggest that efficacy may be lower in females than males even when similar disease burden is seen between the groups [9, 13]. In addition, the treatment retention rate was markedly lower for female patients treated with TNFi compared to males [9].

Secukinumab, an interleukin (IL)-17A inhibitor, has demonstrated sustained improvement in the signs and symptoms of active AS in the MEASURE clinical trial program [5, 6, 12, 14, 15]. The impact of sex on the efficacy of secukinumab has not been thoroughly evaluated and although comparative effectiveness in the real-world setting between TNFi and secukinumab has been previously reported, stratification by sex was not investigated further [16, 17]. In this post hoc analysis, we report efficacy and safety data pooled from five phase 3 MEASURE studies with respect to sex in patients with active AS treated with secukinumab through 52 weeks.

## METHODS

### Study design and patients

Pooled data from MEASURE 1 (NCT01358175), MEASURE 2 (NCT01649375), MEASURE 3 (NCT02008916), MEASURE 4 (NCT02159053), and MEASURE 5 (NCT02896127) studies in patients with active AS were analyzed. The design, eligibility criteria, methodology and statistical analysis of these individual studies have been published elsewhere [5, 6, 12, 14, 15]. Briefly, patients aged  $\geq 18$  years diagnosed with AS, fulfilling the modified New York criteria, with a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score  $\geq 4$  (on a 0–10 scale) and spinal pain score  $\geq 40$  mm (on a 0–100 mm visual analogue scale), despite treatment with the maximum tolerated dose of NSAIDs, were included in these studies.

Key exclusion criteria were total spinal ankylosis, evidence of infection or cancer on chest radiography, active systemic infection within 2 weeks prior to randomization and previous treatment with cell-depleting therapies or biological agents other than TNFi agents. A flowchart of the key inclusion and exclusion criteria of MEASURE 1, 2, 3, 4, and 5 studies is presented in online Supplementary Figure S1.

In MEASURE 1 and MEASURE 3, patients were randomized to receive intravenous (i.v.) secukinumab 10 mg/kg at baseline and Weeks 2 and 4, followed by subcutaneous (s.c.) secukinumab 150 or 75 mg (MEASURE 1) or s.c. secukinumab 300 or 150 mg (MEASURE 3) every 4 weeks (q4w) starting at Week 8 or matched placebo [12]. In MEASURE 2 and MEASURE 5, patients were randomized to receive s.c. secukinumab 75 or 150 mg (MEASURE 2) or 150 mg (MEASURE 5) at baseline, Weeks 1, 2 and 3 and q4w starting at Week 4 or matched placebo [6, 12]. In MEASURE 4, patients were randomized to receive s.c. secukinumab 150 mg with loading doses (150 mg LD), without loading doses (150 mg no load), or placebo at baseline, Weeks 1, 2, and 3 and every 4 weeks starting at Week 4 [14, 15]. Based on the clinical response, placebo-treated patients were switched to receive secukinumab at Week 16 or 24 in

MEASURE 1 study, whereas all patients receiving placebo in MEASURE 2, 3, 4, and 5 studies were switched to receive secukinumab at Week 16.

Efficacy results at Week 16 are presented for the following treatment groups: (a) secukinumab 300 mg i.v. LD (secukinumab 300 mg i.v. LD followed by secukinumab 300 mg s.c.); (b) secukinumab 150 mg i.v. LD (secukinumab 150 mg i.v. LD followed by secukinumab 150 mg s.c.); (c) secukinumab 150 mg s.c. LD (secukinumab 150 mg s.c. LD followed by secukinumab 150 mg s.c.); (d) secukinumab 150 mg no load (secukinumab 150 mg s.c. no load followed by secukinumab 150 mg s.c.) and (e) placebo. At Week 52, efficacy results are presented for the following groups: (i) Any secukinumab 300 mg (secukinumab 300 mg i.v. LD) and (ii) Any secukinumab 150 mg (secukinumab 150 mg i.v. LD, 150 mg i.v. no-load, 150 mg s.c. LD).

