Improvement of functioning and health with ixekizumab in the treatment of active nonradiographic axial spondyloarthritis in a 52-week, randomized, controlled trial

Walsh, J.A.; Magrey, M.N.; Baraliakos, X.; Inui, K.; Weng, M.Y.; Lubrano, E.; ... ; Kiltz, U.

Arthritis Care & Research
Vol. 74, No. 3, March 2022, pp 451–460
DOI 10.1002/acr.24482

American College of Rheumatology
Empowering Rheumatology Professionals

Improvement of Functioning and Health With Ixekizumab in the Treatment of Active Nonradiographic Axial Spondyloarthritis in a 52-Week, Randomized, Controlled Trial

Jessica A. Walsh,[1] Marina N. Magrey,[2] Xenofon Baraliakos,[3] Kentaro Inui,[4] Meng-Yu Weng,[5] Ennio Lubrano,[6] Désirée van der Heijde,[7] Annelies Boonen,[8] Lianne S. Gensler,[9] Vibeke Strand,[10] Jürgen Braun,[3] Theresa Hunter,[11] Xiaoqi Li,[11] Baojin Zhu,[11] Luis León,[11] David Marcelino Sandoval Calderon,[11] and Uta Kiltz[3]

Objective. To evaluate the effect of ixekizumab on self-reported functioning and health in patients with active nonradiographic axial spondyloarthritis (SpA).

Methods. COAST-X was a randomized, controlled trial conducted in patients with nonradiographic axial SpA over 52 weeks. Participants were randomized at a ratio of 1:1:1 to receive 80 mg of ixekizumab subcutaneously every 4 weeks or 2 weeks or placebo for 52 weeks. Self-reported functioning and health end points included the Medical Outcomes Study Short Form 36 (SF-36) health survey, Assessment of Spondyloarthritis International Society (ASAS) health index, and European Quality of Life-5 Dimensions-5 Level (EQ-5D-5L) health-utility descriptive system.

Results. Compared to placebo, ixekizumab treatment resulted in improvement of SF-36 physical component summary scores from baseline, with a score of 4.7 improving to 8.9 with ixekizumab therapy every 4 weeks ($P < 0.05$) and a score of 9.3 with ixekizumab therapy every 2 weeks ($P < 0.01$); the greatest improvements were observed in the domains of physical functioning, role-physical, and bodily pain at weeks 16 and 52. A higher proportion of patients receiving ixekizumab therapy every 2 weeks reported ≥3 improvements based on the ASAS health index from baseline to weeks 16 and 52 ($P < 0.05$). Significantly more patients receiving ixekizumab every 4 weeks reported improvements in "good health status" on the ASAS health index (ASAS score of ≤5) at weeks 16 and 52 ($P < 0.05$). Patients receiving ixekizumab reported improvements on the EQ-5D-5L compared to those who received placebo at week 16 (0.11 versus 0.17 for patients receiving treatment every 4 weeks and 0.19 for patients receiving treatment every 2 weeks; $P < 0.05$), which remained consistent at week 52. There were no clinical meaningful differences in responses based on the ixekizumab dosing regimen for patients who received ixekizumab therapy every 2 weeks or every 4 weeks.

Conclusion. In patients with nonradiographic axial SpA, therapy with ixekizumab was superior to placebo in the improvement of self-reported functioning and health at weeks 16 and 52.

INTRODUCTION

Axial spondyloarthritis (SpA) is a chronic inflammatory disease affecting mainly the axial skeleton (1). The term "axial SpA" encompasses patients with either radiographic axial SpA, which is also referred to as ankylosing spondylitis (AS), or nonradiographic axial SpA, which is defined by a diagnosis of axial SpA with the absence of definite sacroiliitis on radiograph (2). Among all patients with axial SpA, the proportion of patients with nonradiographic axial SpA varies. Ranges from 40% to 60% have been

ClinicalTrials.gov identifier: NCT02757352) and EudraCT database no. 2015-003938-27.
Supported by Eli Lilly and Company.
[1]Jessica A. Walsh, MD: University of Utah School of Medicine and Salt Lake City Veterans Affairs Medical Center, Salt Lake City, Utah; [2]Marina N. Magrey, MD: MetroHealth Medical Center and Case Western Reserve University School of Medicine, Cleveland, Ohio; [3]Xenofon Baraliakos, MD, PhD, Jürgen Braun, MD, PhD, Uta Kiltz, MD: Ruhr-University Bochum, Bochum, Germany, and Osaka City University Graduate School of Medicine, Osaka, Japan; [4]Kentaro Inui, MD: Osaka City University Graduate School of Medicine, Osaka, Japan; [5]Meng-Yu Weng, MD: National Cheng Kung University Medical College and Hospital, Tainan, Taiwan; [6]Ennio Lubrano, MD, PhD: University of Molise, Campobasso, Italy; [7]Désirée van der Heijde, MD, PhD: Leiden University Medical Center, Leiden, The Netherlands; [8]Annelies Boonen, MD, PhD: Maastricht University Medical Center and Caphri Research Institute, Maastricht University, Maastricht, The Netherlands; [9]Lianne S. Gensler, MD: University of California, San Francisco; [10]Vibeke Strand, MD: Stanford University School of Medicine, Palo Alto, California; [11]Theresa Hunter, PhD, Xiaoqi Li, PhD, Baojin Zhu, PhD, Luis León, PhD, David Marcelino Sandoval Calderon, MD: Eli Lilly and Company, Indianapolis, Indiana.

SIGNIFICANCE & INNOVATIONS

- Self-reported functioning and health measurements are important in understanding the impact of treatment from the perspective of the patient.
- Ixekizumab improves overall functioning and health in patients with nonradiographic axial spondyloarthritis, measured by Study Short Form 36, Assessment of Spondyloarthritis International Society health index, and European Quality of Life-5 Dimensions-5 Level health-utility descriptive system.
- Improved overall functioning and health is reported regardless of treatment regimen (80 mg ixekizumab every 2 weeks or 80 mg ixekizumab every 4 weeks).

reported (3–5). The burden of the disease is similar between individuals with nonradiographic axial SpA and individuals with AS (6–8). Patients with these conditions have comparable levels of pain, fatigue, and morning stiffness and have a patient profile characterized by impaired physical function and work productivity and an overall reduction in functioning and health.

