Secukinumab provided significant and sustained improvement in the signs and symptoms of ankylosing spondylitis: results from the 52-week, Phase III China-centric study, MEASURE 5

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Abstract

Background: Secukinumab demonstrated sustained efficacy in patients with ankylosing spondylitis (AS) through 5 years in pivotal Phase III studies. Here, we present efficacy and safety results (52-week) of secukinumab in patients with AS from the MEASURE 5 study.

Methods: MEASURE 5 was a 52-week, Phase III, China-centric study. Eligible patients were randomly assigned (2:1) to receive subcutaneous secukinumab 150 mg or placebo weekly for the first five doses and then once every 4 weeks (q4w). All placebo patients switched to secukinumab 150 mg q4w starting at Week 16. Primary endpoint was Assessments of SpondyloArthritis international Society (ASAS) 20 at Week 16. Randomization was stratified by region (China *vs.* non-China).

Results: Of 458 patients (secukinumab 150 mg, $N = 305$; placebo, $N = 153$) randomized, 327 (71.4%) were from China and 131 (28.6%) were not from China. Of these, 97.7% and 97.4% patients completed Week 16 and 91.1% and 95.3% (placebo-secukinumab) patients completed Week 52 of treatment. The primary endpoint was met; secukinumab significantly improved ASAS20 response at Week 16 *vs.* placebo (58.4% *vs.* 36.6%; $P < 0.0001$); corresponding rate in the Chinese population was 56.0% *vs.* 38.5% ($P < 0.01$). All secondary efficacy endpoints significantly improved with secukinumab 150 mg in the overall population at Week 16; responses were maintained with a trend toward increased efficacy from Week 16 to 52. No new or unexpected safety signals were reported up to Week 52.

Conclusions: Secukinumab 150 mg demonstrated rapid and significant improvement in signs and symptoms of AS. Secukinumab was well tolerated and the safety profile was consistent with previous reports. Efficacy and safety results were comparable between the overall and Chinese populations.

Trial registration: ClinicalTrials.gov, NCT02896127; https://clinicaltrials.gov/ct2/show/NCT02896127?term=NCT02896127&draw=2&rank=1.

Keywords: Ankylosing spondylitis; Biologics; Cytokines; Interleukin 17A; Tumor necrosis factor

Introduction

Ankylosing spondylitis (AS) is a chronic debilitating axial disease associated with inflammation and irreversible structural damage of the sacroiliac joints and spine, with significant disability, pain, stiffness, and reduced health-related quality of life.[1,2] The most common extra-articular manifestations include uveitis, peripheral arthritis, enthesitis, psoriasis, and inflammatory bowel disease (IBD).[3] The estimated prevalence of AS is from 0.1% to 1.4% in the global population and about 0.3% to 0.5% in the Chinese population.[4,5] Clinical features, diagnosis, pathogenic mechanisms of the disease, and therapies are mostly similar

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between the Chinese population and other ethnic groups worldwide.[6]

Non-steroidal anti-inflammatory drugs (NSAIDs) are recommended as the first-line therapy for AS.[7-10] Conventional disease-modifying anti-rheumatic drugs (cDMARDs) are either not recommended or reported to be inefficacious in managing the symptoms of axial disease. Similarly, with tumor necrosis factor inhibitors (TNFi), the recommended first-line biologics for the management of AS according to established guidelines,[7-10] a number of patients do not respond or respond inadequately, report a loss of efficacy over time, relapse upon discontinuation, or have intolerance and long-term safety issues.[7-12] Interleukin (IL)-17 plays a crucial role in the pathogenesis of AS. IL-17-inhibitors are reported to be effective in managing AS-associated symptoms and have been recommended in patients who are primary non-responders to TNFi.[7-10]

Secukinumab, a human monoclonal antibody that directly inhibits IL-17A, demonstrated sustained efficacy in patients with active AS in the pivotal Phase III MEASURE 1 and 2 studies over 5 years and had a consistent safety profile with long-term therapy.[13-17] In a pooled analysis from the MEASURE 1 and 2 studies, secukinumab 150 mg demonstrated sustained efficacy and consistent safety in Asian patients with AS through 52 weeks.[18] Specifically, in a cohort of patients with active AS in the MEASURE 1 extension trial, secukinumab 150 mg demonstrated sustained efficacy and consistent safety over 4 years.[19] The secukinumab 150 mg dose has been approved in more than 94 countries worldwide, including in the United States and European Union, for the treatment of AS.

The MEASURE 5 study was conducted to assess the efficacy, safety, and tolerability of self-administered subcutaneous (s.c.) secukinumab over 52 weeks of treatment in patients with active AS despite current or previous NSAID, DMARD, and/or TNFi therapy. The 52-week efficacy and safety results from this study are presented here.

Methods

Ethics approval

The study protocol (https://clinicaltrials.gov/, NCT02896127) and its amendment to introduce the primary efficacy analysis after all patients completed Week 16 were reviewed and approved by the Independent Ethics Committee or Institutional Review Board (IRB) for each center. A list of IRBs is presented in Supplementary Table 1, http://links.lww.com/CM9/A318. The study was conducted according to the the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E6 Guideline for Good Clinical Practice that has its origin in the *Declaration of Helsinki*.[20] Written informed consent was obtained from all enrolled patients.

Patients

Patients enrolled in the study were ≥18 years of age and had moderate to severe AS with prior documented radiological evidence (X-ray or radiologist's report) fulfilling the modified New York criteria[21]; active AS assessed by Bath Ankylosing Spondylitis Disease Activity Index[22] (BASDAI) score of ≥4; spinal pain score ≥4 cm on a 10 cm visual analog scale (VAS); and total back pain score ≥40 mm on a 100 mm VAS. Patients should have had an inadequate response to previous treatment with at least two NSAIDs. Patients on scheduled NSAIDs were required to be on a stable dose for at least 2 weeks before randomization. Patients previously treated with TNFi (no more than one) could participate if they had an inadequate response to an approved dosage for ≥3 months or were intolerant to at least one dose (hereafter collectively referred to as TNFi-incomplete responders [IR]) and were included after appropriate washout periods before randomization. Patients could continue to receive the following medications at a stable dose: sulfasalazine (≤3 g/day), methotrexate (≤25 mg/week), glucocorticoids (≤10 mg/day prednisone or equivalent), and NSAIDs. Key exclusion criteria included total spinal ankylosis, malignancy in the past 5 years, active systemic infection within 2 weeks before randomization, history of ongoing, chronic, or recurrent infectious disease or evidence of tuberculosis infection (either a positive purified protein derivative skin test or a positive QuantiFERON TB-Gold test), known infection with human immunodeficiency viruses, hepatitis B or C at screening or randomization, and previous treatment with cell-depleting therapies or biologic agents other than TNFi. Detailed inclusion and exclusion criteria are listed in Supplementary Table 2, http://links.lww.com/CM9/A318.

