Arthritis & Rheumatology
Vol. 73, No. 1, January 2021, pp 110–120
DOI 10.1002/art.41477

American College of Rheumatology
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Improvement of Signs and Symptoms of Nonradiographic Axial Spondyloarthritis in Patients Treated With Secukinumab: Primary Results of a Randomized, Placebo-Controlled Phase III Study

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Objective. To report the primary (1-year) results from PREVENT, the first phase III study evaluating secukinumab in patients with active nonradiographic axial spondyloarthritis (SpA).

Methods. A total of 555 patients were randomized (1:1:1) to receive subcutaneous secukinumab 150 mg with a loading dose (loading dose [LD] group), secukinumab 150 mg without a loading dose (non–loading dose [NL] group), or placebo weekly and then every 4 weeks starting at week 4. The NL group received placebo at weeks 1, 2, and 3 to maintain blinding. Switch to open-label secukinumab or standard of care was permitted after week 20. The study had 2 independent analysis plans, per European Union and non-US (plan A; week 16) and US (plan B; week 52) regulatory requirements. The primary end point was 40% improvement in disease activity according to the Assessment of SpondyloArthritis international Society (ASAS40) criteria at week 16 (in the LD group) and at week 52 (in the NL group) in tumor necrosis factor inhibitor (TNFi)–naive patients. Safety analyses included all patients who received ≥1 dose of study treatment.

Results. Overall, 481 patients completed 52 weeks of treatment, including 84.3% (156 of 185) in the LD group, 89.7% (165 of 184) in the NL group, and 86.0% (160 of 186) in the placebo group. The proportion of patients who switched to open-label or standard of care between weeks 20 and 48 was 50.8% in the LD group, 47.3% in the NL group, and 64.0% in the placebo group. Both primary and all secondary end points were met at week 16. The proportion of TNFi-naive patients who met ASAS40 was significantly higher for LD at week 16 (41.5%) and NL at week 52 (39.8%) versus placebo (29.2% at week 16 and 19.9% at week 52; both $P < 0.05$). No new safety findings were reported.

Conclusion. Our findings indicate that secukinumab 150 mg provides significant and sustained improvement in signs and symptoms of nonradiographic axial SpA through 52 weeks. Safety was consistent with previous reports.

INTRODUCTION

Axial spondyloarthritis (SpA) is a chronic inflammatory disease of the spine, which includes nonradiographic axial SpA and ankylosing spondylitis (AS) (1–6). The prevalence of axial SpA is reported to be 0.32–1.4% (1,2,4,5,7). Patients with AS have structural damage in the sacroiliac (SI) joints and/or the spine that is visible on radiographs (1,3,4,8). Patients with nonradiographic axial SpA do not exhibit definitive radiographic sacroiliitis but have a disease burden comparable to that of patients with AS, including inflammatory back pain (IBP; predominantly in the pelvis and lower back), morning stiffness, nocturnal awakening, fatigue, and

A video abstract of this article can be found at https://players.brightcove.net/656326989001/default_default/index.html?videoId=6178634034001".

ClinicalTrials.gov identifier: NCT02696031.
Supported by Novartis Pharma, Basel, Switzerland.

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Dr. Deodhar has received consulting fees, speaking fees, and/or honoraria from AbbVie, Boehringer Ingelheim, GlaxoSmithKline, and Janssen (less than $10,000 each), and from Eli Lilly, Novartis, Pfizer, and UCB (more than $10,000 each) and research grants from those companies. Dr. Blanco has received consulting fees, speaking fees, and/or honoraria

reduced spinal mobility (1,3,4,6,8). The prevalence of nonradiographic axial SpA is reported to be ~0.1–0.4% in the general population, more prevalent in women, and ~16–37% in patients with IBP (1,4,7,9,10). The epidemiology of nonradiographic axial SpA is evolving due to heterogeneity in definition, slow progression, and diagnostic delays (1,6,7,9,10).

The average delay in diagnosis of nonradiographic axial SpA is estimated to be 6–8 years (4,6,7,11,12). The reported rate of progression from nonradiographic axial SpA to AS varies from ~10% to 40% of patients over 2–10 years, with a lifetime risk of progression of ~50% (6,8–10,13). Early diagnosis of nonradiographic axial SpA is important for the management of disease symptoms and to potentially limit spinal damage. The Assessment of SpondyloArthritis international Society (ASAS) criteria have been developed for the classification of axial SpA and include patients with early disease, with or without radiographic evidence of sacroiliitis (1–4).

According to the ASAS/European League Against Rheumatism (EULAR) (14) and the American College of Rheumatology (ACR)/Spondylitis Association of America (SAA)/Spondyloarthritis Research and Treatment Network (SPARTAN) (15) treatment guidelines, nonsteroidal antiinflammatory drugs (NSAIDs) are recommended as first-line pharmacologic therapy in patients with nonradiographic axial SpA. Biologic disease-modifying antirheumatic drugs are recommended in patients with active disease and objective signs of inflammation (elevated C-reactive protein [CRP] level and/or evidence of sacroiliitis on magnetic resonance imaging [MRI]) despite treatment with NSAIDs. Interleukin-17 (IL-17) is expressed by multiple cells in both the innate and adaptive immune systems and plays a crucial role in the pathogenesis of axial SpA, driving inflammation, enthesitis, and structural damage (16,17). According to the 2019 update of the ACR/SAA/SPARTAN treatment guidelines, IL-17 inhibitors are recommended over the use of a second tumor necrosis factor inhibitor (TNFi) agent in patients with AS with primary nonresponse to the first TNFi agent (15). Secukinumab, a human monoclonal antibody that directly inhibits IL-17A, has provided significant and sustained improvement in the signs and symptoms of AS, as evidenced in the phase III MEASURE studies (18–20).

PREVENT is the first phase III study evaluating the efficacy, safety, and tolerability of secukinumab 150 mg, with or without loading doses, in patients with active nonradiographic axial SpA. Here, we report the efficacy up to week 52 and the safety results for the entire treatment period (including at least 52 weeks of exposure for all patients and up to 104 weeks of exposure for some patients) from the PREVENT study.