Pharmacologic treatment with nonsteroidal antiinflammatory drugs (NSAIDs) is recommended for patients with axial SpA as a first-line treatment for improving back pain and stiffness (1,9,10). Second-line treatment comprises biologic disease-modifying antirheumatic drugs (bDMARDs) such as tumor necrosis factor inhibitors (TNFi) (9). However, patients with nonradiographic axial SpA had limited approved therapeutic options until recently. In the US, certolizumab pegol (11), ixekizumab, and secukinumab are the only biologic currently approved by the US Food and Drug Administration for the treatment of nonradiographic axial SpA, whereas in Europe, adalimumab (12), certolizumab pegol (13), etanercept (14), and golimumab (15) have been approved by the European Medicines Agency for the treatment of this disease. Approximately 60% of patients with nonradiographic axial SpA are treated with bDMARDs; however, patients often switch to another biologic due to inadequate response or intolerance (16–18). Thus, there remains a significant unmet need for patients with nonradiographic axial SpA.

Ixekizumab is an immunoglobulin G4 monoclonal antibody that selectively targets interleukin-17A with high affinity and has recently been approved in the US and European Union for the treatment of patients with active AS and nonradiographic axial SpA (19,20). The present study, COAST-X, investigated the efficacy and safety of ixekizumab in the nonradiographic axial SpA population. Ixekizumab had beneficial effects on disease activity, and it is important to note that these effects translated to improvement in the overall functioning and health of our study population. Here, we present results on self-reported functioning and health overall in individuals with nonradiographic axial SpA as measured by the Medical Outcomes Study 36-Item Short Form (SF-36) health survey, the Assessment of Spondyloarthritis International Society (ASAS) health index, and European Quality of Life-5 Dimensions (EQ-5D) descriptive system through 52 weeks of treatment.

PATIENTS AND METHODS

Study design. The COAST-X study is a phase III multicenter, randomized, controlled trial (RCT) with a 52-week duration, evaluating the efficacy and safety of ixekizumab in patients with active nonradiographic axial who are bDMARD-naive. Study protocol was reviewed and approved by applicable local ethics review boards. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committees at all sites where these studies were conducted. The RCT follows the principles of good clinical practice, standards set by the International Council for Harmonization, and local laws and regulations and conducted in accordance with the Declaration of Helsinki and its later amendments or comparable ethical standards. All enrolled patients provided written informed consent prior to study

Dr. Walsh has received consulting fees from AbbVie, Celgene, Novartis, UCB, Amgen, Pfizer and Eli Lilly and Company (less than $10,000 each) and research support from those companies. Dr. Magrey has receiving consulting fees from Eli Lily and Company, Janssen, Pfizer, and UCB (less than $10,000 each). Dr. Baraliakos has received consulting fees from AbbVie, Bristol Myers Squibb, Celgene, Janssen, MSD, Novartis, Pfizer, Roche, and UCB (< $10,000) and research support from those companies. Dr. Inui has received speaking fees from Chugai Pharmaceutical, Mitsubishi Tanabe Pharma, Daiichi Sankyo, Ono Pharmaceutical, Janssen, Pfizer, Eisai, Eli Lilly and Company, Novartis, and UCB (less than $10,000 each) and research support from those companies. Dr. Weng has received consulting fees from Eli Lilly and Company, Janssen, Novartis, Pfizer, and Roche (less than $10,000 each). Dr. Lubrano has received consulting fees from AbbVie, Bristol Meyers Squibb, Eli Lilly and Company, Janssen, MSD, Novartis, and Pfizer(less than $10,000 each). Dr. van der Heijde has received consulting fees from AbbVie, Amgen, Astellas, AstraZeneca, BMS, Boehringer Ingelheim, Celgene, Cyxone, Daiichi, Eisai, Eli Lilly and Company, Galapagos, Gilead, GlaxoSmithKline, Janssen, Merck, Novartis, Pfizer, Regeneron, Roche, Sanofi, Takeda, and UCB Pharma (less than $10,000 each) and is Director of Imaging Rheumatology at Imaging Rheumatology International. Dr. Boonen has received consulting fees from Eli Lilly and Company, Novartis, and UBC (less than $10,000 each) and has received research support from AbbVie and Celgene. Dr. Gensler has consulting fees from AbbVie, Eli Lilly and Company, GSK, Gilead, and Pfizer (less than $10,000 each) and from UCB and Novartis (more than $10,000 each). Dr. Strand has received consulting fees from AbbVie, Amgen, Arena, AstraZeneca, Bayer, Bioventus, BMS, Boehringer Ingelheim, Celltrion, Corrona, Crescendo/Myriad, EMD Serono, Equillium, Flexion, Genentech/Roche, Glenmark, GSK, Horizon, Inmedix, Janssen, Kypha, Eli Lilly, Merck, Novartis, Pfizer, Regeneron Pharmaceuticals Inc., Samsung, Samumed, Sandoz, Sanofi, Servier, Setpoint, TwoXARand, and UCB (less than $10,000 each). Dr. Braun has received consulting fees from AbbVie, Amgen, Celgene, Eli Lilly and Company, Janssen, MSD, Novartis, Pfizer, Sanofi, and UCB (less than $10,000 each). Drs. Hunter, Li, Zhu, León, and Sandoval own stocks or stock options in Eli Lilly and Company. Dr. Kiltz has received consulting fees from AbbVie, Amgen, Biogen, Eli Lilly and Company, Hexal, Janssen, MSD, Novartis, Pfizer, Roche, and UCB (less than $10,000 each) and research support from those companies.

Address correspondence to Uta Kiltz, MD, Rheumazentrum Ruhrgebiet, Ruhr-University Bochum, Claudiusstrasse 45, 44649 Herne, Germany. Email: uta.kiltz@elisabethgruppe.de.

Submitted for publication March 9, 2020; accepted in revised form September 4, 2020.

participation. Data sets generated and/or analyzed during the present study are available from the corresponding author upon reasonable request.

Study participants. Inclusion criteria have been previously detailed (21). Briefly, eligible patients were ages 18 years or older with an established diagnosis of axial SpA by a physician who fulfilled the ASAS classification criteria for nonradiographic axial SpA (22). Patients meeting the radiographic criterion of definite sacroiliitis according to the modified New York criteria (according to central reading by 2 readers and an adjudicator in case of a discrepancy) were excluded (23). Patients were also required to have disease activity at screening and at baseline (defined as having a Bath Ankylosing Spondylitis Disease Activity Index score of ≥4 and total back pain score of ≥4 on a 0–10 scale), an inadequate response to 2 or more NSAIDs or a history of intolerance to NSAIDs, and no prior treatment with bDMARDs. Patients were also required to have objective signs of inflammation, which was defined as evidence of sacroiliitis on magnetic resonance imaging (MRI; central reading by 2 readers and an adjudicator in case of a discrepancy) and/or elevated C-reactive protein (CRP) levels (>5 mg/liter). Active sacroiliitis on MRI was determined using the ASAS definition (22,24). Participants were allowed to continue background medications, including NSAIDs, conventional synthetic DMARDs (csDMARDs; methotrexate, hydroxychloroquine, and sulfasalazine), glucocorticoids, and analgesics that may be allowed if treated at a stable dose for at least 4 weeks prior to baseline randomization. If used, csDMARDs were not to be used in any combination with other csDMARDs.