All study protocols and its amendments were reviewed and approved by the independent ethics committee or institutional review board for each participating center. The study was conducted according to the International Council for Harmonization (ICH) E6 Guideline for Good Clinical Practice (GCP) that has its origin in the Declaration of Helsinki. Written informed consent was obtained from all enrolled patients. Data were collected in accordance with the GCP guidelines by the study investigators and analyzed by the sponsor.

### Assessments

This analysis assessed by sex included proportion of patients achieving Assessment of SpondyloArthritis international Society (ASAS)20, ASAS40, AS Disease Activity Score C-reactive Protein (CRP)—Inactive Disease (ASDAS-CRP ID), ASDAS—Clinically Important Improvement (CII) responses and the mean change from baseline in BASDAI, Bath Ankylosing Spondylitis Metrology Index (BASMI), Bath Ankylosing Spondylitis Functional Index (BASFI), Short Form (36)—Physical Component Summary (SF-36 PCS), Functional Assessment of Chronic Illness Therapy—Fatigue (FACIT-

Fatigue) scores with secukinumab (up to Week 52) and placebo (up to Week 16). Baseline predictor analysis was also conducted to assess the impact of sex at Week 52 on the proportions of ASAS40 and ASDAS-CRP ID responders and the mean changes in BASDAI score from baseline. Overall safety and tolerability data were pooled by sex.

### Statistical Analyses

Descriptive efficacy summaries are based on data as observed at Weeks 16 and 52 and are presented by treatment group (secukinumab or placebo) assigned at randomization.

In the baseline predictor analyses, univariate logistic regression analyses were first conducted to select potential baseline predictors. All the variables with  $P$  values  $< 0.20$  from the univariate analyses were included in the multivariable logistic regression or generalized linear model (GLM) for further selection. Only those variables with  $P$  values  $< 0.05$  were retained in the final models. Treatment group and sex, as a mandatory factor of primary interest, were included in the final models. To assess the impact of sex in 'any secukinumab' group as an independent variable on the binary efficacy outcomes of ASAS40 and ASDAS-CRP ID, a multivariate logistic regression analysis was performed. To assess the impact of sex on the continuous efficacy outcome of BASDAI change from baseline to Week 52, a GLM was used.

Pooled safety analyses by sex included all patients who received at least one dose of secukinumab.

## RESULTS

### Baseline demographics and disease characteristics

In total, 1031 male and 396 female patients with active AS who received secukinumab (males [ $n = 642$ ]; females [ $n = 243$ ]) or placebo (males [ $n = 389$ ]; females [ $n = 153$ ]) from MEASURE 1–5 studies, were included in this analysis. A total of 590 (91.9%) males and 211 (86.8%)

females completed 52 weeks of secukinumab treatment, with a total mean (SD) exposure of 112.5 (73.2) weeks in males and 128.8 (80.1) weeks in females. The rates of discontinuation were slightly higher in females (12.3%) vs. males (8.4%) in 'any secukinumab' group with major reasons for discontinuation of the secukinumab treatment in the females being adverse events (4.5%) followed by lack of efficacy (4.1%).

Demographic and baseline disease characteristics by sex were reported in Table 1. Smoking status, high sensitivity C-reactive protein (hs-CRP), prior TNFi exposure, BASMI occiput-to-wall distance, BASMI tragus-to-wall distance were all higher in males and Maastricht Ankylosing Spondylitis Enthesitis Score (MASES) was higher in females. In particular, a significantly higher proportion of male patients were TNFi-naïve ( $P = 0.0026$ ) and current smokers ( $P < 0.0001$ ) than female patients. The hs-CRP levels, mean BASMI score (Linear), BASMI occiput-to-wall distance and BASMI tragus-to-wall distance were significantly higher in males ( $P < 0.0001$ ); on the contrary, mean MASES score was significantly higher in females ( $P < 0.0001$ ). The mean baseline BASDAI score was  $\sim 7$  across 'Any secukinumab' group and placebo groups in both males and females.