PATIENTS AND METHODS

Patients. Patients with a clinical diagnosis of nonradiographic axial SpA who were age ≥18 years were included if they met the ASAS classification criteria for axial SpA (IBP ≥6 months, disease onset at <45 years of age, and sacroiliitis on MRI with ≥1 SpA feature or HLA–B27 positive with ≥2 SpA features) plus objective signs of inflammation (MRI with SI joint inflammation [by central reading] and/or high-sensitivity CRP [hsCRP] greater than the upper limit of normal [ULN; as defined by the central laboratory]). Patients previously treated with a TNFi (no more than 1) could participate if they had an inadequate response or were intolerant. Patients could continue to receive the following medications at a stable dose: sulfasalazine (≤3 gm/day), methotrexate (≤25 mg/week), corticosteroids (≤10 mg/day prednisone or equivalent), and NSAIDs. At randomization, patients were stratified according to objective signs of inflammation based on their CRP and MRI status (positive or negative) at screening. A positive CRP was defined as a value greater than the ULN (hsCRP >5 mg/liter) by the central laboratory. MRI positivity was defined as the presence of inflammatory lesions in the SI joints on MRI according to the ASAS/Outcome Measures in Rheumatology definition (21) as assessed by a central reader.

from AbbVie, Pfizer, Roche, Bristol Myers Squibb, Janssen, Sanofi, Eli Lilly, and MSD (less than $10,000 each) and research support from AbbVie, MSD, and Roche. Dr. Dokoupilová has received research support from AbbVie, Eli Lilly, GlaxoSmithKline, Novartis, Pfizer, UCB, Sanofi-Aventis, and Hexal. Dr. Hall has received consulting fees, speaking fees, and/or honoraria from Novartis, Merck, Janssen, Pfizer, Eli Lilly, and UCB (less than $10,000 each) and research support from AbbVie, UCB, Janssen, and Merck. Dr. Kameda has received consulting fees, speaking fees, and/or honoraria from AbbVie, Astellas, Bristol Myers Squibb, Chuagi, Eisai, Gilead, Janssen, Novartis, Pfizer, and UCB (less than $10,000 each) and from Asahi-Kasei, Eli Lilly, and Mitsubishi-Tanabe (more than $10,000 each), and research support from AbbVie, Asahi-Kasei, Astellas, Chugai, Eisai, Mitsubishi-Tanabe, and Novartis. Dr. Kivitz has received consulting fees and/or honoraria from AbbVie, Janssen, Boehringer Ingeleheim, Pfizer, Sanofi, Genzyme, Flexion, and Regeneron (less than $10,000 each) and owns stock or stock options in Pfizer, Sanofi, Regeneron, Amgen, GlaxoSmithKline, and Gilead. Dr. Poddubnyy has received consulting fees, speaking fees, and/or honoraria from AbbVie, Bristol Myers Squibb, Celgene, Janssen, Eli Lilly, MSD, Novartis, Pfizer, Roche, and UCB (less than $10,000 each) and research support from AbbVie, MSD, Novartis, and Pfizer. Dr. van de Sande has received consulting fees, speaking fees, and/or honoraria from AbbVie, Novartis, Eli Lily, and MSD (less than $10,000 each) and research support from Novartis, Eli Lilly, Boehringer Ingelheim, Janssen, and UCB. Ms Wiksten and Drs. Porter, Richards, and Haemmerle own stock or stock options in Novartis. Dr. Braun has received consulting fees, speaking fees, and/or honoraria from AbbVie, Amgen, Celgene, Chugai, MSD, Novartis, Eli Lilly, and UCB (less than $10,000 each) and research support from AbbVie, Amgen, Bristol Myers Squibb, Boehringer, Celgene, Celltrion, Centocor, Chugai, Medac, MSD, Mundipharma, Novartis, Pfizer, Roche, Sanofi-Aventis, and UCB.

The data sets generated during and/or analyzed at the end of the present 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 on the basis of scientific merit. All data provided is 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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Submitted for publication March 28, 2020; accepted in revised form July 31, 2020.

Key exclusion criteria included evidence of sacroiliitis meeting the modified New York criteria for AS (22) (assessed centrally), active ongoing inflammatory conditions other than axial SpA, including active inflammatory bowel disease (IBD) or uveitis, evidence of ongoing infection or malignant process on chest radiograph, active systemic infection within 2 weeks before randomization, history of ongoing, chronic, or recurrent infectious disease or evidence of tuberculosis infection, known infection with HIV, hepatitis B, or hepatitis C at screening or randomization, history of lymphoproliferative disease or any known malignancy or malignancy of any organ system within the past 5 years, and previous treatment with biologic agents other than TNFi. Detailed eligibility criteria are listed in Supplementary Table 1, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41477/abstract.

The study protocol was reviewed and approved by the Independent Ethics Committee or Institutional Review Board for each center. The study was conducted according to ICH E6 Guideline for Good Clinical Practice that has its origin in the Declaration of Helsinki (23). Written informed consent was obtained from all enrolled patients.

Study design. PREVENT (ClinicalTrials.gov identifier: NCT02696031) is an ongoing randomized, double-blind, placebo-controlled 2-year phase III study with an extension of up to 2 years in patients with nonradiographic axial SpA. The study had 2 independent analysis plans per European Union and non-US regulatory requirements (plan A [week 16]) and US regulatory requirements (plan B [week 52]). The study was initiated on April 29, 2016 (first patient's first visit) and is being conducted across 130 sites in 24 countries.

Randomization and blinding. Eligible patients were randomized (1:1:1) via Interactive Response Technology to receive subcutaneous secukinumab 150 mg with a loading dose (150 mg loading dose [LD] group), 150 mg without a loading dose (150 mg non–loading dose [NL] group), or placebo at baseline and weeks 1, 2, and 3, followed by every 4 weeks starting at week 4 (Supplementary Figure 1, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41477/abstract). The 150 mg NL group received placebo at weeks 1, 2, and 3 to maintain blinding. Study treatment was self-administered throughout the study using syringes prefilled with 150 mg/1 ml secukinumab or 1 ml placebo.

Switch to open-label subcutaneous secukinumab 150 mg or standard of care was permitted after week 20 for inadequate responders based on clinical judgment of disease activity by the investigator and the patient. No specific efficacy parameter for inadequate response was mandated. In cases in which the chosen standard of care was a TNFi, a 12-week washout period was required. All investigators, site personnel, and patients remained blinded with regard to the originally randomized treatment assignment until the week 52 database lock. Starting at week 52, all patients (except those who switched to standard of care) received open-label secukinumab 150 mg up to week 100, unless they had discontinued study treatment. Starting at week 104, all patients who complete the core phase of the trial can continue in an additional 2-year extension phase. A follow-up visit is conducted 12 weeks after the last administration of study treatment for all patients.

Data were collected in accordance with Good Clinical Practice guidelines by the study investigators and analyzed by the sponsor. Efficacy data up to week 52 and safety data for the entire treatment period up to the data cutoff date of July 1, 2019 are presented here.