Interventions. COAST-X interventions have been previously described (21). Briefly, patients were randomly assigned at a ratio of 1:1:1 to receive subcutaneous injections of ixekizumab (80 mg) every 4 weeks, subcutaneous injections of ixekizumab (80 mg) every 2 weeks, or placebo every 2 weeks. At week 0, patients assigned to ixekizumab treatment regimens were randomly assigned at a 1:1 ratio to receive a starting dose of either 80 mg ixekizumab or 160 mg ixekizumab (2 injections of 80 mg each). To maintain blinding of the study participants, all patients received 2 injections at week 0 and 1 injection every 2 weeks during the remainder of the blinded treatment dosing period. Ixekizumab and its matching placebo were visually indistinguishable from each other. Starting at week 16, patients were able to switch to open-label ixekizumab every 2 weeks or subsequent TNFi treatment (after receiving open-label treatment every 2 weeks for at least 8 weeks) if their disease activity required escalation of treatment at investigator discretion with no specific predefined criteria. Patients who had switched to open-label treatment continued to be followed up during the study. Patients, investigators, and all other personnel involved in the conduct of the study were blinded to individual treatment assignments through the 52-week blinded period. For patients who switched to open-label treatment with ixekizumab every 2 weeks, the study site personnel, patient, and study team remained blinded to the initial randomization.

Outcome measures. The effects of ixekizumab on functioning and health were assessed using 3 secondary major end points: SF-36, the ASAS health index, and EQ-5D-5 level (EQ-5D-5L). Assessments were recorded at weeks 0 (baseline), 4, 8, 16, 36, and 52 with the SF-36 and ASAS health index and at weeks 0, 16, and 52 with the EQ-5D-5L.

The SF-36 is a 36-item patient-administered measure designed as a short, generic assessment of health including the following domains: physical functioning (PF), role-physical (RP), bodily pain (BP), general health (GH), vitality (VT), role-emotional (RE), social functioning (SF), and mental health (MH) (25,26). Domain scores range from 0 to 100, with higher scores indicating better levels of function and/or better health. The physical component summary (PCS) and mental component summary (MCS) scores are calculated based on differential weighting of normalized and z-transformed 8 domain scores with normative scores of 50. Domain scores are answered based on Likert-type scales of 1 to 5. Version 2 of the SF-36 (the acute version) utilizes a 1-week recall period and has been used in the COAST-X study (25). Domains (scale 0–100, with higher scores indicating better health) were used in the spydergrams (27) as well as changes in the least squares mean (LSM) from baseline in PSC and MSC scores (Figure 1). T scores for SF-36 domains or component scores are based on the general US population norms of 2009. The calculation of age/gender–matched norms for each domain in the spydergrams (Figure 1) are based on 1998 US population norms and matched to the distribution of the protocol population.

The ASAS health index is a disease-specific health index designed to assess global functioning and health in patients with SpA. It covers areas of physical, emotional, and social functioning based on categories summarized in the ASAS/World Health Organization International Classification of Functioning, Disability, and Health core set for AS (28). This 17-item instrument has sum scores ranging from 0 (good health) to 17 (poor health) (29). Each item consists of one question that the patient needs to respond to with either "I agree" (score 1), "I do not agree" (score 0), or "not applicable" (only for items 7 and 8). If the patients choose "not applicable," the sum score is analyzed based on $n = 16$ or $n = 15$. A score of "1" is given where the item is affirmed, indicating adverse health. All item scores were summed to yield a total score or index (29). An improvement of ≥3 from baseline on the ASAS health index represents a clinically meaningful change and attaining a "good health status" is defined by having a score of ≤5 (30).

The EQ-5D-5L provides societal preferences for health states (health utility) based on 5 dimensions of health: mobility,

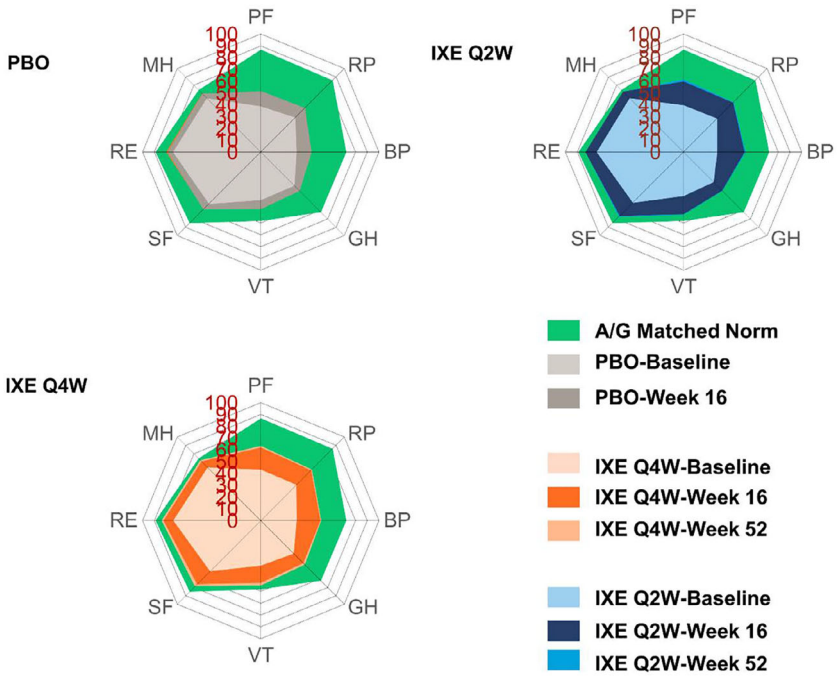

Figure 1. Medical Outcomes Study Short Form 36 (SF-36) health survey domain scores at baseline, week 16, and week 52 in the intent-to-treat population of the COAST-X trial. Subgroups included patients who received 80 mg of ixekizumab every 2 weeks (IXE Q2W), patients who received 80 mg of ixekizumab every 4 weeks (IXE Q4W), and patients who received placebo (PBO). Spydergrams depict modified baseline observation carried forward SF-36 domain scores (0–100 scale) and US age- and gender-matched normative values (A/G Matched Norm). SF-36 age- and gender-matched norms are based on the 1998 US population norms and patient counts for each age and gender distribution of the protocol population. BP = bodily pain; GH = general health MH = mental health; PF = physical functioning; RE = role-emotional; RP = role-physical; SF = social functioning; VT = vitality.

self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension can be scored on a 5-level scale: no problems, slight problems, moderate problems, severe problems, and extreme problems. The patient's completed EQ-5D-5L descriptive system was converted into a societal utility value using an available UK population–based algorithm providing a health-utility index score between −0.59 (very severe health, i.e., "worse than death") and 1.0 (perfect health [continuous variable]) (31).