Study design

MEASURE 5 was a 52-week, randomized, double-blind, placebo-controlled, parallel-group, multicenter, Phase III, China-centric study [Figure 1] conducted from October 2016 to March 2019 at 44 centers in four countries: China (24), the Czech Republic (5), Republic of Korea (6), and the United Kingdom (9).

Randomization and interventions

After an initial screening period of up to 10 weeks, eligible patients were randomly assigned (2:1) using an Interactive Response Technology system to receive either s.c. secukinumab 150 mg or placebo; randomization was stratified by region (China *vs.* non-China). Patients received treatment at baseline, and Weeks 1, 2, and 3, followed by every 4 weeks (q4w) starting at Week 4 until Week 48 [Figure 1]. Starting at Week 16, all patients received open-label secukinumab 150 mg, including all placebo patients (hereafter referred to as placebo-switchers). The end of treatment visit occurred at Week 52 and a post-treatment follow-up visit occurred 12 weeks after the last dose (for all patients regardless of whether they completed the study or discontinued prematurely). After all patients completed Week 16, a primary endpoint analysis was conducted. Although unblinding occurred at the Week 16 analysis, all patients, investigators, and site staff remained blinded throughout the study to the treatment group assigned at randomization (secukinumab 150 mg or placebo). The study was planned to enroll no more than 30% TNFi-IR patients.

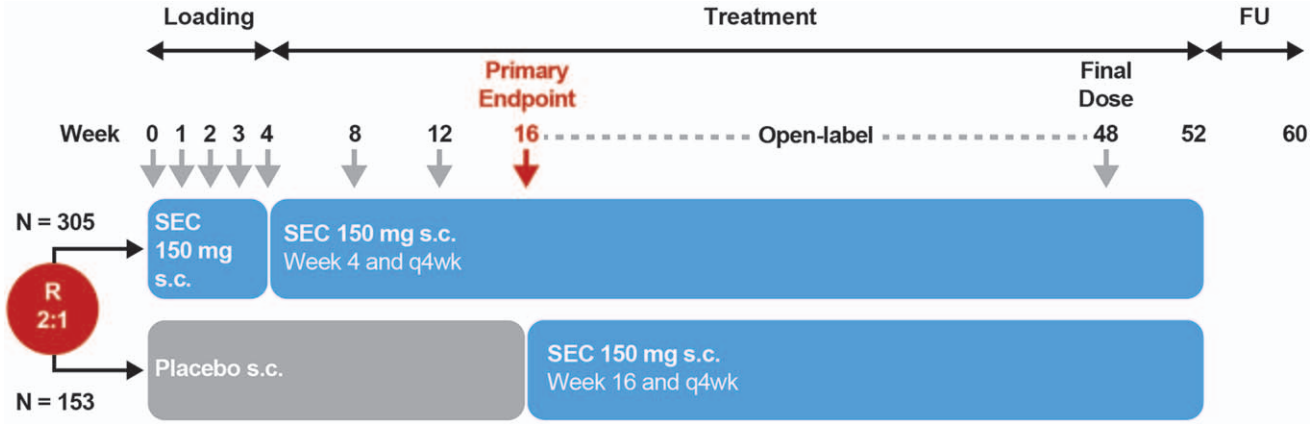

Figure 1: Study design of MEASURE 5. The patients were stratified at randomization according to the region (China [*N* = 327] and non-China [*N* = 131; Czech Republic, Republic of Korea and UK]). An end of treatment visit at Week 52 and a post-treatment follow-up visit at Week 60 were done after the last study treatment administration for all patients (regardless of whether they completed the entire study as planned or discontinued prematurely). FU: Follow-up; *N*: Number of randomized patients; q4wk: Every 4 weeks, R: Randomization; s.c.: Subcutaneous; SEC: Secukinumab.

Data were collected in accordance with Good Clinical Practice guidelines by the study investigators and were analyzed by the sponsor. Data presented here, from the primary analysis at Week 16 to the end-of-study analysis at Week 52 (1-year), were collected from October 18, 2016 (first patient first visit) to March 19, 2019 (last patient last visit).

Efficacy outcomes

Primary objective

The primary objective was to demonstrate that the efficacy of s.c. secukinumab 150 mg is superior to placebo based on the proportion of patients achieving an Assessments of SpondyloArthritis international Society (ASAS) 20 response at Week 16. ASAS20 is defined as a relative improvement of ≥20% and an absolute improvement of ≥1 unit (on a 10-unit scale) in at least three out of four main ASAS domains (patient global assessment of disease activity, back pain, physical function, and inflammation), with no worsening of ≥20% and ≥1 unit (on a 10-unit scale) in the remaining domain.[23]

Secondary objectives

The secondary objective was to demonstrate that the efficacy of s.c. secukinumab 150 mg is superior to placebo for the following parameters at Week 16: (1) the proportion of patients achieving an ASAS40 response (improvement of ≥40% and absolute improvement of ≥2 units [on a 10-unit scale] in at least three of the four main ASAS domains, with no worsening at all in the remaining domain); (2) change from baseline of high-sensitivity C-reactive protein (hsCRP); (3) ASAS5/6 response (≥20% improvement in five of the six ASAS response domains, defines as the four main ASAS domains, along with hsCRP, and lateral spinal mobility); (4) change from baseline in total BASDAI (questions on a 0 to 10 scale captured as a continuous VAS, pertaining to the five major symptoms of AS: fatigue, spinal pain, joint pain/swelling, areas of localized tenderness [enthesitis or inflammation of tendons and ligaments], and morning stiffness duration and severity); (5) change from baseline in the Short Form 36 Physical Component Summary (scores range from 0 [maximum disability] to 100 [no disability] for individual domains, with a normative composite summary score of 50); (6) change from baseline in Ankylosing Spondylitis Quality of Life (scores range from 0 [best quality] to 18 [poorest quality]) scores; and (7) ASAS partial remission (a score of <2 units in each of the four core ASAS domains).[23-26]

The overall safety and tolerability of secukinumab *vs.* placebo up to Week 16 was assessed by adverse events (AEs), serious AEs (SAEs), laboratory assessments, and vital signs. Safety data during the entire treatment period are presented for the "Any secukinumab 150 mg" group, which included all patients who received a dose of secukinumab (ie, those originally randomized to secukinumab 150 mg as well as placebo-switchers after receiving their first dose of secukinumab 150 mg).