Outcome measures. Based on differences in regional regulatory requirements, there were 2 predefined hierarchical analysis plans for the primary and secondary objectives. An interim analysis was conducted for the week 16 end points when all patients had completed week 24 (analysis plan A). A separate firewalled team (to maintain blinding) conducted the study up to the second interim analysis, which was conducted when all patients had completed week 52 (analysis plan B). Full details on the outcome measures are provided in Supplementary Table 2, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41477/abstract.

Primary objective. The primary objective was to demonstrate that secukinumab 150 mg LD at week 16 (analysis plan A) and 150 mg NL at week 52 (analysis plan B) were superior to placebo in TNFi-naive patients with active nonradiographic axial SpA, based on the proportion of patients achieving an ASAS40 response (24).

Secondary objectives. Secondary objectives comprised week 16 end points (analysis plan A) and a combination of week 16 and week 52 end points (analysis plan B) (Supplementary Table 2). These were assessed in the overall population and included ASAS40 response (40% improvement in disease activity according to the ASAS criteria), ASAS5/6 response (20% improvement in 5 of 6 domains) (24), change from baseline in total Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) (25), BASDAI50 response (50% decrease in BASDAI score from baseline), change from baseline in hsCRP level, change from baseline in Bath Ankylosing Spondylitis Functional Index (BASFI), SI joint edema score (Berlin Active Inflammatory Lesions Scoring, range 0–24) on MRI (oblique coronal views of the pelvis including both SI joints were obtained for each patient; scores of 2 central readers were averaged), ASAS20 response, change from baseline in Short Form 36 (SF-36) physical component summary (PCS) (26), change from baseline in Ankylosing Spondylitis Quality of Life (ASQoL) (27), ASAS partial remission response (24), and inactive disease according to the Ankylosing Spondylitis Disease Activity Score using the CRP level (ASDAS-CRP) (28).

The overall safety and tolerability of secukinumab versus placebo for the entire treatment period was assessed by adverse events (AEs), serious AEs (SAEs), adjudicated major adverse cardiovascular events (MACE), laboratory assessments, and vital signs. Safety data are presented separately for individual treatment groups (secukinumab 150 mg LD or NL and placebo) and for the "any secukinumab" group, which included all patients originally randomized to receive secukinumab and all placebo patients who had started open-label secukinumab treatment.

Statistical analysis. The sample sizes for analysis plans A and B were calculated so as to have 91% and 97% power, respectively, for the primary end point, with a 5% Type I error rate for comparison between secukinumab 150 mg and placebo. The assumed ASAS40 response rates (primary end point) for the corresponding plans were 47.1% and 43.0%, respectively, for secukinumab 150 mg compared with 27.9% and 21.7%, respectively, for placebo. Based on this estimation, at least 185 patients were needed to have 90% power to show superiority versus placebo. Efficacy analyses were performed on the full analysis set, which comprised all patients who were randomized and had study treatment assigned.

Primary and secondary end points were analyzed according to a predefined statistical hierarchy (Supplementary Figures 2 and 3, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41477/abstract). End points are shown in the order of the testing strategy. The family-wise Type I error rate was set to 5% and was controlled with the applied sequential testing strategy. All end points are shown with unadjusted *P* values with statistical significance only claimed for end points within the predefined hierarchy which met significance based on adjusted *P* values corrected for multiplicity of testing. For all exploratory end points unadjusted *P* values are shown. The primary analysis in the TNFi-naive population was conducted via logistic regression with treatment group and stratification (CRP level or MRI) as factors and weight as a covariate.

Missing values were imputed as nonresponders (by nonresponder imputation [NRI]) for binary variables and via a mixed-effects model repeated measures (MMRM; valid under the missing at random assumption) for continuous variables up to week 20. MMRM analysis included treatment group, CRP level or MRI stratification group, TNFi therapy status, and analysis visit as factors and baseline score of the respective end point and weight as continuous covariates. Treatment-by–analysis visit and baseline score–by–analysis visit were included as interaction terms in the model. An unstructured covariance structure was assumed for the model. The significance of treatment effect for the secukinumab regimens was determined from the pairwise comparisons