### Efficacy by sex

A comparable proportion of male versus female patients achieved an ASAS40 response at Week 16 across all secukinumab groups, which was sustained or further improved at Week 52 in males ('Any secukinumab' 300 mg: 61.7% and 150 mg: 60.0%) versus females ('Any secukinumab' 300 mg: 68.4% and 150 mg: 56.2% at Week 52) (Fig. 1A). A similar trend in the decrease of mean BASDAI scores was observed in male versus female patients at Week 16 across all secukinumab groups, which was improved at Week 52: 'Any secukinumab' 300 mg (males:  $-3.6$  vs. females:  $-3.7$ ) and 'Any secukinumab' 150 mg groups (males:  $-3.4$  vs. females:  $-3.5$ ) (Fig. 1B). Other efficacy parameters including ASAS20, ASDAS-CRP ID and ASDAS-CRP CII responses, as well as mean

**Table 1** Demographic and baseline disease characteristics by sex

| Characteristic mean (SD) unless specified otherwise | Any secukinumab |                   | Placebo         |                   | P value* |
|---|-----------------|-------------------|-----------------|-------------------|----------|
|   | Male<br>N = 642 | Female<br>N = 243 | Male<br>N = 389 | Female<br>N = 153 |          |
| Age (years)   | 38.9 (11.4)     | 41.6 (12.2)       | 39.1 (12.4)     | 43.5 (12.6)       | < 0.0001 |
| Weight (kg)   | 79.7 (18.4)     | 70.8 (17.8)       | 78.6 (15.1)     | 71.4 (16.5)       | < 0.0001 |
| BMI (kg/m <sup>2</sup> )                            | 26.2 (5.5)      | 26.6 (6.3)        | 25.9 (4.5)      | 27.0 (6.1)        | 0.0307   |
| Current smoking (yes), n (%)                        | 239 (37.2)      | 42 (17.3)         | 148 (38.0)      | 33 (21.6)         | < 0.0001 |
| Time since first diagnosis of AS (years)            | 6.5 (7.7)       | 6.0 (7.6)         | 6.8 (8.2)       | 6.2 (7.5)         | 0.2322   |
| hs-CRP (mg/L)                                       | 18.3 (28.2)     | 10.7 (18.1)       | 17.9 (22.9)     | 10.0 (14.8)       | < 0.0001 |
| TNFi naïve, n (%)                                   | 489 (76.2)      | 170 (70.0)        | 297 (76.3)      | 101 (66.0)        | 0.0026   |
| MASES   | 2.4 (3.1)       | 4.6 (3.8)         | 2.3 (3.0)       | 4.9 (3.9)         | < 0.0001 |
| ASDAS-CRP   | 3.81 (0.8)      | 3.6 (0.9)         | 3.83 (0.9)      | 3.65 (0.8)        | < 0.0001 |
| BASDAI  | 6.7 (1.4)       | 7.1 (1.4)         | 6.7 (1.3)       | 7.1 (1.4)         | < 0.0001 |
| BASMI linear (cm)                                   | 3.9 (1.8)       | 3.3 (1.4)         | 3.9 (1.7)       | 3.5 (1.5)         | < 0.0001 |
| BASMI occiput-to-wall distance (cm)                 | 4.8 (6.0)       | 2.6 (4.2)         | 5.3 (7.3)       | 2.5 (4.0)         | < 0.0001 |
| BASMI tragus-to-wall distance (cm)                  | 14.7 (5.2)      | 12.1 (2.9)        | 15.2 (5.3)      | 12.5 (3.3)        | < 0.0001 |
| BASFI   | 6.1 (2.0)       | 6.3 (2.1)         | 6.1 (1.9)       | 6.1 (2.2)         | 0.3065   |

*ASDAS* Ankylosing Spondylitis Disease Activity Score, *BASDAI* Bath Ankylosing Spondylitis Disease Activity Index, *BASFI* Bath Ankylosing Spondylitis Functional Index, *BASMI* Bath Ankylosing Spondylitis Metrology Index, *hs-CRP* high sensitivity C-reactive protein, *PBO* placebo, *SD* standard deviation, *TNFi* tumor necrosis factor inhibitor

change from baseline in BASFI, BASMI, SF-36 PCS, and FACIT-Fatigue at Weeks 16 and 52 are shown in Table 2.