Exploratory objectives

The exploratory objective was to assess the primary and secondary endpoints at time points other than Week 16. Pre-specified sub-group analyses based on previous use of TNFi therapy were performed for key efficacy endpoints. Other exploratory endpoints included the Ankylosing Spondylitis Disease Activity Score (ASDAS), which is a composite index to assess disease activity. The ASDAS-CRP includes total back pain (BASDAI question 2), patient global assessment of disease activity, peripheral pain/swelling (BASDAI question 3), duration of morning stiffness (BASDAI question 6), and CRP in mg/L. The response is categorized in disease activity states, with inactive disease reflected by a value below 1.3. In addition, change from baseline in Maastricht Ankylosing Spondylitis Enthesitis Score (MASES) was assessed in all patients. The MASES assessment included 13 enthesitis sites: 1st costochondral (bilateral), 7th costochondral (bilateral), posterior superior iliac spine (bilateral), anterior superior iliac spine (bilateral), iliac crest (bilateral), 5th lumbar

spinous process, and proximal achilles (bilateral). In addition, the lateral epicondyle of the humerus and the lateral condyle of the femur were assessed.[27]

Statistical analyses

The sample size for MEASURE 5 was calculated to provide sufficient power for secukinumab 150 mg *vs.* placebo with a 2.5% type I error rate, and was two-sided for comparison between secukinumab and placebo using Fisher exact test. The ASAS20 response rate (primary endpoint) was estimated to be 58.1% for the secukinumab 150 mg group compared with placebo (36.8%) at Week 16. Based on this estimation, at least 276 patients in total (184 patients in the secukinumab 150 mg group and 92 patients in the placebo group) were needed to achieve 90% power to compare secukinumab 150 mg with placebo in the overall population. The target population was increased to 300 patients in the secukinumab 150 mg group and 150 patients in the placebo group to ensure sufficient safety data in Chinese patients. Efficacy analyses were performed on the full analysis set, which was comprised of all patients who were randomized and assigned to study treatment. Efficacy data are presented separately for the overall and Chinese populations.

Closed testing procedures were used to maintain a family-wise type-I-error rate of 5% across the treatment groups and endpoints. A pre-defined hierarchical hypothesis testing strategy was used to adjust for multiplicity of testing based on analyses of primary and secondary variables for the overall population [Supplementary Figure 1, http://links.lww.com/CM9/A318].

The primary endpoint was analyzed using a logistic regression model with treatment and randomization stratum (region) as factors and weight as a covariate. Odds ratios and 95% confidence intervals were calculated to compare secukinumab 150 mg with placebo. Statistical analyses were based on logistic regression for binary efficacy variables (eg, ASAS20/40) and a mixed-effects repeated measures model (MMRM) for continuous variables (eg, hsCRP) with treatment, analysis visit, and TNFi use as factors, and baseline score and weight as covariates. Treatment and baseline score by analysis visit were included as interaction terms in the model. For the change in hsCRP level, the $\log_e$ ratio of the post-baseline value to the baseline value was used to normalize the distribution of the hsCRP level at each assessment time point. For the primary analysis, a missing response was considered as a non-responder and discontinued patients were considered non-responders for all subsequent visits after the time of discontinuation. A sensitivity analysis was performed using multiple imputation to handle missing responses; continuous endpoints were analyzed via MMRM analysis with a missing at random assumption to Week 52.

The safety analysis included all patients who received at least 1 dose of secukinumab. AEs are reported as exposure-adjusted incidence rates (EAIR) per 100 patient-years over the entire treatment period, which refers to the cumulative treatment period (ie, events started after the first dose of study treatment or events present before the first dose of study treatment but which increased in severity based on preferred term and events that had an onset on or before the last dose date plus 84 days). Safety results were summarized using descriptive statistics.

Results

Patient characteristics

A total of 563 patients were screened from October 2016 to March 2019, of which 458 (81.3%) were randomized (secukinumab 150 mg, $N = 305$; placebo, $N = 153$). Of the 458 patients randomized, 327 (71.4%) were from China, and the remaining 131 (28.6%) were from the Czech Republic, Republic of Korea, or the United Kingdom. In the overall population, >95% of patients in the two groups completed the 16-week evaluation period, and >90% completed Week 52 [Figure 2]. In the Chinese population, the rate of completion was 89.9% (196/218) and 92.7% (101/109), in the secukinumab 150 mg and placebo groups at Week 52, respectively. The most frequent reason for discontinuation was patient or guardian decision.

Baseline demographic and disease characteristics were comparable between treatment groups in the overall and Chinese populations [Table 1]. In the overall population, the total mean (standard deviation) age was 34.4 (10.3) years, the majority (83.8%) were male, and 80.6% of patients were of Asian origin. In the overall population, 21% of patients were TNFi-IR, while the proportion of TNFi-IR patients in the Chinese population was slightly higher at 23.5%.

Efficacy

Short-term (16-week) efficacy

The primary endpoint was met; ASAS20 response rate improved significantly with secukinumab 150 mg (58.4%) at Week 16 *vs.* placebo (36.6%; $P < 0.0001$) in the overall population; the corresponding rates were 56.0% *vs.* 38.5% ($P < 0.01$) in the Chinese population [Figure 3A]. ASAS40 response rates also improved significantly with secukinumab 150 mg (43.9%) at Week 16 *vs.* placebo (17.0%; $P < 0.0001$) in the overall population; the corresponding rates were 41.7% *vs.* 16.5% ($P < 0.0001$) in the Chinese population [Figure 3B]. Significant improvements were reported in all other secondary endpoints at Week 16 for secukinumab 150 mg *vs.* placebo in the overall population; similar results were observed in the Chinese population [Table 2].