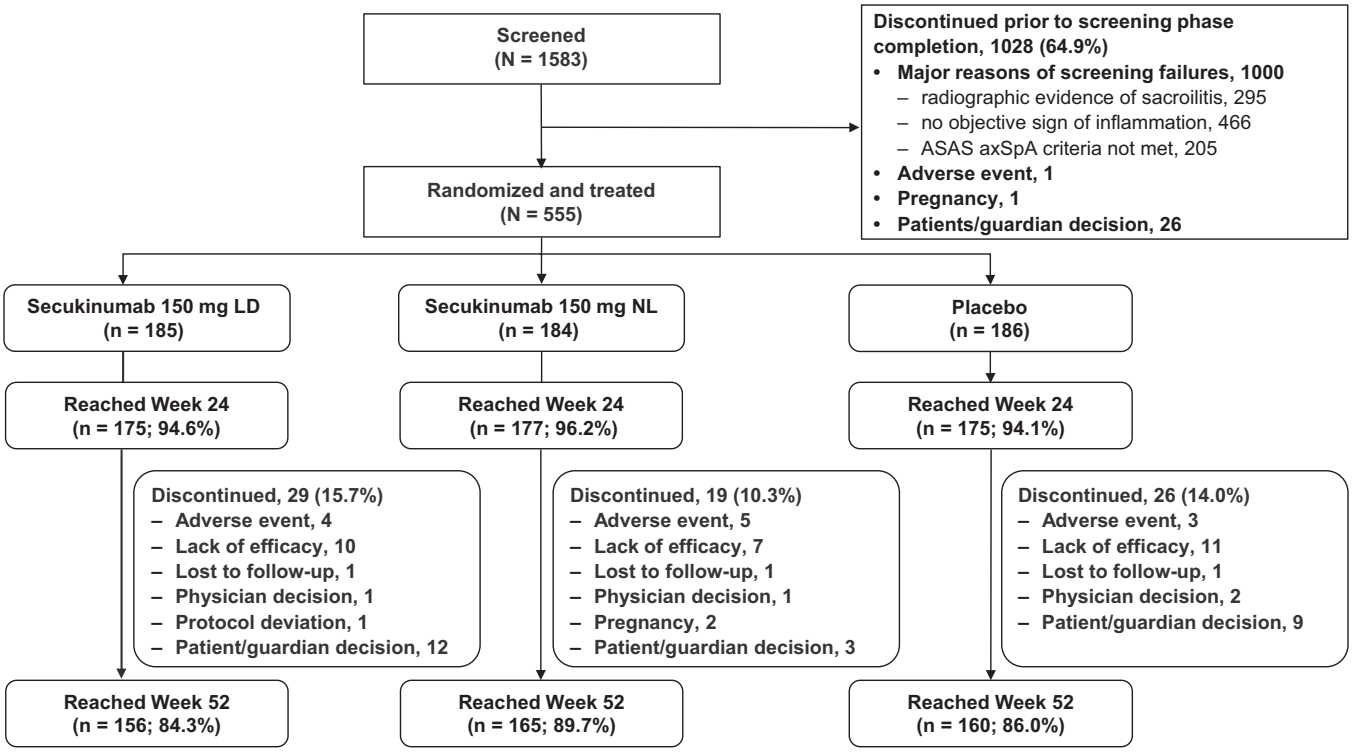

Figure 1. Patient disposition through week 52. Of 1,583 patients screened, 555 (35.1%) were randomized. A patient can have more than 1 reason for screening failure. The main reasons for screening failure based on inclusion and exclusion criteria are presented in Supplementary Table 3, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41477/abstract. The majority (84–89%) of patients completed week 52. Discontinuations are presented for the whole treatment period from baseline to week 52. ASAS = Assessment of SpondyloArthritis international Society; axSpA = axial spondyloarthritis; LD = with loading; NL = without loading.

performed between secukinumab regimens and placebo at week 16. 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.

Safety analyses included all patients who received ≥1 dose of study medication. 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 (i.e., events started after the first dose of study treatment or events present prior to the first dose of study treatment but increased in severity based on preferred term and on or before last dose plus 84 days). Patients switching to standard of care were counted in their previous treatment until the end of the washout phase.

RESULTS

A total of 1,583 patients were screened for eligibility, and 1,028 patients (64.9%) discontinued prior to the completion of the screening phase, either due to not meeting the eligibility criteria or for other reasons such as patient decision. The main reasons for screen failures based on inclusion and exclusion criteria are presented in Supplementary Table 3, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41477/abstract. A total of 555 patients were randomized, of which 94.6% of the patients in the secukinumab 150 mg LD group (175 of 185), 96.2% of the patients in the secukinumab 150 mg NL group (177 of 184), and 94.1% of the patients in the placebo group (175 of 186) completed 24 weeks of treatment. Completion rates at week 52 in the corresponding groups were 84.3% (156 of 185), 89.7% (165 of 184), and 86.0% (160 of 186). The detailed patient disposition through week 52 is presented in Figure 1. Demographic and baseline disease characteristics were comparable across treatment groups (Table 1). The majority of randomized patients (90.3%) were TNFi-naive. The proportion of patients who switched to either open-label secukinumab or standard of care between weeks 20 and 52, based on clinical judgment of disease activity by the investigator and the patient, was 50.8% in the 150 mg LD group (94 of 185, with 94 switching to open-label secukinumab and 2 subsequently switched to

Table 1. Demographic and baseline disease characteristics of the patients with nonradiographic axial SpA*

Variable	Secukinumab 150 mg with loading (n = 185)	Secukinumab 150 mg without loading (n = 184)	Placebo (n = 186)
Age, mean ± SD years	39.10 ± 11.45	39.80 ± 11.68	39.30 ± 11.47
Sex, no. (%) men	80 (43.2)	84 (45.7)	91 (48.9)
Race, no. (%) white	176 (95.1)	165 (89.7)	167 (89.8)
BMI, mean ± SD kg/m^2	27.13 ± 5.50	27.17 ± 5.75	26.87 ± 5.61
Time since diagnosis, mean ± SD years	2.75 ± 4.63	2.12 ± 3.05	2.96 ± 5.01
Symptom duration, mean ± SD years	8.72 ± 9.27	8.57 ± 8.64	8.39 ± 8.34
HLA–B27 positive, no. (%)	136 (73.5)	117 (63.6)	129 (69.4)
Elevated hsCRP (>5 mg/liter), no. (%)	104 (56.2)	107 (58.2)	105 (56.5)
hsCRP, mean ± SD mg/liter	13.17 ± 27.21	9.67 ± 15.82	10.76 ± 21.34
Historic or current SI joint inflammation on MRI, no. (%)	132 (71.4)	134 (72.8)	139 (74.7)
SI joint inflammation on MRI score, mean ± SD	2.80 ± 3.83	2.24 ± 3.29	2.70 ± 3.96
TNFi-naive, no. (%)	164 (88.6)	166 (90.2)	171 (91.9)
Smoker at baseline, no. (%)	45 (24.3)	40 (21.7)	47 (25.3)
History of uveitis, no. (%)	21 (11.4)	26 (14.1)	18 (9.7)
History of IBD, no. (%)	2 (1.1)	3 (1.6)	5 (2.7)
Total back pain (0–100-mm VAS), mean ± SD	73.30 ± 13.02	72.0 ± 14.48	70.90 ± 12.52
Nocturnal back pain (0–100-mm VAS), mean ± SD	70.90 ± 17.42	70.80 ± 16.43	70.10 ± 14.72
BASDAI score, mean ± SD	7.08 ± 1.33	6.93 ± 1.45	6.76 ± 1.24
BASFI score, mean ± SD	6.24 ± 2.04	5.92 ± 2.04	5.89 ± 1.90
ASDAS-CRP score, mean ± SD	3.70 ± 0.87	3.59 ± 0.78	3.49 ± 0.81
Concomitant NSAIDs, no. (%)	154 (83.2)	153 (83.2)	156 (83.9)
Concomitant MTX			
No. (%)	17 (9.2)	15 (8.2)	23 (12.4)
Median mg/week	15	15	20
Concomitant sulfasalazine			
No. (%)	29 (15.7)	24 (13.0)	29 (15.6)
Median gm/day	2	2	2
Concomitant steroids			
No. (%)	14 (7.6)	17 (9.2)	17 (9.1)
Median mg/day	5	10	6.7

* SpA = spondyloarthritis; BMI = body mass index; hsCRP = high-sensitivity C-reactive protein; SI = sacroiliac; MRI = magnetic resonance imaging; TNFi = tumor necrosis factor inhibitor; IBD = inflammatory bowel disease; VAS = visual analog scale; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; BASFI = Bath Ankylosing Spondylitis Functional Index; ASDAS-CRP = Ankylosing Spondylitis Disease Activity Score using the CRP level; NSAIDs = nonsteroidal antiinflammatory drugs; MTX = methotrexate.

standard of care treatment with TNFi), 47.3% in the 150 mg NL group (87 of 184; 86 switched to open-label secukinumab and 1 to standard of care), and 64.0% (119 of 186 to open-label secukinumab) in the placebo group.