There was no significant impact of sex as an independent predictor of treatment response to ‘Any secukinumab’ group on ASAS40 response rates (OR, 1.30;  $P = 0.10$ ) or the change from baseline in BASDAI score (OR,  $-0.10$ ;  $P = 0.48$ ) at Week 52. However, a significant impact of sex on treatment response to ‘Any secukinumab’ group was observed for ASDAS-CRP ID in male patients (OR, 1.70;  $P = 0.002$ ) when compared with female patients at Week 52 (Table 3).

## Safety

During the entire safety reporting period, treatment-emergent adverse events were reported in the ‘Any secukinumab’ group for 550

males (85.8%) and 220 females (90.5%) (Table 4). The most frequent treatment-emergent AE during the entire safety period was nasopharyngitis in both males and females. The proportion of male patients with non-fatal SAEs was comparable to that of female patients (11.5% vs. 9.9%, respectively). A higher proportion of female patients experienced AEs that led to treatment discontinuation, as compared to male patients (12.3% and 8.4%, respectively) (Table 4). There were four male patients who reported ulcerative colitis vs. one female patient; Crohn’s disease was reported in one male patient, which led to study discontinuation. *Candida* infection was reported in one female patient, which was resolved and, was not considered to be related to study medication, and did not lead to study discontinuation.