Significant improvements were seen in the exploratory endpoints. A higher proportion of patients achieved ASDAS-CRP inactive disease at Week 16 on secukinumab 150 mg (14.8%) *vs.* placebo (3.3%; $P < 0.001$) in the overall population; similar results were reported in the Chinese population (13.8% *vs.* 3.7%; $P < 0.01$) [Supplementary Figure 2, http://links.lww.com/CM9/A318]. A greater improvement in MASES score at Week 16 was observed with secukinumab 150 mg *vs.* placebo in the overall (–0.77 *vs.* –0.49; $P = 0.08$) and Chinese (–0.86 *vs.* –0.57; $P = 0.05$) [Supplementary Figure 3, http://links.lww.com/CM9/A318] populations.

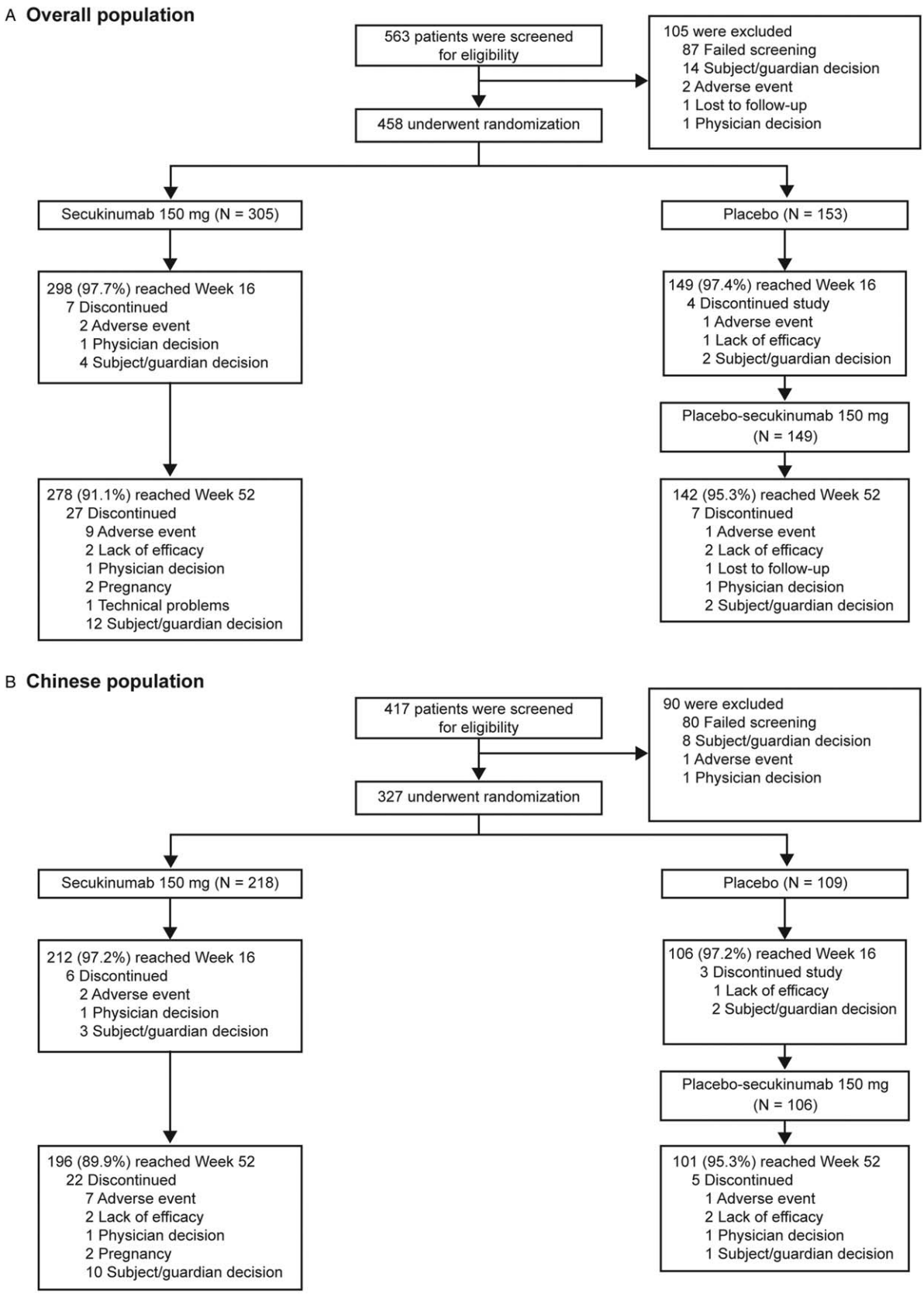

Figure 2: Patient disposition through Week 52. A total of 563 patients were screened, of whom 458 (81.3%) were randomized (secukinumab 150 mg: $N = 305$ and placebo: $N = 153$). The most frequent reason for screening failure was history of ongoing, chronic or recurrent infectious disease (32.4% of screen failures). The majority (>90%) of patients completed Week 52 in both overall and Chinese populations. *N*: Number of randomized patients.

Table 1: Baseline demographics and disease characteristics of patients with active AS.

Items	Overall population		Chinese population	
	Secukinumab 150 mg (*N* = 305)	Placebo (*N* = 153)	Secukinumab 150 mg (*N* = 218)	Placebo (*N* = 109)
Age (years), mean (SD)	35.1 (10.38)	33.0 (10.02)	32.6 (9.06)	31.3 (8.56)
Male, *n* (%)	252 (82.6)	132 (86.3)	179 (82.1)	96 (88.1)
Caucasian, *n* (%)	64 (21.0)	23 (15.0)	0	0
Time since AS diagnosis (years), mean (SD)	5.66 (6.40)	5.28 (6.02)	5.01 (4.91)	5.0 (5.09)
HLA-B27 positive at baseline, *n* (%)	276 (90.5)	142 (92.8)	203 (93.1)	103 (94.5)
TNFi-naïve, *n* (%)	240 (78.7)	122 (79.7)	164 (75.2)	86 (78.9)
Methotrexate use at randomization, *n* (%)	20 (6.6)	9 (5.9)	16 (7.3)	8 (7.3)
Sulfasalazine use at randomization, *n* (%)	75 (24.6)	37 (24.2)	61 (28.0)	29 (26.6)
Corticosteroid use at randomization, *n* (%)	15 (4.9)	5 (3.3)	2 (0.9)	1 (0.9)
Total BASDAI score, mean (SD)	6.91 (1.38)	6.87 (1.25)	6.86 (1.41)	6.86 (1.23)
hsCRP (mg/L), median (min-max)	7.50 (0.3–157.9)	7.80 (0.3–126.8)	8.65 (0.3–157.9)	8.20 (0.3–126.8)
Total back pain score (0–100 mm scale), mean (SD)	71.6 (14.51)	70.5 (13.44)	70.6 (14.50)	70.9 (13.94)
MASES score, mean (SD)	1.6 (2.50)	1.3 (2.23)	1.3 (2.15)	1.2 (2.03)