Efficacy. Results of hypothesis tests according to the predefined testing strategy in analysis plans A and B are presented in Supplementary Tables 4 and 5, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41477/abstract.

Primary objectives. The primary end points as per analysis plan A and analysis plan B were met (Figure 2A); ASAS40 response in TNFi-naive patients was significantly higher in the secukinumab 150 mg LD group (41.5%) compared with the placebo group (29.2%) at week 16 ($P = 0.0197$) and significantly higher in the secukinumab 150 mg NL group (39.8%) compared with the placebo group (19.9%) at week 52 ($P = 0.0021$).

Secondary objectives. The secukinumab 150 mg LD and NL regimens showed significant improvement versus placebo across all predefined secondary end points for analysis plan A at week 16 (Table 2). The total BASDAI score (Figure 2B) was significantly improved from baseline in patients treated with 150 mg LD (–2.35) or NL (–2.43) versus placebo (–1.46; $P = 0.0006$ and $P = 0.0002$, respectively), with improvement versus placebo seen as early as week 1 (–0.87 in the LD group and –0.82 in the NL group versus –0.48 in the placebo group). The proportion of BASDAI50 responders (Figure 2C) was significantly higher in patients treated with 150 mg LD (37.3%) or 150 mg NL (37.5%) versus placebo

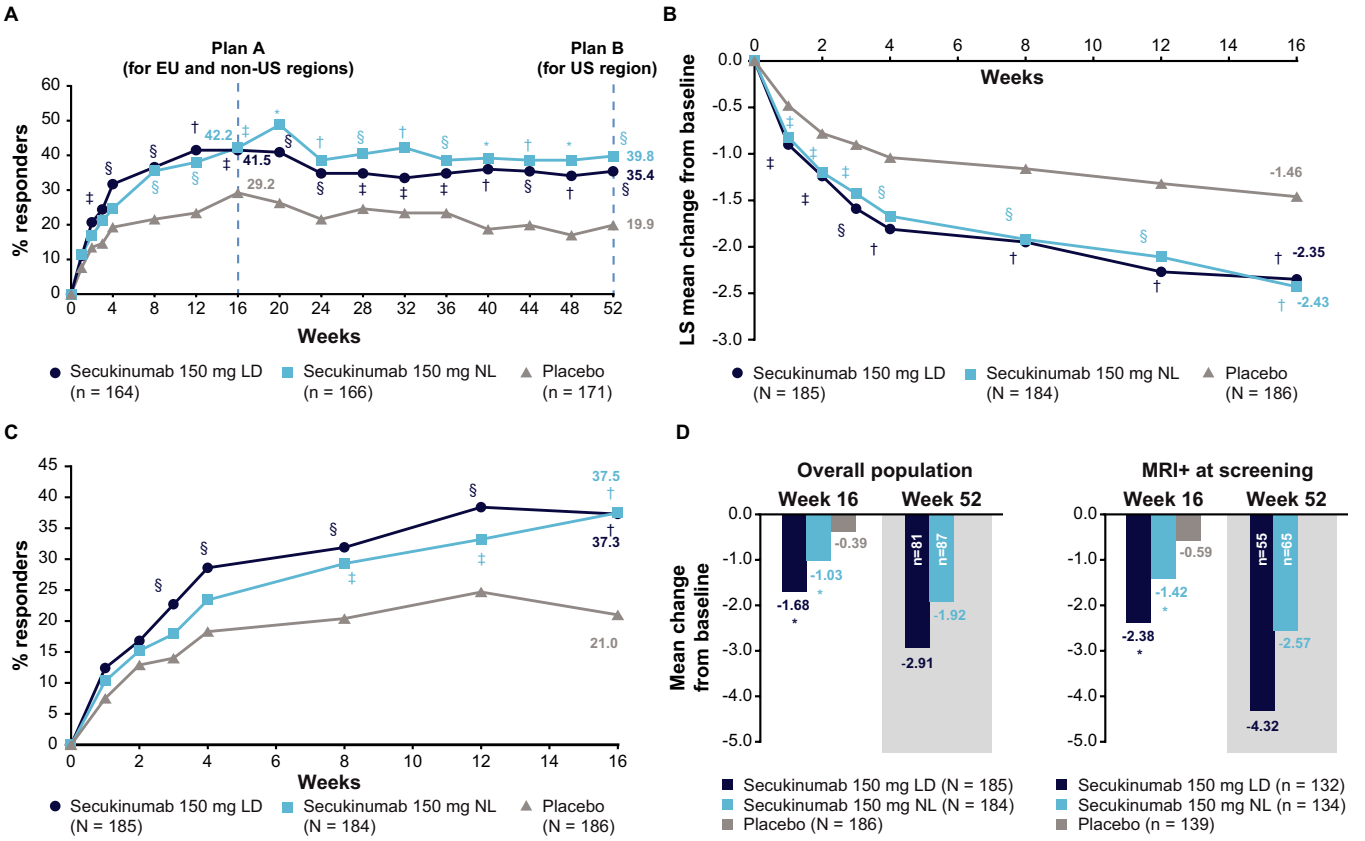

Figure 2. Primary and key secondary outcomes through week 52 based on statistical hierarchy. **A**, Assessment of SpondyloArthritis international Society criteria for 40% improvement (ASAS40) response at week 16 (analysis plan A for European Union [EU] and non-US region regulatory requirements) and week 52 (analysis plan B for US regulatory requirements) in tumor necrosis factor inhibitor–naive patients randomized to receive secukinumab 150 mg with loading (LD), secukinumab 150 mg without loading (NL), or placebo (primary objective). **B**, Total Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score in each treatment group through week 16. **C**, BASDAI criteria for 50% improvement response in each treatment group through week 16. **D**, Sacroiliac (SI) joint edema score on magnetic resonance imaging (MRI) in the overall population and in the subgroup of patients who were MRI-positive at screening (defined as the presence of inflammatory lesions in the SI joints on MRI according to the ASAS/Outcome Measures in Rheumatology definition). The mean baseline SI joint edema score was 3.56 in the group with loading and 2.64 in the group without loading in the overall population and 5.23 in the group with loading and 3.48 in the group without loading in the subgroup of patients who were MRI-positive at screening. For SI joint edema score at week 16, *P* values were determined by an analysis of covariance model based on multiple imputation (missing at random assumption), and data are presented as the least squares (LS) mean change. Observed data (shaded) for SI joint edema score at week 52 are shown for secukinumab-treated patients who did not switch treatment. * = $P < 0.0001$; † = $P < 0.001$; § = $P < 0.01$; ‡ = $P < 0.05$, versus placebo.