Statistical analysis. Efficacy analyses were conducted on the intent-to-treat population regardless of the starting dose. The primary analysis for continuous outcomes (e.g., the SF-36 and ASAS health index) used a mixed-effects repeated measures model with treatment, geographic region (Europe and non-Europe), screening of MRI/CRP status, baseline value, visit, baseline value by visit interaction, and treatment by visit interaction as fixed factors at week 0 (baseline), 4, 8, 16, 36, and 52. When using mixed-effects repeated measures modeling, there was no prior imputation for missing data. Analyses for ASAS health index responses and good health status used logistic regression, which included treatment, geographic region, and MRI/CRP status at baseline. For continuous outcomes of EQ-5D-5L, analysis of covariance models included treatment, geographic region, screening MRI/CRP status, and baseline value. Modified baseline observation carried forward (BOCF) for missing data imputation was used with the EQ-5D-5L. For patients determined to be treatment nonresponders at the discretion of investigators who had treatment switched to open-label ixekizumab every 2 weeks, only data up to switching were included in the analyses, with data afterward treated as missing with nonresponder imputation. In patients who discontinued the study drug due to an adverse event, modified BOCF was used. In patients who discontinued the study drug for any other reason, the last nonmissing observation before discontinuation was carried forward. Patients who were randomized without at least 1 post-baseline observation were not included in the modified BOCF analysis except for those discontinuing study treatment due to the occurrence of an adverse event.

Subgroup analysis was conducted for all functioning and health end points of the proportion of patient achieving an ASAS criteria for 40% improvement (ASAS40) response at week 16 using the intent-to-treat population. A logistic regression model with treatment, subgroup, and the interaction of subgroup by treatment included as factors was used for analysis. Treatment group differences were evaluated within each category of the subgroup using Fisher's exact test, regardless of whether the interaction was statistically significant. Missing data was imputed using nonresponder imputation.

Table 1. Demographic and baseline characteristics of the study population*

Variable	Ixekizumab, 80 mg every 4 weeks (n = 96)	Ixekizumab, 80 mg every 2 weeks (n = 102)	Placebo (n = 105)
Age, years	40.9 ± 14.5	40.0 ± 12.0	39.9 ± 12.4
Female sex, no. (%)	46 (48)	53 (52)	61 (58)
BMI, kg/m^2	27.6 ± 5.4	27.3 ± 5.7	27.0 ± 5.8
Race, no. (%)			
White	80 (83)	83 (81)	76 (73)
Asian	13 (14)	11 (11)	17 (16)
Other	3 (3)	8 (8)	11 (11)
Positive for HLA–B27, no. (%)	71 (75)	73 (72)	77 (74)
Age at onset of axial SpA, years	30.1 ± 9.7	29.8 ± 9.5	30.1 ± 9.8
Duration of nonradiographic SpA symptoms, years	11.3 ± 10.7	10.6 ± 10.1	10.1 ± 8.3
Concomitant baseline medication, no. (%)			
NSAIDs	81 (84)	95 (93)	96 (91)
Methotrexate	17 (18)	15 (15)	17 (16)
Sulfasalazine	23 (24)	27 (26)	21 (20)
Glucocorticoids	8 (8)	20 (20)	14 (13)
SF-36 PCS score	33.5 ± 7.4	31.9 ± 7.5	32.6 ± 8.2
SF-36 MCS score	47.2 ± 11.8	47.7 ± 12.8	48.3 ± 11.7
ASAS health index score	8.6 ± 3.4	9.6 ± 3.4	9.0 ± 3.7
EQ-5D-5L score†	0.49 ± 0.23	0.44 ± 0.25	0.47 ± 0.22

* Values are the mean ± SD except where indicated otherwise. Percentages were calculated based on the number of patients with non-missing values. ASAS = Assessment of Spondyloarthritis International Society; BMI = body mass index; EQ-5D-5L = European Quality of Life-5 Dimensions-5 Level; MCS = mental component summary; NSAIDs = nonsteroidal antiinflammatory drugs; PCS = physical component summary; SF-36 = Medical Outcomes Study Short Form 36 health survey; SpA = spondyloarthritis.
† EQ-5D-5L UK population-based Index Score.

RESULTS

Of the 303 patients with nonradiographic axial SpA who were enrolled in the present study, 96 received ixekizumab every 4 weeks, 102 received ixekizumab every 2 weeks, and 105 received placebo (Table 1). Baseline characteristics and disease activity values at baseline were similar between the randomized treatment groups. Study patients had a mean ± SD age of 40.3 ± 13.0 years; 53% (160) of 303 patients were female, and 79% (239) were White. Patients had a mean ± SD body mass index of 27.3 ± 5.6 kg/m^2. Disease duration since nonradiographic axial SpA diagnosis was mean ± SD 10.7 ± 9.7 years, and the mean ± SD age at onset of disease was 30.0 ± 9.6 years. The proportion of HLA–B27–positive patients was 73.7% (221 of 300). The proportion of the 303 patients receiving concomitant baseline medications included the following: NSAIDs (89.8% [272]), methotrexate (16.2% [49]), sulfasalazine (23.4% [71]), and glucocorticoids (13.9% [42]).

Baseline mean ± SD scores were 32.6 ± 7.7 for SF-36 PCS score, 47.8 ± 12.1 for SF-36 MCS score, 9.1 ± 3.6 for ASAS health index score, and 0.47 ± 0.23 for EQ-5D-5L. By week 52, 62 (59%) of 105 patients who received placebo had switched to open-label ixekizumab treatment every 2 weeks as compared to 40 (42%) of 96 patients who received ixekizumab every 4 weeks and 42 (41%) of 102 patients who received ixekizumab every 2 weeks. At week 52, 34 (32%) of 105 patients who received placebo had completed the full 52-week placebo-controlled period receiving double-blind study medication compared to 52 (54%) of 96 patients who received ixekizumab every 4 weeks and 52 (51%) of 102 patients who received ixekizumab every 2 weeks.