N: Number patients randomized; AS: Ankylosing spondylitis; SD: Standard deviation; *n*: Number of responders; HLA-B27: Human leukocyte antigen B27; TNFi: Tumor necrosis factor inhibitors; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; hsCRP: High sensitivity C-reactive protein; MASES: Maastricht Ankylosing Spondylitis Enthesis Score.

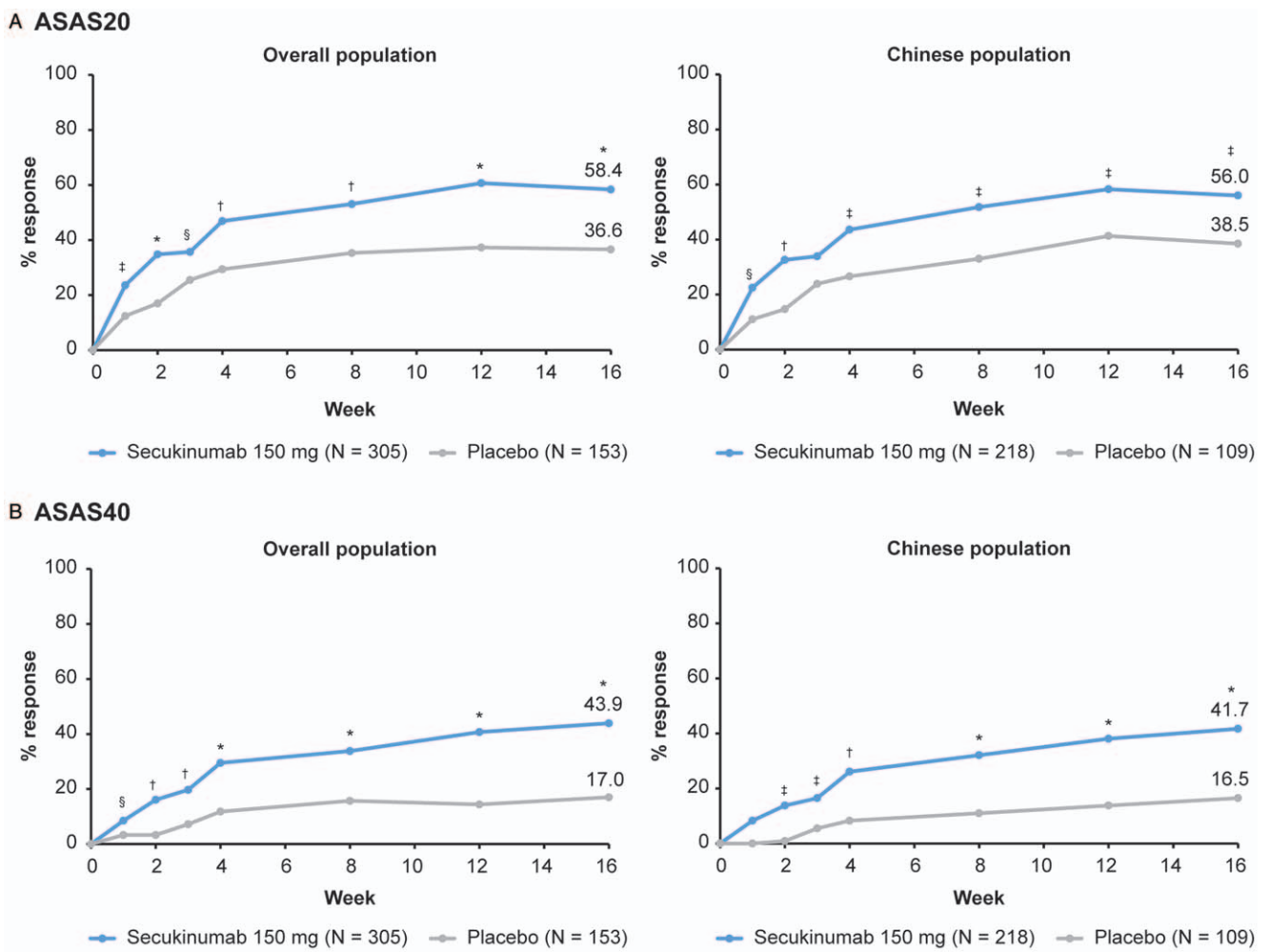

Figure 3: ASAS20 (A) and ASAS40 (B) response rates in patients with active AS through Week 16. $^{*}P < 0.0001$; $^{\dagger}P < 0.001$; $^{\ddagger}P < 0.01$; $^{\S}P < 0.05$ *vs.* placebo (*P* values are adjusted for the overall population and unadjusted for the Chinese population). Missing values were imputed as non-response (NRI). AS: Ankylosing spondylitis; ASAS: Assessment of SpondyloArthritis international Society; *N*: Total number of randomized patients; NRI: Non-responders imputation.

Table 2: Efficacy endpoint results at Weeks 16 and 52 (full analysis set) of patients with active AS.