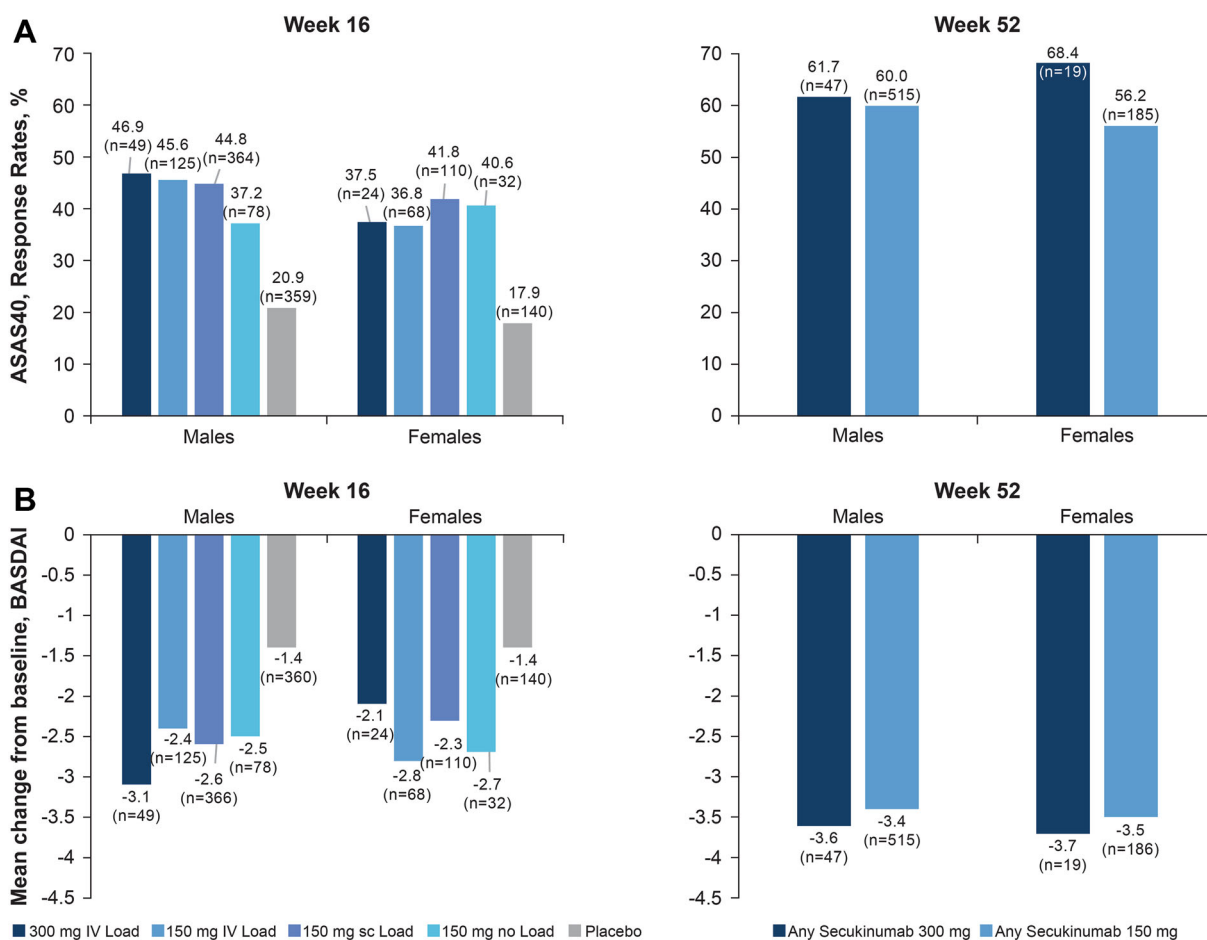


## DISCUSSION

This is the first post hoc analysis reporting efficacy and safety by sex from a large, pooled dataset of 1427 patients with active AS from five pooled randomized clinical trials of secukinumab [5, 6, 12, 14, 15]. Although there is a gap of knowledge on the performance of different efficacy outcome measures according to sex, secukinumab generally demonstrated comparable treatment responses for male and female AS patients both at Weeks 16 and 52. Furthermore, although for some outcome measures, females at Week 16 were behind males in terms of response rates (37.5% vs. 46.9%), they

reached and even outperformed male patients by Week 52 (68.4% vs. 61.7%). The observed differences in efficacy after 16 weeks of treatment were no longer evident at Week 52, suggesting that longer term follow up might be needed to assess the full magnitude of response in female patients. This analysis also demonstrated a high retention rate for different doses of secukinumab at Week 52 for both males and females (91.9% vs. 86.8%, respectively), with even higher mean treatment exposure for female patients (128.8 weeks vs. 112.5 weeks).

The differences in immune responses, sex hormones, and genetic predisposition might contribute to variable disease manifestations and therapeutic response to biologics in men



**Fig. 1** ASAS40 response rates and mean change from baseline in BASDAI score at Week 16 and 52 by sex. Data is presented as observed. *ASAS* Assessments of

SpondyloArthritis international Society, *BASDAI* Bath Ankylosing Spondylitis Disease Activity Index, *n* total number of patients evaluated in the treatment group

**Table 2** Summary of efficacy responses by sex

| Variable,  | Week | Any secukinumab<br>300 mg |                            | Any secukinumab<br>150 mg |                             | Placebo                   |                             |
|--|------|---------------------------|----------------------------|---------------------------|-----------------------------|---------------------------|-----------------------------|
|  |      | Male<br>( <i>N</i> = 50)  | Female<br>( <i>N</i> = 26) | Male<br>( <i>N</i> = 592) | Female<br>( <i>N</i> = 217) | Male<br>( <i>N</i> = 389) | Female<br>( <i>N</i> = 153) |
| ASAS20, % ( <i>n</i> )                                 | 16   | 69.4 (49)                 | 50 (24)                    | 62.6 (567)                | 62.9 (210)                  | 39.8 (359)                | 37.9 (140)                  |
|  | 52   | 83.0 (47)                 | 73.7 (19)                  | 75.7 (515)                | 74.6 (185)                  | –                         | –                           |