Greater improvements in all patient-reported outcomes, including physical function and health status, were reported in both ixekizumab treatment groups versus the placebo group at weeks 16 and 52 (Figures 2–5), measured by LSM changes in SF-36 PCS scores from baseline to week 4 (4.3 for patients receiving ixekizumab every 4 weeks and 5.2 for patients receiving ixekizumab every 2 weeks compared to 2.0 for patients receiving placebo; $P = 0.015$ and $P < 0.001$, respectively), and improvements continued through week 52 of the trial (8.9 for patients receiving ixekizumab every 4 weeks and 9.3 for patients receiving ixekizumab every 2 weeks compared to 4.7 for patients receiving placebo; $P = 0.012$ and $P = 0.006$, respectively) (Figure 2). Statistically significant improvement was reported in SF-36 MCS score at week 36 in the patients who received ixekizumab every 4 weeks (a mean score of 5.33 for the ixekizumab group compared to a mean score of 2.35 for the placebo group; $P = 0.035$), with nonsignificant improvements also noted at other time points (data not shown). The beneficial effect of ixekizumab treatment on SF-36 domains at weeks 16 and 52 are shown in Figure 1, whereas modest improvements compared to baseline and age- and gender-matched norms were reported in the placebo group (Figure 1). The largest improvements were

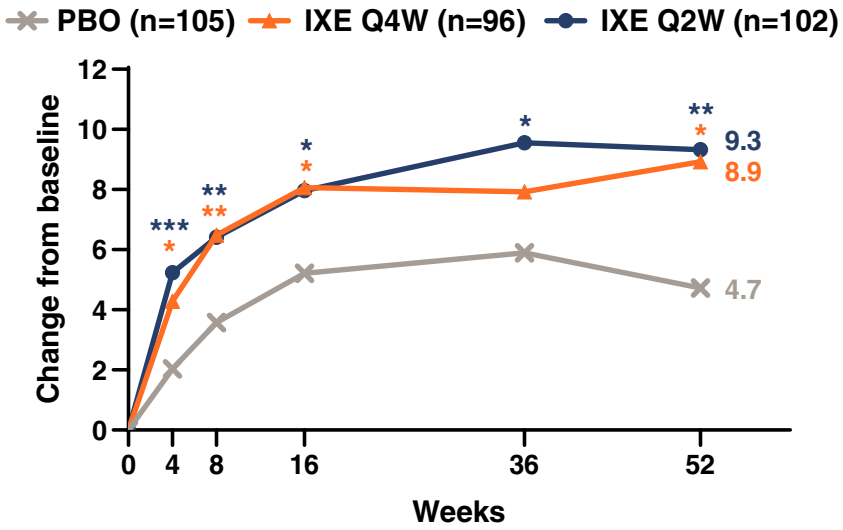

Figure 2. Medical Outcomes Study Short Form 36 health survey physical component summary scores, with least squares mean change from baseline observed in the intent-to-treat population of the COAST-X trial. Subgroups included patients who received 80 mg of ixekizumab every 2 weeks (IXE Q2W), patients who received 80 mg of ixekizumab every 4 weeks (IXE Q4W), and patients who received placebo (PBO). Comparisons between the ixekizumab treatment groups and the placebo group were made using a mixed-effects model for repeated measures. * = $P < 0.05$; ** = $P < 0.01$; *** = $P < 0.001$.

reported in PF, RP, BP, and SF domains. Improvements in RE, VT, SF, and MH domains approached those seen in matched US normative values.

At baseline, ASAS health index scores were symmetrically distributed with a median score of 9.0 (Supplementary Figure 1, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24482/abstract). At week 16, score distributions shifted to a median score of 6.0 (Supplementary Figure 1). Patients treated with ixekizumab every 2 weeks showed significant improvements in ASAS health index scores at week 16 (−2.74 for the patients who received ixekizumab every 2 weeks versus −1.76 for the patients who received placebo; $P = 0.023$), with numerically greater improvements in ASAS health index changes from baseline in both ixekizumab groups compared to the placebo group through week 52 (Figure 3).

ASAS health index improvements of ≥3 from baseline to week 16 were reported by 40.4% of the patients who received

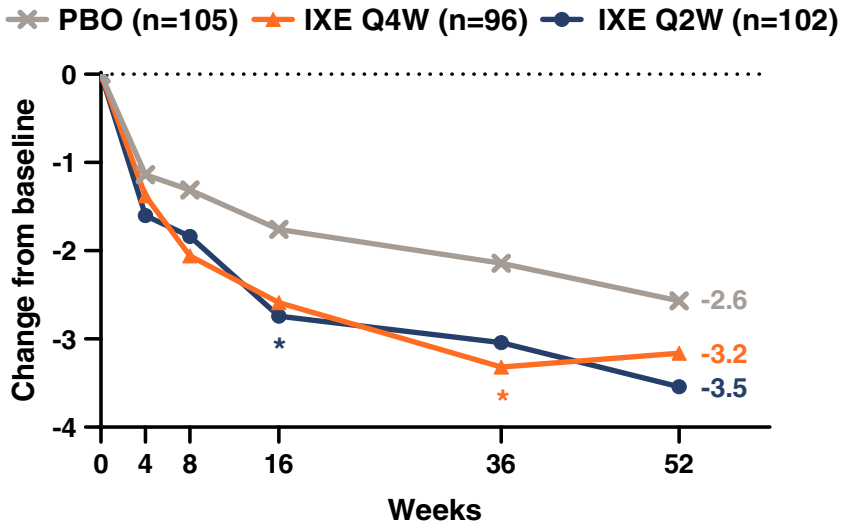

Figure 3. Assessment of Spondyloarthritis International Society health index least squares mean change from baseline in the intent-to-treat population of the COAST-X trial. Subgroups included patients who received 80 mg of ixekizumab every 2 weeks (IXE Q2W), patients who received 80 mg of ixekizumab every 4 weeks (IXE Q4W), and patients who received placebo (PBO). Comparisons between the ixekizumab treatment groups and the placebo group were made using a mixed-effects model for repeated measures. * = $P < 0.05$.