Items	Week	Overall population		Chinese population	
		Secukinumab 150 mg ($N=305$)	Placebo ($N=153$)	Secukinumab 150 mg ($N=218$)	Placebo ($N=109$)
ASAS20[‖]	16	58.4 [*]	36.6	56.0 [‡]	38.5
	52	76.1	–	77.3	–
ASAS40[‖]	16	43.9 [*]	17.0	41.7 [*]	16.5
	52	60.6	–	60.5	–
hsCRP[¶]	16	0.39 (1.05)[*]	1.05 (1.07)	0.33 (1.06)[*]	0.97 (1.09)
	52	0.36 (1.06)	–	0.29 (1.07)	–
ASAS5/6[‖]	16	47.2[*]	17.6	45.9[*]	17.4
	52	63.2	–	63.9	–
BASDAI[**]	16	−2.79 (0.13)[*]	−1.50 (0.18)	−2.63 (0.14)[*]	−1.37 (0.20)
	52	−3.63 (0.14)	–	−3.65 (0.15)	–
SF-36 PCS[**]	16	7.43 (0.38)[*]	4.60 (0.53)	7.18 (0.39)[*]	4.07 (0.56)
	52	9.68 (0.45)	–	9.67 (0.47)	–
ASQoL[**]	16	−4.83 (0.27)[*]	−2.93 (0.38)	−4.50 (0.31)[†]	−2.50 (0.44)
	52	−6.04 (0.29)	–	−6.11 (0.31)	–
ASAS PR[‖]	16	16.7[‡]	6.5	15.1[§]	6.4
	52	28.1	–	29.5	–

[*] $P<0.0001$; [†] $P<0.001$; [‡] $P<0.01$; [§] $P<0.05$ *vs.* placebo (P values are adjusted for the overall population and un-adjusted for the Chinese population). Missing values were imputed as non-response (NRI) at Week 16, multiple imputation (MI) at Week 52 for binary variables and MMRM for continuous variables through Week 52; [‖]% responders; [¶]Exponentially transformed LSM (SE), the geometric mean ratio of post-baseline/baseline, a value <1 indicates a reduced CRP; [**]LS mean change (SE) from baseline. AS: Ankylosing spondylitis; *N*: Total number of randomized patients; *n*: Number of responders; ASAS: Assessment of SpondyloArthritis international Society; hsCRP: High sensitivity C-reactive protein; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; SF-36 PCS: Short form-36 physical component summary; ASQoL: Ankylosing Spondylitis Quality of Life; PR: Partial remission; NRI: Non-responders imputation; MMRM: Mixed-effect model repeated measure; LSM: Least squares mean; SE: Standard error; CRP: C-reactive protein; LS: Least squares.

One-year (52-week) efficacy

Improvements reported at Week 16 in the overall and Chinese populations were further improved across most efficacy endpoints at Week 52 [Table 2]. Efficacy results (observed data) at Week 52 across all endpoints in patients originally randomized to secukinumab 150 mg and placebo-switchers for the overall and Chinese populations are presented in Supplementary Table S3, http://links.lww.com/CM9/A318.

ASDAS-CRP inactive disease response and MASES score (observed data) were further improved or sustained in secukinumab-treated patients at Week 52. ASDAS-CRP inactive disease response with secukinumab 150 mg was 27.2% ($n=268$) in the overall population and 26.8% ($n=190$) in the Chinese population at Week 52 [Supplementary Figure 2, http://links.lww.com/CM9/A318]. MASES score with secukinumab 150 mg was –1.2 (2.36; $n=272$) in the overall population and –1.0 (2.16; $n=194$) in the Chinese population at Week 52 [Supplementary Figure 3, http://links.lww.com/CM9/A318].

Efficacy analysis in TNFi-naïve and TNFi-IR subgroups

The ASAS20 response rates improved in the overall population regardless of prior TNFi therapy status being naïve (58.3% for secukinumab 150 mg *vs.* 36.9% for placebo; $P<0.001$) or IR (58.5% *vs.* 35.5%, respectively) at Week 16; in the Chinese population, the corresponding rates for TNFi- naïve patients were 54.3% *vs.* 37.2% ($P<0.05$) and 61.1% *vs.* 43.5% for TNFi-IR patients [Figure 4]. ASAS40 response rates also improved significantly with secukinumab 150 mg at Week 16 *vs.* placebo in both the overall and Chinese populations. Similar efficacy results were observed at Week 16 across all other endpoints in patients grouped by prior TNFi therapy status [Supplementary Table 4, http://links.lww.com/CM9/A318]. Responses reported at Week 16 in the overall and Chinese populations sustained or further improved across all the efficacy endpoints at Week 52 (observed data) in patients originally randomized to secukinumab 150 mg and placebo-switchers, which were grouped by prior TNFi therapy status (naïve or IR) [Supplementary Table 5, http://links.lww.com/CM9/A318].

Safety

Up to week 16

The proportion of patients with treatment-emergent AEs was 67.8% and 59.5% in the secukinumab 150 mg and placebo groups, respectively. The most frequent treatment-emergent AEs in both the secukinumab and placebo groups were upper respiratory tract infection, hyperlipidemia, and nasopharyngitis [Table 3]. The rates of selected AEs of interest are shown in Table 3. Only three patients (two in the secukinumab 150 mg group and one in the placebo group) discontinued the study treatment due to AEs.

No cases of IBD were reported. Uveitis was reported in three (1.0%) patients in the secukinumab 150 mg group and one (0.7%) patient in the placebo group. No major adverse cardiac events (MACE), treatment-emergent anti-drug antibodies, or deaths were reported.