Table 2. Secondary end points according to the statistical hierarchy of analysis plans A and B*

Variable	Secukinumab 150 mg with loading (n = 185)	Secukinumab 150 mg without loading (n = 184)	Placebo (n = 186)	*P*, with loading versus placebo	*P*, without loading versus placebo
ASAS40 (overall population), % responders					
Week 16	40.0	40.8	28.0	0.0108	0.0087
Week 52	33.5	38.0	19.4	0.0015	0.0016
ASAS5/6 at week 16, % responders	40.0	35.9	23.7	0.0005	0.0094
BASDAI at week 16, LSM ± SEM change from baseline	−2.35 ± 0.20	−2.43 ± 0.20	−1.46 ± 0.21	0.0006	0.0002
BASDAI50, % responders					
Week 16	37.3	37.5	21.0	0.0001	0.0002
Week 52	30.8	35.3	19.9	0.0056	0.0061
High-sensitivity CRP at week 16, LSM ± SEM change from baseline†	0.64 ± 1.08	0.64 ± 1.08	0.91 ± 1.08	0.0002	0.0002
BASFI at week 16, LSM ± SEM change from baseline	−1.75 ± 0.20	−1.64 ± 0.20	−1.01 ± 0.21	0.0041	0.0143
SI joint edema score on MRI at week 16, LSM ± SEM change from baseline‡§	−1.68 ± 0.24	−1.03 ± 0.18	−0.39 ± 0.15	<0.0001¶	<0.0001¶
ASAS20 at week 16, % responders	56.8	58.2	45.7	0.0260	0.0149
SF-36 PCS at week 16, LSM ± SEM change from baseline	5.71 ± 0.68	5.57 ± 0.69	2.93 ± 0.71	0.0006	0.0011
ASQoL at week 16, LSM ± SEM change from baseline‡§	−3.45 ± 0.41	−3.62 ± 0.41	−1.84 ± 0.42	0.0008	0.0002
ASAS partial remission at week 16, % responders	21.6	21.2	7.0	<0.0001	0.0001
ASDAS-CRP inactive disease (<1.3) at week 52, % responders§	15.7	23.9	10.2	0.0577	0.0003

* The study included 2 independent analysis plans: plan A (week 16) per European Union and non-US regulatory requirements, and plan B (week 52) per US regulatory requirements. Nonresponder imputation analysis was used for binary variables and a mixed-effects model repeated measures was used for continuous variables. *P* values are unadjusted. Data are presented only for the secondary end points assessed according to the statistical hierarchy as shown in Supplementary Figures 2 and 3, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41477/abstract. ASAS40 = Assessment of SpondyloArthritis international Society criteria for 40% improvement; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; ASAS5/6 = 20% improvement in 5 of 6 domains of the ASAS criteria; BASDAI 50 = 50% decrease in BASDAI score from baseline; BASFI = Bath Ankylosing Spondylitis Functional Index; SF-36 = Short Form 36; PCS = physical component summary.

† Exponentially transformed least squares mean (LSM) for the geometric mean ratio of postbaseline value to baseline value. A value of <1 indicates a reduced C-reactive protein (CRP) value postbaseline.

‡ Continuous end points at week 52 were analyzed using nonparametric methods; detailed results are presented in Supplementary Table 9, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41477/abstract.

§ For the secukinumab 150 mg with loading dose group at week 52, sacroiliac (SI) joint edema score on magnetic resonance imaging (MRI), Ankylosing Spondylitis Quality of Life (ASQoL) score, and inactive disease according to the Ankylosing Spondylitis Disease Activity Score using the CRP level (ASDAS-CRP) were not significant according to the testing hierarchy.

¶ *P* values were determined by an analysis of covariance model based on multiple imputation (missing at random assumption).

(21.0%; $P = 0.0001$ and $P = 0.0002$, respectively). Secukinumab 150 mg LD and NL regimens significantly reduced the SI joint edema score on MRI (Figure 2D) in the overall study population versus placebo (−1.68 and −1.03, respectively, versus −0.39; both $P < 0.0001$).

For analysis plan B, significance versus placebo was achieved for the majority of secondary end points for both the LD and NL regimens at weeks 16 and 52 (Table 2). Significance versus placebo was not achieved for the 150 mg LD group at week 52 for inactive disease according to ASDAS-CRP (Table 2). Therefore, the subsequent end points in the hierarchical testing sequence, SI joint edema score on MRI and ASQoL for the 150 mg LD group, were not tested. Of the patients who switched to open-label secukinumab between weeks 20 and 52, 16.0% in the 150 mg LD group (15 of 94), 24.4% in the 150 mg NL group (21 of 86), and 10.9% in the placebo group (13 of 119) had actually achieved ASAS40 at the time of treatment switch. Notably, these patients were imputed as nonresponders for the week 52 analyses of binary end points.

Exploratory outcomes. In the overall population, the mean change from baseline in ASDAS-CRP score (by MMRM) was −1.07 for the 150 mg LD group and −1.12 for the 150 mg NL group versus −0.60 for the placebo group at week 16 (both $P < 0.0001$). An ASDAS-CRP major improvement response (by NRI) at week 16 was achieved in 24.9% of the patients in the 150 mg LD group and 25.5% of the patients in the 150 mg NL group versus 9.7% of the patients in the placebo group ($P = 0.0008$ and $P = 0.0001$, respectively). ASDAS-CRP clinically important improvement (by NRI) at week 16 was achieved in 49.7% of the patients in the 150 mg LD group and 53.3%