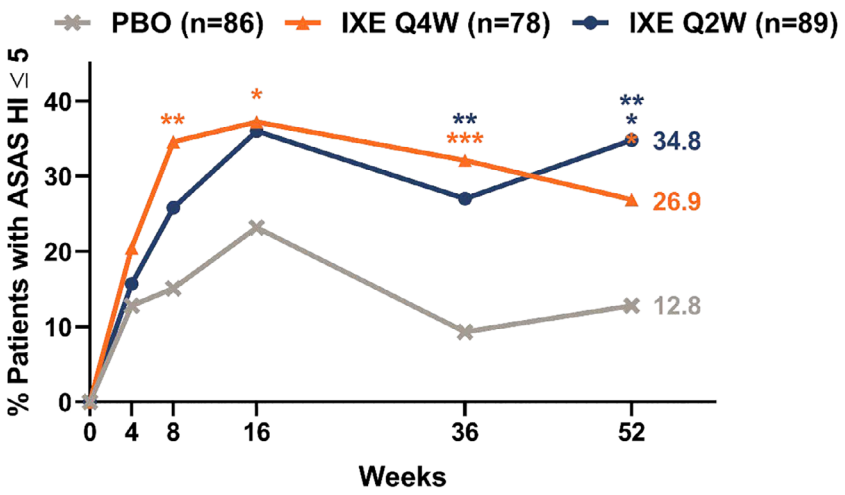

Figure 4. Percentage of patients achieving an Assessment of Spondyloarthritis International Society health index (ASAS HI) score of ≤5, indicating "good health status," in the intent-to-treat population of the COAST-X trial. Missing data were imputed with a nonresponder imputation. Subgroups included patients who received 80 mg of ixekizumab every 2 weeks (IXE Q2W), patients who received 80 mg of ixekizumab every 4 weeks (IXE Q4W), and patients who received placebo (PBO). Comparisons between the ixekizumab treatment groups and the placebo group were made using a logistic regression model. * = $P < 0.05$; ** = $P < 0.01$; *** = $P < 0.001$.

ixekizumab every 4 weeks ($P = 0.198$) and 49.0% of the patients who received ixekizumab every 2 weeks ($P = 0.017$) versus 32 (31.7%) of 101 patients who received placebo. Improvements on the ASAS health index were also observed at week 52 in 31 (33.0%) of 94 patients who received ixekizumab every 4 weeks ($P = 0.027$) and 35 (34.3%) of 102 patients who received ixekizumab every 2 weeks ($P = 0.02$) compared to 19 (18.8%) of 101 patients who received placebo (Supplementary Figure 2, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24482/abstract). Proportions of patients reporting "good health status" (ASAS health index score of ≤5 with a baseline score of >5) at week 16 included 29 (37.2%) of 78 patients who received ixekizumab treatment every 4 weeks ($P = 0.034$) and 32 (36.0%) of 89 patients who received ixekizumab therapy every 2 weeks compared to 19 (22.1%) of 86 patients who received placebo (Figure 4). At week 52, responses of "good health status" on the ASAS health index were reported by 21 (26.9%) of 78 patients who received ixekizumab every 4 weeks ($P = 0.02$) and 31 (34.8%) of 89 patients who received ixekizumab every 23 weeks ($P < 0.001$) compared to 11 (12.8%) of 86 patients who received placebo. A significantly higher score of ASAS health index responses of ≤5 was reported in the patient group that received ixekizumab therapy every 4 weeks compared to the patient group that received placebo from week 8 (34.6% [27 of 78] versus 15.1% [13 of 86]; $P = 0.005$).

Patients in each ixekizumab treatment group reported greater increases in health utility scores compared to the patients in the placebo group, as measured by the EQ-5D-5L (Figure 5). At week 16, patients treated with ixekizumab reported significant

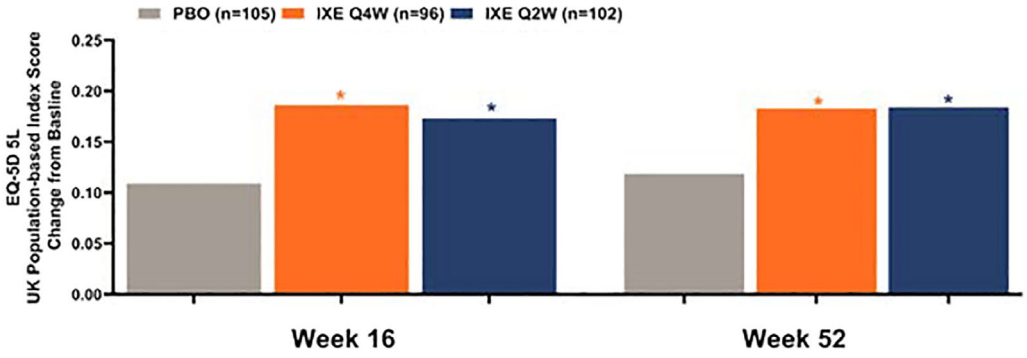

Figure 5. European Quality of Life-5 Dimensions-5 Level (EQ-5D-5L) UK population–based index scores, with the least squares mean change from baseline in the intent-to-treat population of the COAST-X trial. Missing data were imputed using modified baseline observation carried forward. Subgroups included patients who received 80 mg of ixekizumab every 2 weeks (IXE Q2W), patients who received 80 mg of ixekizumab every 4 weeks (IXE Q4W), and patients who received placebo (PBO). Comparisons between the ixekizumab treatment groups and the placebo group were made using a logistic regression model. * = $P < 0.05$.

improvements on the EQ-5D-5L compared to patients who received placebo (0.19 for patients who received ixekizumab every 4 weeks and 0.17 for patients who received ixekizumab every 2 weeks versus 0.11 for patients who received placebo; $P = 0.011$ and $P = 0.033$, respectively, for the ixekizumab groups and placebo group), and changes maintained at week 52 (0.18 for both patients treated with ixekizumab every 4 weeks and every 2 weeks versus 0.12 for patients who received placebo; $P = 0.041$ and $P = 0.036$, respectively, for the ixekizumab groups and placebo group).

Changes in self-reported functioning and health outcomes were further analyzed in a subgroup analysis of ASAS40 responders (n = 95) versus nonresponders (n = 198) at week 16 (Supplementary Table 1, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24482/abstract). Significantly greater improvements were reported in LSM changes from baseline in SF-36 PCS scores (placebo: 14.4 versus 3.8, ixekizumab every 4 weeks: 13.6 versus 4.4, and ixekizumab every 2 weeks: 13.6 versus 4.4; $P < 0.001$), ASAS health index scores (placebo: −4.5 versus −1.3, ixekizumab every 4 weeks: −4.7 versus −1.3, and ixekizumab every 2 weeks: −4.5 versus −1.8; $P < 0.001$), ASAS health index responses of ≤5 (placebo: 46.7% versus 17.9%, ixekizumab every 4 weeks: 79.2% versus 18.5%, and ixekizumab every 2 weeks: 68.8% versus 18.9%; $P < 0.05$, $P < 0.001$, and $P < 0.01$, respectively), ASAS health index improvements of ≥3 (placebo: 68.4% versus 24.7%, ixekizumab every 4 weeks: 69.7% versus 24.6%, and ixekizumab every 2 weeks: 70.7% versus 36.8%; $P < 0.01$), and LSM changes from baseline on the EQ-5D-5L (placebo: 0.31 versus 0.09, ixekizumab every 4 weeks: 0.29 versus 0.11, and ixekizumab every 2 weeks: 0.33 versus 0.08; $P < 0.001$).