| ASDAS-CRP inactive disease,<br>% ( <i>n</i> )          | 16   | 20.4 (49)                 | 20.8 (24)                  | 15.5 (567)                | 14.9 (208)                  | 4.2 (360)                 | 2.2 (139)                   |
|  | 52   | 25.5 (47)                 | 31.6 (19)                  | 25.2 (515)                | 22.6 (186)                  | –                         | –                           |
| ASDAS-CRP CII*, % ( <i>n</i> )                         | 16   | 65.3 (49)                 | 45.8 (24)                  | 60.1 (567)                | 48.6 (208)                  | 23.4 (359)                | 21.6 (139)                  |
|  | 52   | 68.1 (47)                 | 63.2 (19)                  | 74.2 (515)                | 62.9 (186)                  | –                         | –                           |
| BASFI, mean change from<br>baseline (SD)/ <i>n</i>     | 16   | – 2.7<br>(2.6)/<br>49     | – 2.2<br>(3.1)/24          | – 2.1<br>(2.3)/<br>569    | – 2.1 (2.4)/<br>210         | – 1.1<br>(2.2)/<br>360    | – 0.8 (2.2)/<br>140         |
|  | 52   | – 3.1<br>(2.4)/<br>47     | – 3.6<br>(2.6)/19          | – 2.9<br>(2.4)/<br>515    | – 2.9 (2.7)/<br>186         | –                         | –                           |
| BASMI, mean change from<br>baseline (SD)/ <i>n</i>     | 16   | – 0.4<br>(0.8)/<br>49     | – 0.3<br>(0.7)/25          | – 0.6<br>(0.8)/<br>557    | – 0.3 (0.8)/<br>207         | – 0.3<br>(0.8)/<br>354    | – 0.2 (0.9)/<br>136         |
|  | 52   | – 0.5<br>(0.9)/<br>48     | – 0.6<br>(1.0)/19          | – 0.8<br>(0.9)/<br>505    | – 0.6 (0.9)/<br>183         | –                         | –                           |
| SF-36 PCS, mean change from<br>baseline (SD)/ <i>n</i> | 16   | NA <sup>†</sup>           | NA <sup>†</sup>            | 6.8 (7.0)/<br>531         | 7.0 (7.8)/<br>185           | 3.5 (7.0)/<br>330         | 3.1 (7.1)/<br>109           |
|  | 52   | NA <sup>†</sup>           | NA <sup>†</sup>            | 8.6 (7.7)/<br>487         | 9.3 (8.5)/<br>172           | –                         | –                           |
| FACIT-F, mean change from<br>baseline (SD)/ <i>n</i>   | 16   | NA <sup>†</sup>           | NA <sup>†</sup>            | 7.7 (9.3)/<br>289         | 9.1 (11.8)/<br>132          | 4.7 (9.4)/<br>201         | 4.6 (10.5)/<br>90           |
|  | 52   | NA <sup>†</sup>           | NA <sup>†</sup>            | 9.8 (10.4)/<br>265        | 12.0 (12.0)/<br>123         | –                         | –                           |