Table 3. Safety profile up to week 20 and over the entire treatment period*

	Secukinumab 150 mg with loading (n = 185)	Secukinumab 150 mg without loading (n = 184)	Any secukinumab (n = 369)†	Placebo (n = 186)
Up to week 20 (safety set)				
Any AE, no. (%)	119 (64.3)	107 (58.2)	226 (61.2)	101 (54.3)
Any serious AE, no. (%)	2 (1.1)	4 (2.2)	6 (1.6)	5 (2.7)
Discontinuation due to any AE, no. (%)	0 (0)	3 (1.6)	3 (0.8)	3 (1.6)
Death	0 (0)	0 (0)	0 (0)	0 (0)
Most common AEs, no. (%)‡				
Nasopharyngitis	27 (14.6)	19 (10.3)	46 (12.5)	23 (12.4)
Diarrhea	14 (7.6)	9 (4.9)	23 (6.2)	7 (3.8)
Headache	17 (9.2)	5 (2.7)	22 (6.0)	7 (3.8)
Upper respiratory tract infection	11 (5.9)	11 (6.0)	22 (6.0)	7 (3.8)
Selected AEs, no. (%)				
Serious infections	1 (0.5)	1 (0.5)	2 (0.5)	0 (0)
IBD (preferred term)	0 (0)	1 (0.5)	1 (0.3)	0 (0)
MACE	0 (0)	0 (0)	0 (0)	1 (0.5)
Uveitis	2 (1.1)	0 (0)	2 (0.5)	1 (0.5)
Entire treatment period (safety set)§				
Any AE, no. (%)	162 (87.6)	156 (84.8)	431 (79.4)	121 (65.1)
Any serious AE, no. (%)	20 (10.8)	12 (6.5)	39 (7.2)	8 (4.3)
Discontinuation due to any AE, no. (%)	7 (3.8)	13 (7.1)	24 (4.4)	3 (1.6)
Death	0 (0)	0 (0)	0 (0)	0 (0)
Most common AEs, no. (EAIR/100 patient-years)¶				
Nasopharyngitis	56 (25.4)	43 (17.6)	122 (19.4)	32 (32.5)
Upper respiratory tract infection	25 (9.6)	24 (9.0)	59 (8.4)	13 (12.4)
Diarrhea	23 (8.8)	20 (7.4)	50 (7.1)	10 (9.5)
Headache	26 (10.1)	12 (4.3)	46 (6.5)	9 (8.6)
Selected AEs, no. (EAIR/100 patient-years)				
Serious infections	5 (1.8)	5 (1.7)	12 (1.6)	1 (0.9)
IBD	3 (1.1)	1 (0.3)	7 (0.9)	0 (0)
MACE	0 (0)	0 (0)	0 (0)	1 (0.9)
Uveitis	5 (1.8)	2 (0.7)	9 (1.2)	2 (1.8)
Malignancies	0 (0)	0 (0)	3 (0.4)	0 (0)
Suicide attempt	0 (0)	1 (0.3)	1 (0.1)	0 (0)

* IBD = inflammatory bowel disease; MACE = major adverse cardiovascular event.
† The "any secukinumab" group (n = 369 for up to week 20 and n = 543 for the entire treatment period) included patients originally randomized to receive secukinumab and patients originally randomized to receive placebo who switched to open-label secukinumab 150 mg.
‡ Adverse events (AEs) with a frequency of >5% up to week 20, presented in descending order in the "any secukinumab" group. Events are listed according to preferred term in the Medical Dictionary for Regulatory Activities (MedDRA), version 21.1.
§ The entire treatment period includes safety data up to the cutoff date July 1, 2019 and includes at least 52 weeks of exposure for all patients and up to 104 weeks of exposure for some patients. The cumulative exposure was 286.1 patient-years for the secukinumab 150 mg with loading group, 291.3 patient-years for the secukinumab 150 mg without loading group, 757.9 patient-years for the "any secukinumab" group, and 109.3 patient-years for the placebo group.
¶ AEs that occurred with an exposure-adjusted incidence rate (EAIR) of >5.0 cases per 100 patient-years in the "any secukinumab" group over the entire treatment period. Events are listed according to preferred term in the MedDRA, version 21.1.

of the patients in the 150 mg NL group versus 30.6% of the patients in the placebo group (P = 0.0009 and P < 0.0001, respectively). In patients with a positive MRI at screening, the SI joint edema score on MRI using multiple imputation was –2.38 for the 150 mg LD group and –1.42 for the 150 mg NL group versus –0.59 for the placebo group (both P < 0.0001) at week 16 (Figure 2D). The corresponding score (observed data) at week 52 in patients originally randomized to receive secukinumab who did not switch treatment was –2.91 for the 150 mg LD group (n = 81) and –1.92 for the 150 mg NL group (n = 87) in the overall population and –4.32 for the 150 mg LD group (n = 55) and –2.57 for the 150 mg NL group (n = 65) with MRI positivity at screening (Figure 2D).

Observed data across all prespecified efficacy end points for the overall population at week 16 and at week 52 for patients who did not switch treatment are presented in Supplementary Table 6, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41477/abstract. Additional efficacy data (observed) at week 52 for all secukinumab-treated patients (including patients who did not switch treatment and those who switched to open-label secukinumab or standard of care) and for placebo patients who switched to open-label secukinumab are presented in Supplementary Tables 7 and 8, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41477/abstract. The change from baseline to week 52 in SI joint total edema score on MRI

and ASQoL scores are presented in Supplementary Table 9, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41477/abstract.

Safety. Table 3 shows safety results for this study up to week 20, when all patients were still receiving the treatment to which they were originally randomized, and for the entire treatment period (up to the data cutoff date of July 1, 2019). All patients remaining in the study had completed the week 52 visit by the data cutoff date, with many having completed up to 2 years of treatment. The mean duration of exposure was 564.8 days (286.1 patient-years in total), 578.3 days (291.3 patient-years in total), and 214.6 days (109.3 patient-years in total) for the 150 mg LD, 150 mg NL, and placebo groups, respectively. The mean exposure in the "any secukinumab" group (all patients randomized to receive secukinumab and patients who switched to open-label secukinumab after originally being randomized to receive placebo) was 509.8 days, with a cumulative exposure of 757.9 patient-years over the entire treatment period.

The overall incidence of treatment-emergent AEs up to week 20 was 61.2% for the "any secukinumab" group and 54.3% for placebo. Most AEs reported up to week 20 were mild or moderate in severity for all treatment groups. The most frequent treatment-emergent AEs in terms of crude incidence rates up to week 20 were nasopharyngitis, diarrhea, headache, and upper respiratory tract infection in both the secukinumab and placebo groups (Table 3). Most AEs reported during the entire treatment period were mild or moderate in severity across all treatment groups.