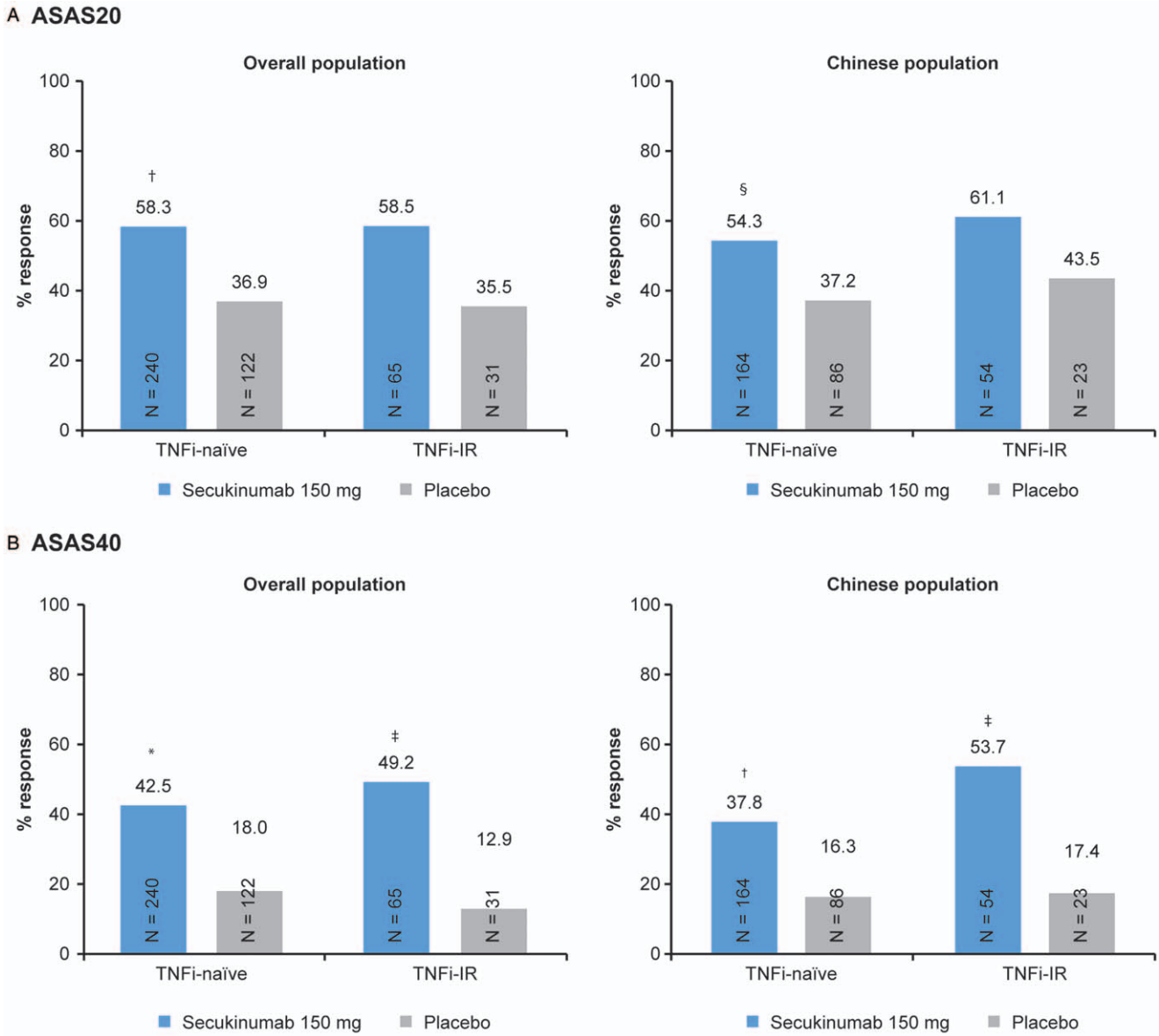

Figure 4: ASAS20 (A) and ASAS40 (B) response rates in patients with active AS at Week 16 by baseline TNFi therapy status. $^{*}P < 0.0001$; $^{\dagger}P < 0.001$; $^{\ddagger}P < 0.01$; $^{\S}P < 0.05$ *vs.* placebo (*P* values are un-adjusted for all). Missing values were imputed as non-response (NRI). AS: Ankylosing spondylitis; ASAS: Assessment of SpondyloArthritis international Society; IR: inadequate responder; *N*: Total number of randomized patients; NRI: Non-responders imputation; TNFi: Tumor necrosis factor inhibitor.

Treatment-emergent SAEs were reported in ten (3.3%) patients in the secukinumab 150 mg group and in three (2.0%) patients in the placebo group. Differences for any specific primary system organ classes were generally small; the largest difference was observed for infections and infestations reported in four (1.3%) patients in the secukinumab 150 mg group and in one (0.7%) patient in the placebo group. All SAEs were reported in single subjects only. The incidence and rates of AEs or SAEs in the Chinese population were comparable with the overall population.

Entire treatment period (52-week)

Over the entire treatment period, the mean exposure was 368.6 days for the "Any secukinumab 150 mg" group. The pattern of AEs remained overall similar to that observed in the 16-week analyses, with slightly higher incidences. The EAIR of treatment-emergent AEs was 80.4 in the "Any secukinumab 150 mg" group [Table 3]. The most frequent treatment-emergent AEs and selected AEs of interest were similar to the 16-week period and are shown in Table 3. Only a few patients (2.2%) discontinued study treatment due to AEs in the "Any secukinumab 150 mg" group.

A total of two IBD events (0.45%) were reported during the entire treatment period, both reported as non-serious ulcerative colitis; of these, one occurred during the follow-up phase. Neither event was considered by the investigator to be related to study treatment. A total of 10 cases of uveitis were reported in the "Any secukinumab 150 mg" group during the entire treatment period and were mild to moderate in nature; all subsequently resolved. MACE was reported by the investigator in one patient (lacunar

Table 3: Summary clinical safety for overall population with active AS.

Variables	Placebo-controlled period (16-week)		Entire treatment period (52-week)
	Secukinumab 150 mg ($N = 304$)*	Placebo ($N = 153$)	Any secukinumab 150 mg ($N = 453$)†
Total exposure			
Mean (SD)	112.9 (9.86)	111.1 (13.32)	368.6 (75.05)
Patient-years	94.0	46.5	457.1
Any AE, *n* (%)	206 (67.8)	91 (59.5)	364 (80.4)
Any SAE, *n* (%)	10 (3.3)	3 (2.0)	33 (7.3)
Discontinuation due to AE, *n* (%)	2 (0.7)	1 (0.7)	10 (2.2)
Death, *n* (%)	0	0	0
Most frequent AEs‡	***n* (%)**		***n* (EAIR/100 patient-year)**
Upper respiratory tract infection	68 (22.4)	29 (19.0)	146 (41.3)
Hyperlipidemia	17 (5.6)	2 (1.3)	26 (6.0)
Nasopharyngitis	16 (5.3)	10 (6.5)	46 (10.9)
Selected AEs of interest	***n* (%)**		***n* (EAIR/100 patient-year)**
Serious infections	4 (1.3)	1 (0.7)	9 (2.0)
Candida infection (HLT)	3 (1.0)	0 (0.0)	5 (1.1)
Oral candidiasis	1 (0.3)	0 (0.0)	2 (0.4)
Ulcerative colitis	0 (0.0)	0 (0.0)	2 (0.4)
MACE§	0 (0.0)	0 (0.0)	1 (0.2)
Uveitis	3 (1.0)	1 (0.7)	10 (2.2)
Neutropenia‖ (PT)	0 (0.0)	0 (0.0)	2 (0.4)