DISCUSSION

Nonradiographic axial SpA is a chronic inflammatory disease that affects the functioning and health of patients in a similar fashion to AS (radiographic axial SpA). The efficacy of ixekizumab as reported in this 52-week placebo-controlled trial illustrate clinically relevant and statistically significant differences as measured by the SF-36, ASAS health index, and EQ-5D-5L. ASAS40 responders reported greater improvements compared to nonresponders across all end points assessed. Patterns of response appeared similar between the 2 dosing regimens, although the study was not designed to statistically compare dosing groups.

Compared to age- and gender-matched population norms, impairments in function and health were present at baseline and largest in the SF-36 physical domains, and significant improvements in SF-36 PCS scores were reported at nearly all time points in patients who received ixekizumab treatment compared to patients who received placebo. Baseline mental domain scores approached age- and gender-matched matched norms; yet despite small margins for improvement, improvements in SF-36 MCS scores were numerically greater with ixekizumab therapy compared to placebo.

Importantly, the improvements in functioning and health, as measured by the SF-36 PCS, occurred rapidly, with statistically significant improvements at the first time point assessed (week 4) between the ixekizumab and placebo groups. In contrast, statistically significant improvements in functioning and health, as measured by the ASAS health index, were first observed at slightly later time points (weeks 8–16). Within limitations of comparison, we might speculate that emotional aspects and the financial impact of disease, which are included in the ASAS health index, are less likely to change quickly after treatment initiation and thus may be less sensitive to early improvement.

The positive overall functioning and health outcomes reported by patients with nonradiographic axial SpA in this 52-week placebo-controlled trial are consistent with results from phase III placebo-controlled studies with anti-TNF agents in nonradiographic axial SpA (12,15,32–35). However, 29–48% of patients with nonradiographic axial SpA still have active disease (based on ASAS20 responses at week 12) despite TNFi treatment (12–15); therefore, alternative treatments for TNFi are valuable.

The main strength of the present study was the sizeable patient numbers included in each group, which provided valuable information of the efficacy of ixekizumab on self-reported health and functioning outcomes in patients with nonradiographic axial SpA through week 52 of the trial. A limitation of the study is the lack of data in patients who had been previously exposed to TNFi. Another limitation of the study is that patients were allowed to switch to open-label therapy with no prespecified switching criteria. Switching to open-label therapy occurred only at the discretion of the principal investigator, which accounts for a significant proportion of patients assessed as "nonresponders."

In conclusion, ixekizumab was superior to placebo in improving overall functioning and health in patients with nonradiographic axial SpA at week 16 and 52. Ixekizumab therapy every 4 weeks and every 2 weeks was effective in showing significant levels of improvement in the study patients. These findings demonstrate that ixekizumab is effective in improving the overall functioning and health of patients affected with active nonradiographic axial SpA.

ACKNOWLEDGMENTS

The authors thank the study participants, caregivers, and investigators.

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 submitted for publication. Dr. Barbhaiya 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. van der Heijde, Braun, Hunter, León, Sandoval Calderon.

Acquisition of data. Inui, Braun, Li.
Analysis and interpretation of data. Walsh, Magrey, Baraliakos, Inui, Weng, Lubrano, van der Heijde, Boonen, Gensler, Strand, Braun, Hunter, Li, Zhu, León, Sandoval Calderon, Kiltz.

ROLE OF THE STUDY SPONSOR

Sponsorship for this study and article processing charges were funded by Eli Lilly and Company. Eli Lilly and Company contributed to study design, data collection, data analysis, data interpretation, manuscript preparation, and the decision to submit the paper for publication. An advisory committee was involved in the study design and data interpretation, together with authors from Eli Lilly and Company (Indianapolis, Indiana). Authors had full access to all group-level data in the study but not individual-level data that would risk unblinding those authors who were also study investigators. Authors had final responsibility for the decision to submit for publication. Elsa Mevel, PhD, provided writing and editorial assistance for this article, and funding for this assistance was provided by the study sponsor.

ADDITIONAL DISCLOSURES

Authors Hunter, Li, Zhu, León, and Sandoval are employees of Eli Lilly and Company.