The most frequent treatment-emergent AEs and selected AEs of interest are shown in Table 3. A total of 14 cases of uveitis in 11 patients were reported; 9 in the secukinumab groups (4 de novo cases) and 2 in the placebo group. All uveitis cases were mild to moderate in severity, none of them were reported as SAEs, and none led to treatment interruption or discontinuation. A total of 7 patients receiving secukinumab reported IBD (5 Crohn's disease and 2 ulcerative colitis). Two patients had a history of IBD. Three of the IBD cases led to treatment interruption or discontinuation. No cases of IBD were reported in the placebo group. Suicide attempts were reported in 2 patients with a history of depression; 1 in a patient who had switched to a TNFi as standard of care ~10 months before the event and 1 in a patient in the secukinumab 150 mg NL group. Three malignancy cases were reported in patients in the placebo group who switched to open-label secukinumab: a malignant melanoma (reported as an SAE), a squamous cell carcinoma of the tongue, and a basal cell carcinoma. All malignancy events led to discontinuation of study medication as required by the protocol, although none of these cases were considered by the investigator to be related to study medication. Grade 3 neutropenia was reported in 3 patients: 1 patient in the secukinumab 150 mg LD group and 2 patients in the placebo group who switched to open-label secukinumab. Grade 4 neutropenia was reported in 1 patient in the placebo group. There were no MACE events reported in the secukinumab groups, with 1 case of myocardial infarction in the placebo group. No deaths, tuberculosis reactivation, esophageal candidiasis, or hepatitis B reactivation were reported.

DISCUSSION

PREVENT is the first randomized placebo-controlled phase III study evaluating the efficacy and safety of secukinumab treatment in patients with nonradiographic axial SpA and the largest randomized controlled trial of a biologic therapy in nonradiographic axial SpA to date. The retention rate was high, with 95.0% of randomized patients completing week 24 and 86.7% completing week 52. Secukinumab 150 mg met both primary end points (ASAS40 response) at weeks 16 and 52 in TNFi-naive patients with nonradiographic axial SpA. ASAS40 and all predefined secondary end points in the overall study population were met at week 16 and the majority were met at week 52, demonstrating that secukinumab provided significant improvement in disease activity, physical function, quality of life, and objective signs of inflammation in nonradiographic axial SpA patients who were either naive to prior biologic therapy or had demonstrated an inadequate response to TNF inhibition. The treatment effect of both secukinumab regimens (LD and NL) was observed early and was sustained through week 52. While the study was not powered to compare differences between dose regimens, the LD regimen was associated with a more rapid onset of action compared with the NL regimen for most efficacy end points up to week 16.

The efficacy outcomes of this study are consistent with previous phase III studies, which evaluated the efficacy of TNF or IL-17 inhibitors in patients with nonradiographic axial SpA over a shorter duration, ranging from 12 to 16 weeks (29–33). The ASAS40 response of 29.2% for placebo in the present study is higher than that observed in trials with other biologics. In the ABILITY-1 study, 36.0% of adalimumab-treated patients with nonradiographic axial SpA achieved an ASAS40 response at week 12 compared with 15.0% of placebo-treated patients (29). The ASAS40 responses at week 16 were 56.7% (golimumab) versus 23.0% (placebo) in the GO-AHEAD study (30). In the EMBARK study, the ASAS40 response rate was 32.0% in the etanercept group versus 16.0% in the placebo group at week 12 (31). In the C-axSpAnd study, the ASAS40 response rate was 47.8% in the certolizumab pegol group versus 11.4% in the placebo group at week 12 (32). In a recently published study, the ASAS40 response rates were 35.0% with ixekizumab versus 19.0% with placebo at week 16 in patients with nonradiographic axial SpA (33).

High response rates to placebo in clinical studies is the subject of ongoing debate and research. The expectation for the efficacy of newer biologics, particularly in biologic-naive patients, and the subjective nature of the majority of the outcome measures used in axial SpA studies may be potential reasons for the high response to

placebo observed in the present study. This would be expected to be reflected particularly in end points such as ASAS20 and ASAS40 responses, with high hurdle efficacy end points having a lower placebo response. This is indeed reflected in the present study, with lower placebo response rates and greater differentiation observed for partial remission according to ASAS and inactive disease according to the ASDAS-CRP. Moreover, low responses to placebo were also observed for end points using objective measures, in particular hsCRP levels and SI joint edema reduction on MRI.

Overall, treatment with secukinumab 150 mg (LD or NL) was well tolerated in patients with nonradiographic axial SpA. No new or unexpected safety signals were identified during the entire treatment period. The safety profile was consistent with the established safety profile across approved indications (34), with rates of IBD and uveitis being consistent with previously reported data with secukinumab in patients with AS (18,20).

The strengths of this study include the fact that it is the largest interventional phase III study to date in patients with nonradiographic axial SpA and allowed for the inclusion of patients with previous exposure to TNFi. The study is also notable for its 52-week placebo-controlled treatment period. However, the ability of patients to switch to open-label secukinumab or standard of care (TNFi) treatment based on the judgment of the physician and the patient after week 20 (as requested by regulatory authorities) led to the limitation that by week 52 many patients were no longer receiving the treatment that they were originally randomized to receive. In turn, while the efficacy analysis took the most conservative approach for the primary and all binary secondary end point analyses by defining these patients as nonresponders, a proportion of these patients across all treatment groups had achieved ASAS40 at the time of switch to open-label secukinumab or standard of care treatment.

In conclusion, secukinumab 150 mg demonstrated rapid and significant improvement in the signs and symptoms of nonradiographic axial SpA in both TNFi-naive patients and the overall study population by week 16, which was sustained through week 52. Secukinumab was well tolerated, with no new or unexpected safety signals identified. The PREVENT study results, combined with the results from the MEASURE program (18,20) in patients with radiographic axial SpA, demonstrate that secukinumab can be a viable option to treat the entire spectrum of axial SpA, i.e., from early to late stage or from nonradiographic axial SpA to radiographic axial SpA.

ACKNOWLEDGMENTS

The authors thank the patients and the investigators who participated in the study. The authors also thank John Gallagher (Novartis Pharmaceuticals UK Ltd., UK) and Abhijit Shete (Novartis Pharma AG, Basel, Switzerland) for medical guidance and editorial support.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Deodhar had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Deodhar, Wiksten, Porter, Richards, Haemmerle, Braun.

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ROLE OF THE STUDY SPONSOR

The study was designed by the scientific steering committee and Novartis personnel. All authors had access to the data, contributed to the interpretation, and collaborated in the development of the manuscript. The first draft of the manuscript was written by a medical writer, employed by the study sponsor (Niladri Maity, Novartis Healthcare Pvt., Ltd., Hyderabad, India), under the guidance of the authors. All authors critically reviewed and provided feedback on subsequent versions for important intellectual content. All authors approved the final version of the manuscript to be submitted for publication and vouch for the accuracy and completeness of the data and fidelity of this report to the study protocol. Statistical analyses were performed by statisticians employed by the study sponsor (Novartis Pharma AG, Basel, Switzerland). Publication of this article was not contingent upon approval by Novartis.

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