*One patient in the secukinumab 150 mg group was randomized but never treated, as discontinued before treatment; †Includes patients originally randomized to secukinumab and placebo-switchers; ‡AEs with frequency >5% sorted in descending order in secukinumab 150 mg during the 16-week placebo-controlled period. Events listed according to preferred term in the Medical Dictionary for Regulatory Activities (MedDRA) version 21.1; §The event was assessed by a MACE adjudication committee and did not meet MACE criteria; ‖For absolute neutropenia, Grade 3 events reported in one patient on secukinumab 150 mg and two patient on placebo groups. Grade 4 event was reported in one patient on placebo group. AS: Ankylosing spondylitis; *N*: Total number of patients; SD: Standard deviation; AE: Adverse event; SAE: Serious adverse event; *n*: Number of responders; EAIR: Exposure-adjusted incidence rate; HLT: High level term; MACE: Major adverse cardiac event; PT: Preferred term.

infarction). However, this event was assessed by a MACE adjudication committee and did not meet MACE criteria. For absolute neutropenia, Grade 3 events were infrequent (one patient on secukinumab 150 mg and two patients on placebo). A grade 4 event was reported in one patient in the placebo group. No deaths were reported during the entire treatment period.

The proportion of patients with an SAE was low (7.3%), with infection and infestation being the most frequent SAE by primary system organ class reported in 9 (2.0%) patients in the "Any secukinumab 150 mg" group.

Discussion

Secukinumab demonstrated rapid and significant improvement in the signs and symptoms of AS in both the overall and Chinese populations over 16 weeks, which were further improved through 52 weeks. The majority of patients completed 52 weeks of treatment, reflecting a high retention rate. The baseline demographic and disease characteristics were balanced in both the overall and Chinese populations and were generally comparable with the pivotal MEASURE studies, except for a lower mean age, shorter disease duration, and higher rate of human leukocyte antigen (HLA)-B27 positive patients. The mean age was 35.1 years in the MEASURE 5 study compared with 40.1 and 41.9 years in the MEASURE 1 and 2 studies, respectively; similarly, disease duration was 5.66 years compared with 6.5 and 7.0 years, and the proportion of HLA-B27 positive patients was 90.5% compared with 69% and 79% reported in MEASURE 1 and 2.[13] The use of concomitant medication at baseline was comparable to the pivotal MEASURE studies with the exception of a lower use of corticosteroids, with only three patients in the Chinese population (0.9%) using glucocorticoids at baseline compared with 11.5% in the MEASURE studies.

Statistical significance was achieved for the primary and all secondary efficacy variables at Week 16. Secukinumab 150 mg showed a fast onset of response in most of the efficacy endpoints. Higher response rates were reported with secukinumab 150 mg *vs.* placebo in the overall population as early as Week 1 for ASAS20, ASAS40, and BASDAI; at Week 2 for hsCRP and ASAS 5/6, and Week 3 for ASAS partial remission.

In the overall population of the MEASURE 5 study, the ASAS20 and 40 response rates were 58% and 44%, respectively, at Week 16 with secukinumab 150 mg. These results were consistent with findings from the pivotal MEASURE studies (MEASURE 1: 61% and 42%, MEASURE 2: 61% and 36%), with increased response (ASAS20 and 40) rates at Week 52 (MEASURE 5: 76% and 61%, MEASURE 1: 72% and 56%, and MEASURE 2: 74% and 49%), particularly for the ASAS40 response (which is generally considered a more clinically meaningful endpoint than ASAS20).[13] Placebo response was slightly higher in MEASURE 5 compared with the pivotal MEASURE studies for ASAS20, but comparable for

ASAS40. Although head-to-head randomized controlled trials would be considered the best tool to access the clinical efficacy of secukinumab *vs*. TNFi in patients with active AS, the ASAS20 response rates (56%) in the Chinese population achieved with secukinumab in MEASURE 5 was comparable (50%–70%) to those reported in previous Phase III studies with TNFi agents.[28-30]

As biologics have been available for treatment of AS in China for several years, patients' high expectations toward new biologic therapies should be taken into consideration as a potential driver of placebo responses in interventional trials such as MEASURE 5. The efficacy results of the MEASURE 5 study are in line with a previously published pooled analysis of Asian patients with active AS in the MEASURE 1 and 2 trials, thereby confirming the efficacy of secukinumab in patients of Chinese ancestry.[13,18,19]

According to the ASAS-European League Against Rheumatism, the American College of Rheumatology, and Asia Pacific League of Associations for Rheumatology treatment guidelines, secukinumab is recommended in patients with inadequate response to TNFi. In this study, sustained clinical improvements were observed in patients treated with secukinumab regardless of prior TNFi therapy status in both the overall and Chinese populations, with a trend towards slightly higher response rates in patients with an inadequate response to TNFi compared with TNFi-naïve patients at some time points. For the interpretation of the results, it should be noted that 78.7% (240) of patients in the secukinumab group were TNFi-naïve and only 21.3% (65) of patients had a history of an inadequate response to TNFi.

Safety results were consistent with previous reports of the MEASURE 1 and 2 studies, the pooled analysis of Asian patients from the MEASURE 1 and 2 studies, and the results of a retrospective pooled safety analysis of 21 secukinumab clinical trials across different indications and post-marketing surveillance data.[13,15,18]

A limitation of this study is that the groups (China *vs*. non-China) were not balanced; in turn, the overall results are driven largely by the subset of Chinese patients, limiting any direct comparison of Chinese *vs*. non-Chinese patients. In addition, no radiographic or magnetic resonance imaging data are available from this relatively short duration study, which would offer a more objective assessment of efficacy responses, than patient-reported outcomes.

Secukinumab 150 mg demonstrated a rapid and significant improvement in the signs and symptoms of AS in both the overall and Chinese populations. Secukinumab was well tolerated with no new or unexpected safety signals identified. Efficacy and safety results were comparable between the overall and Chinese populations.

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Conflicts of interest

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