Data is presented as observed

*N* total number of patients in the group; *n* total number of evaluable patients in the treatment group

*ASAS* Assessments of SpondyloArthritis international Society, *ASDAS* Ankylosing Spondylitis Disease Activity Score, *BASFI* Bath Ankylosing Spondylitis Functional Index, *BASMI* Bath Ankylosing Spondylitis Metrology Index, *CII* clinically important improvement, *CRP* C-reactive protein, *SF-36 PCS* Short Form-36 Physical Component Summary, *FACIT-F* Functional Assessment of Chronic Illness Therapy-Fatigue, *PBO* placebo, *SD* standard deviation

\*ASDAS-CRP CII is defined as a change  $\geq 1.1$  units

<sup>†</sup> NA, outcomes were not assessed in MEASURE 3 trial, which was the only trial to include secukinumab 300 mg dose

**Table 3** Impact of sex on ASAS40, ASDAS-CRP ID, and BASDAI at week 52

| Predictor   | Variables              |                |                           |                |                              |                |
|---|------------------------|----------------|---------------------------|----------------|------------------------------|----------------|
|   | ASAS40 <sup>a</sup>    |                | ASDAS-CRP ID <sup>a</sup> |                | BASDAI <sup>b</sup>          |                |
|   | Odds ratio<br>(95% CI) | <i>P</i> value | Odds ratio<br>(95% CI)    | <i>P</i> value | Treatment effect<br>(95% CI) | <i>P</i> value |
| Baseline ASDAS-CRP  | NA                     | NA             | 0.66 (0.56,<br>0.79)      | < 0.0001       | NA                           | NA             |
| Baseline BASDAI   | NA                     | NA             | NA                        | NA             | 0.54 (0.45, 0.63)            | < 0.0001       |
| Sex (male vs. female)                                       | 1.3 (1.0, 1.6)         | 0.0992         | 1.7 (1.2, 2.4)            | 0.0019         | – 0.1 (– 0.4, 0.2)           | 0.4824         |
| Age (years)   | 0.98 (0.97,<br>0.99)   | 0.0022         | –                         | –              | 0.02 (0.01, 0.03)            | 0.0004         |
| BMI (< 30 kg/m <sup>2</sup> vs.<br>≥ 30 kg/m <sup>2</sup> ) | 1.4 (1.0, 1.8)         | 0.0349         | 3.0 (1.9, 4.8)            | < 0.0001       | – 0.4 (– 0.8,<br>– 0.1)      | 0.0054         |
| TNFi status (naïve vs. IR)                                  | 1.6 (1.2, 2.0)         | 0.0006         | 1.9 (1.3, 2.8)            | 0.0004         | – 0.4 (– 0.7,<br>– 0.2)      | 0.0024         |
| hsCRP (≥ 5 mg/L vs.<br>< 5 mg/L)                            | 1.7 (1.3, 2.1)         | < 0.0001       | –                         | –              | – 0.5 (– 0.8,<br>– 0.2)      | 0.0002         |
| Current smoker (no vs. yes)                                 | 1.3 (1.0, 1.7)         | 0.0240         | –                         | –              | – 0.3 (– 0.5, 0.0)           | 0.0416         |
| BASMI—occiput- to-wall<br>distance (cm)                     | 0.96 (0.93,<br>0.98)   | 0.0002         | 0.90 (0.87,<br>0.94)      | < 0.0001       | 0.10 (0.05, 0.14)            | < 0.0001       |
| BASMI—Tragus to wall<br>distance (cm)                       | –                      | –              | –                         | –              | – 0.06 (– 0.11,<br>– 0.01)   | 0.0198         |

In the final models, except treatment and sex (which were included mandatorily), only those factors with *P* values < 0.05 were kept

ASAS Assessment of SpondyloArthritis international Society, ASDAS Ankylosing Spondylitis Disease Activity Score, BMI Body Mass Index, CI confidence interval, hs-CRP high sensitivity C-reactive protein, IR inadequate responders, NA not applicable, – not selected in the final model, TNFi tumor necrosis factor inhibitor

<sup>a</sup> Analyses were done using multivariate logistic regression

<sup>b</sup> Analysis was done using generalized linear model

and women with AS. A study by Thaci et al. demonstrated distinct sexual dimorphism in the activation status of the immune system in AS in the Th17 axis; thus, sex-related differences in the clinical features of AS could be attributed to this sexual dimorphism [18]. Although not fully established, few studies have shown that sex hormones could also affect treatment responses to biologics in AS [19–22]. Also, allelic frequencies of the ANKH-gene, which specifically encodes for a progressive ankylosing protein, and tissue non-specific alkaline

phosphatase haplotypes differ between males and females with AS [3].

Although sex differences in terms of prevalence and AS phenotypes are observed across many studies [23], it has been challenging to investigate sex differences in the efficacy of TNFi in the randomized controlled setting as the number of enrolled female patients was low, the analyses were usually not stratified by sex, and most of these trials were not designed or powered to demonstrate treatment responses by sex [24, 25]. Previous pooled efficacy analyses of TNFi treatment reported sex differences [3, 8, 9]