REFERENCES

1. Sieper J, Poddubnyy D. Axial spondyloarthritis. Lancet 2017;390: 73–84.
2. Rudwaleit M, van der Heijde D, Landewe R, Listing J, Akkoc N, Brandt J, et al. The development of Assessment of SpondyloArthritis international Society classification criteria for axial spondyloarthritis (part II): validation and final selection. Ann Rheum Dis 2009;68: 777–83.
3. Strand V, Rao SA, Shillington AC, Cifaldi MA, McGuire M, Ruderman EM. Prevalence of axial spondyloarthritis in United States rheumatology practices: Assessment of SpondyloArthritis International Society criteria versus rheumatology expert clinical diagnosis. Arthritis Care Res (Hoboken) 2013;65:1299–306.
4. Rudwaleit M, Sieper J. Referral strategies for early diagnosis of axial spondyloarthritis. Nat Rev Rheumatol 2012;8:262–8.
5. Protopopov M, Poddubnyy D. Radiographic progression in non-radiographic axial spondyloarthritis. Expert Rev Clin Immunol 2018; 14:525–33.
6. Boonen A, Sieper J, van der Heijde D, Dougados M, Bukowski JF, Valluri S, et al. The burden of non-radiographic axial spondyloarthritis. Semin Arthritis Rheum 2015;44:556–62.
7. Mease PJ, Heijde DV, Karki C, Palmer JB, Liu M, Pandurengan R, et al. Characterization of patients with ankylosing spondylitis and non-radiographic axial spondyloarthritis in the US-Based Corrona Registry. Arthritis Care Res (Hoboken) 2018;70:1661–70.
8. Kiltz U, Baraliakos X, Karakostas P, Igelmann M, Kalthoff L, Klink C, et al. Do patients with non-radiographic axial spondylarthritis differ from patients with ankylosing spondylitis? Arthritis Care Res (Hoboken) 2012;64:1415–22.
9. Van der Heijde D, Ramiro S, Landewe R, Baraliakos X, Van den Bosch F, Sepriano A, et al. 2016 update of the ASAS-EULAR management recommendations for axial spondyloarthritis. Ann Rheum Dis 2017;76:978–91.
10. Ward MM, Deodhar A, Gensler LS, Dubreuil M, Yu D, Khan MA, et al. 2019 update of the American College of Rheumatology/Spondylitis Association of America/Spondyloarthritis research and treatment network recommendations for the treatment of ankylosing spondylitis and nonradiographic axial spondyloarthritis. Arthritis Rheumatol 2019;71:1599–613.
11. Deodhar A, Gensler LS, Kay J, Maksymowych WP, Haroon N, Landewe R, et al. A fifty-two-week, randomized, placebo-controlled trial of certolizumab pegol in nonradiographic axial spondyloarthritis. Arthritis Rheumatol 2019;71:1101–11.
12. Sieper J, van der Heijde D, Dougados M, Mease PJ, Maksymowych WP, Brown MA, et al. Efficacy and safety of adalimumab in patients with non-radiographic axial spondyloarthritis: results of a randomised placebo-controlled trial (ABILITY-1). Ann Rheum Dis 2013;72: 815–22.
13. Landewe R, Braun J, Deodhar A, Dougados M, Maksymowych WP, Mease PJ, et al. Efficacy of certolizumab pegol on signs and symptoms of axial spondyloarthritis including ankylosing spondylitis: 24-week results of a double-blind randomised placebo-controlled Phase 3 study. Ann Rheum Dis 2014;73:39–47.
14. Dougados M, van der Heijde D, Sieper J, Braun J, Maksymowych WP, Citera G, et al. Symptomatic efficacy of etanercept and its effects on objective signs of inflammation in early nonradiographic axial spondyloarthritis: a multicenter, randomized, double-blind, placebo-controlled trial. Arthritis Rheumatol 2014;66:2091–102.
15. Sieper J, van der Heijde D, Dougados M, Maksymowych WP, Scott BB, Boice JA, et al. A randomized, double-blind, placebo-controlled, sixteen-week study of subcutaneous golimumab in patients with active nonradiographic axial spondyloarthritis. Arthritis Rheumatol 2015;67:2702–12.
16. Navarro-Compan V, Plasencia-Rodriguez C, de Miguel E, Diaz Del Campo P, Balsa A, Gratacos J. Switching biological disease-modifying antirheumatic drugs in patients with axial spondyloarthritis: results from a systematic literature review. RMD Open 2017;3: e000524.
17. Deodhar A, Yu D. Switching tumor necrosis factor inhibitors in the treatment of axial spondyloarthritis. Semin Arthritis Rheum 2017;47: 343–50.
18. Glintborg B, Ostergaard M, Krogh NS, Tarp U, Manilo N, Loft AG, et al. Clinical response, drug survival and predictors thereof in 432 ankylosing spondylitis patients after switching tumour necrosis factor alpha inhibitor therapy: results from the Danish nationwide DANBIO registry. Ann Rheum Dis 2013;72:1149–55.
19. Liu L, Lu J, Allan BW, Tang Y, Tetreault J, Chow CK, et al. Generation and characterization of ixekizumab, a humanized monoclonal antibody that neutralizes interleukin-17A. J Inflamm Res 2016;9:39–50.
20. Toussirot E. Ixekizumab: an anti- IL-17A monoclonal antibody for the treatment of psoriatic arthritis. Expert Opin Biol Ther 2018;18: 101–7.
21. Deodhar A, van der Heijde D, Gensler LS, Kim TH, Maksymowych WP, Ostergaard M, et al. Ixekizumab for patients with non-radiographic axial spondyloarthritis (COAST-X): a randomised, placebo-controlled trial. Lancet 2020;395:53–64.
22. Rudwaleit M, Jurik AG, Hermann KG, Landewe R, van der Heijde D, Baraliakos X, et al. Defining active sacroiliitis on magnetic resonance imaging (MRI) for classification of axial spondyloarthritis: a consensual approach by the ASAS/OMERACT MRI group. Ann Rheum Dis 2009; 68:1520–7.
23. Van der Linden S, Valkenburg HA, Cats A. Evaluation of diagnostic criteria for ankylosing spondylitis. A proposal for modification of the New York criteria. Arthritis Rheum 1984;27:361–8.
24. Lambert RG, Bakker PA, van der Heijde D, Weber U, Rudwaleit M, Hermann KG, et al. Defining active sacroiliitis on MRI for classification of axial spondyloarthritis: update by the ASAS MRI working group. Ann Rheum Dis 2016;75:1958–63.
25. Ware JE, Jr. SF-36 health survey update. Spine (Phila Pa 1976) 2000; 25:3130–9.

26. Ware JE, Kosinski M. Interpreting SF-36 summary health measures: a response. Qual Life Res 2001;10:405–13.

27. Strand V, Crawford B, Singh J, Choy E, Smolen JS, Khanna D. Use of "spydergrams" to present and interpret SF-36 health-related quality of life data across rheumatic diseases. Ann Rheum Dis 2009;68:1800–4.

28. Boonen A, Braun J, van der Horst Bruinsma IE, Huang F, Maksymowych W, Kostanjsek N, et al. ASAS/WHO ICF Core Sets for ankylosing spondylitis (AS): how to classify the impact of AS on functioning and health. Ann Rheum Dis 2010;69:102–7.

29. Kiltz U, van der Heijde D, Boonen A, Cieza A, Stucki G, Khan MA, et al. Development of a health index in patients with ankylosing spondylitis (ASAS HI): final result of a global initiative based on the ICF guided by ASAS. Ann Rheum Dis 2015;74:830–5.

30. Kiltz U, van der Heijde D, Boonen A, Akkoc N, Bautista-Molano W, Burgos-Vargas R, et al. Measurement properties of the ASAS Health Index: results of a global study in patients with axial and peripheral spondyloarthritis. Ann Rheum Dis 2018;77:1311–7.

31. Szende A OM, Devlin N. EQ-5D value sets: inventory, comparative review and user guide: Springer; 2007.

32. Maksymowych WP, Dougados M, van der Heijde D, Sieper J, Braun J, Citera G, et al. Clinical and MRI responses to etanercept in early non-radiographic axial spondyloarthritis: 48-week results from the EMBARK study. Ann Rheum Dis 2016;75:1328–35.

33. Sieper J, Kivitz A, van Tubergen A, Deodhar A, Coteur G, Woltering F, et al. Impact of certolizumab pegol on patient-reported outcomes in patients with axial spondyloarthritis. Arthritis Care Res (Hoboken) 2015;67:1475–80.

34. Sieper J, Kivitz A, van Tubergen A, Deodhar A, Szegvari B, Nurminen T, et al. Long-term maintenance of improvements in patient-reported outcomes with certolizumab pegol in patients with axial spondyloarthritis, including ankylosing spondylitis and non-radiographic axial spondyloarthritis: 96-week results of the Rapid-Axspa study. Value Health 2014;17:A385–6.

35. Van der Heijde D, Joshi A, Pangan AL, Chen N, Betts K, Mittal M, et al. ASAS40 and ASDAS clinical responses in the ABILITY-1 clinical trial translate to meaningful improvements in physical function, health-related quality of life and work productivity in patients with non-radiographic axial spondyloarthritis. Rheumatology (Oxford) 2016; 55:80–8.