**Table 4** Treatment emergent AEs during the entire treatment period

| Parameters   | Males ( <i>N</i> = 641) | Females ( <i>N</i> = 243) | Total ( <i>N</i> = 884) |
|--|-------------------------|---------------------------|-------------------------|
| Exposure (weeks), mean (SD)                                | 112.5 (73.2)            | 128.8 (80.1)              | 117.0 (75.5)            |
| Any AEs, <i>n</i> (%)                                      | 550 (85.8)              | 220 (90.5)                | 770 (87.1)              |
| Serious AE, <i>n</i> (%)                                   | 74 (11.5)               | 24 (9.9)                  | 98 (11.1)               |
| Discontinuation due to any AE, <i>n</i> (%)                | 28 (4.4)                | 14 (5.8)                  | 42 (4.8)                |
| Most common AEs, <i>n</i> (%) <sup>a</sup>                 |                         |                           |                         |
| Nasopharyngitis  | 135 (21.1)              | 62 (25.5)                 | 197 (22.3)              |
| Upper respiratory tract infection                          | 127 (19.8)              | 47 (19.3)                 | 174 (19.7)              |
| Diarrhoea  | 61 (9.5)                | 28 (11.5)                 | 89 (10.1)               |
| Headache   | 36 (5.6)                | 33 (13.6)                 | 69 (7.8)                |
| Back pain  | 29 (4.5)                | 28 (11.5)                 | 57 (6.4)                |
| Bronchitis   | 28 (4.4)                | 25 (10.3)                 | 53 (6.0)                |
| Influenza  | 38 (5.9)                | 16 (6.6)                  | 54 (6.1)                |
| Arthralgia   | 40 (6.2)                | 18 (7.4)                  | 58 (6.6)                |
| Ankylosing spondylitis                                     | 34 (5.3)                | 18 (7.4)                  | 52 (5.9)                |
| Oropharyngeal pain   | 33 (5.1)                | 20 (8.2)                  | 53 (6.0)                |
| Cough  | 28 (4.4)                | 17 (7.0)                  | 45 (5.1)                |
| Pharyngitis  | 30 (4.7)                | 20 (8.2)                  | 50 (5.7)                |
| Respiratory tract infection                                | 24 (3.7)                | 16 (6.6)                  | 40 (4.5)                |
| Hypertension   | 31 (4.8)                | 15 (6.2)                  | 46 (5.2)                |
| AEs of special interest, <i>n</i> (EAIR/100 patient years) |                         |                           |                         |
| <i>Candida</i> infection                                   | 0 (0.0)                 | 1 (0.2)                   | –                       |
| Crohn's disease  | 1 (0.1)                 | 0 (0.0)                   | –                       |
| Colitis ulcerative   | 4 (0.3)                 | 1 (0.2)                   | –                       |
| Malignant melanoma   | 1 (0.1)                 | 0 (0.0)                   | –                       |

Events listed according to preferred term in the Medical Dictionary for Regulatory Activities (MedDRA) version 21.1, sorted in descending order of EAIR in the Any secukinumab 150 and 75 mg group for the entire treatment period  
*AE* adverse events, *EAIR* exposure adjusted incidence rate, *N* number of randomized patients, *n* number of evaluable patients

<sup>a</sup> Seen in more than 5% of total patients randomized to secukinumab

with notably lower levels of therapeutic response and treatment adherence in female patients [8, 9, 26–34]. Even though the disease burden at baseline is comparable or worse in female compared to male patients, female patients with AS have demonstrated less efficacy

from biologics as compared with male patients [35–37].

Prevalence of fibromyalgia is higher in female patients and has been suggested as a potential reason for reduced treatment responses to biologics in female patients with AS;

however, this information might also lead to the misdiagnosis of cases of enthesitis for fibromyalgia [38]. In the present pooled analysis, although female patients had higher MASES score, ASAS40 response rates and change from baseline in BASDAI scores were comparable at Week 52, indicating good efficacy on enthesitis irrespective of sex. However, sex appears to have an impact on ASDAS-CRP ID, which is a higher hurdle efficacy endpoint and hence achieved by a small proportion of patients. As CRP levels are a predictor of response, higher CRP at baseline in male patients may have favored males in terms of response to secukinumab treatment as there is bigger window for normalization of CRP levels [39]. This may potentially compromise the clinical interpretation of this outcome measure in assessing the differential treatment effect of secukinumab in achieving disease remission.

The overall safety profile of secukinumab was consistent with previous reports similar across male and female patients [14, 18–20, 23].

## CONCLUSION

In this pooled database of the five MEASURE studies, although some differences between the sexes were observed at Week 16, the sustained improvements through Week 52 across a wide range of efficacy outcomes in AS patients treated with secukinumab 300 mg or 150 mg were generally achieved irrespective of sex. Although sex was not an independent predictor of treatment response to secukinumab as assessed by ASAS40 responder rates and BASDAI change from baseline, the association of ASDAS-CRP ID responder rates with sex warrants further exploration. No differences were observed in the safety profile of secukinumab between male and female patients.

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**Data Availability.** The datasets generated and/or analyzed during the current study are not publicly available. Novartis is committed to sharing with qualified external researchers' access to patient-level data and supporting clinical documents from eligible studies. These requests are reviewed and approved based on scientific merit. All data provided are anonymized to respect the privacy of patients who have participated in the trial in line with applicable laws and regulations. The data may be requested from the corresponding author of the manuscript.

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