Ixekizumab Improves Functioning and Health in the Treatment of Radiographic Axial Spondyloarthritis: Week 52 Results from 2 pivotal studies

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Running Head: Ixekizumab HRQoL in AS

Abstract

Objective: This study evaluated the effect of ixekizumab on self-reported functioning and health in patients with radiographic axial spondyloarthritis (r-axSpA) who were either biologic disease modifying antirheumatic drugs naïve (bDMARD-naïve) or failed at least 1 tumor necrosis factor inhibitor (TNFi).

Methods: In 2 multicenter, randomized, double-blind, placebo-controlled, and active-controlled (bDMARD-naïve only) trials, r-axSpA patients were randomly assigned to receive 80 mg of ixekizumab (every 2 weeks [Q2W] or every 4 weeks [Q4W]), placebo, or adalimumab (bDMARD-naïve only). After 16 weeks, patients who received placebo or adalimumab were re-randomized to receive ixekizumab (Q2W or Q4W) up to Week 52. Functioning and health was measured by the generic Short Form Health Survey 36-item (SF-36) and the disease-specific ASAS Health Index (ASAS HI). Societal health utility was assessed by the European Quality of Life-5 Dimensions-5 Levels (EQ-5D-5L).

Results: At week 16, both doses of ixekizumab in bDMARD-naïve and TNFi-experienced patients resulted in larger improvement in SF-36, ASAS HI, and EQ-5D-5L versus placebo. For SF-36, the largest improvements were seen for the domains of bodily pain, physical function, and role physical. Larger proportion of patients reaching improvement in ASAS HI ≥3, ASAS HI good health status were reported in patients treated with ixekizumab. Improvements were maintained through Week 52.

Conclusion: Ixekizumab significantly improved functioning and health as assessed by both generic and disease specific measures as well as societal health utility values in patients with r-axSpA, as measured by SF-36, ASAS HI, and EQ-5D-5L at Week 16 and improvements were sustained through 52 weeks.

Introduction

Radiographic axial spondyloarthritis (r-axSpA), also referred to as ankylosing spondylitis (AS), is a potentially disabling chronic inflammatory disease of the axial skeleton which affects 0.2-0.5% of the population (1-5). R-axSpA is characterized by inflammation and new bone formation in the sacroiliac joints and spine (6). Patients with r-axSpA present diverse clinical features including inflammatory back pain, limited physical function and activities (standing, walking, reaching, etc), stiffness, fatigue, impaired mental function (depression, anxiety, etc) and restricted social relationships, all of which contribute to reduced overall functioning and health (6-9). Measures that assess the integrated impact of this broad range of different impairments into one instrument, are referred to as 'overall health' or 'health related quality of life' (HRQoL) measures, and provide insight how the disease actually alters the daily life of patients. Therefore, overall health or HRQoL are important outcome measures when assessing the efficacy of treatments.

Current treatment for the management of r-axSpA include non-pharmacological management such as physical therapy and education as well as pharmaceutical treatment. Nonsteroidal anti-inflammatory drugs (NSAIDs) are recommended as first line treatments for improving back pain and stiffness (1, 10). Biologic disease modifying antirheumatic drugs (bDMARDs) such as tumor necrosis factor inhibitors (TNFi) are recommended when NSAIDs fail (10). Treatment with TNFi such as etanercept, infliximab, adalimumab, golimumab and certolizumab have demonstrated a high efficacy on disease activity and improvement of Short Form Health Survey 36-item (SF-36) scores (1, 3). However, approximatively 40% of r-axSpA patients still report high disease activity despite availability of multiple TNFi (11). Consequently, there is a need for alternative treatment options in r-axSpA patients who do not respond to or do not tolerate TNFi (11, 12).

Recently, growing evidence indicates the interleukin (IL)-17 pathway, and in particular IL-17A, plays a critical role in r-axSpA pathogenesis (13, 14). Ixekizumab (IXE) is an immunoglobulin G4 monoclonal antibody which selectively targets IL-17A with very high affinity (15, 16). The Food and Drug Administration (FDA) and the European Medicines Agency (EMA) approved IXE for the treatment of moderate-to-severe plaque psoriasis in adults, for the treatment of active psoriatic arthritis, and for adult patients with AS. Recently, ixekizumab was approved by the FDA for moderate-to-severe paediatric psoriasis. Results from 2 completed phase III randomized, double blind, placebo-controlled trials demonstrated IXE 16 week and 52 week treatment efficacy in bDMARD-naïve (COAST-V) and TNFi experienced (COAST-W) patients with AS (17-19). Previously, we reported statistically significant improvement versus placebo (PBO) at Week 16 of the HRQoL endpoints measured by the mean changes in SF-36 (both IXE doses), and the Assessment of SpondyloArthritis international Society criteria Health Index (ASAS HI; COAST-V, both IXE doses; COAST-W, IXE Q4W only) in bDMARD naïve and TNFi experienced patients (18, 19). In these studies, improvements were sustained through Week 52 (17). In the present study, in addition to improvements of IXE by SF-36 and ASAS HI means through Week 52 in patients with active r-axSpA TNFi non responders, we report the SF-36 domains, the proportion of patients with improvement in ASAS HI ≥3 from baseline, the proportion of patients achieving an ASAS HI 'good health status' (ASAS HI ≤5), and European Quality of Life-5 Dimensions-5 Level (EQ-5D-5L), through 52 weeks.

Patients and Methods

Studies Design

COAST-V (NCT02696785) and COAST-W (NCT02696798) are phase III, multicenter, active (COAST-V only), and PBO randomized controlled trials (RCTs) with a 52-week duration,

evaluating the efficacy and safety of IXE in patients with r-axSpA. The main ethics committee was Schulman Associates IRB, Cincinnati, OH, USA (IRB # 201506061 for COAST-V, and # 201506079 for COAST-W). The full lists of investigators and sites are provided in the primary manuscript supplements (18, 19). Patient enrolment and data collection occurred at 84 sites in 12 countries in COAST-V trial, and in 106 sites located in 15 countries in the COAST-W trial. The studies were approved by the ethical review board at each participating site before the start of the study. The RCTs conform with Good Clinical Practices, International Council for Harmonization, local laws and regulations, and were conducted in accordance with the Declaration of Helsinki principles. All patients enrolled provided written informed consent before participating in the trials.

Participants

Inclusion criteria have been previously detailed (18, 19). Briefly, eligible patients were ≥18 years with established diagnosis of r-axSpA and fulfilling Assessment of SpondyloArthritis international Society (ASAS) criteria (sacroiliitis on radiograph by modified New York criteria and at least 1 SpA feature). The sacroiliac joint radiograph reading was performed centrally by 2 independent readers, with adjudication if necessary. Participants in COAST-V were bDMARD-naïve, whereas in COAST-W, trial participants had failed at least 1 and not more than 2 TNFi prior to enrollment in the trial.

Interventions

COAST-V and COAST-W interventions have been previously described in 16-week results disclosures (18, 19). In COAST-V, patients were randomly assigned using a 1:1:1:1 ratio to IXE 80 mg every 2 weeks (Q2W), IXE 80 mg every 4 weeks (Q4W), adalimumab (ADA) 40 mg Q2W, or PBO. In COAST-W, patients were randomly assigned using a 1:1:1 ratio to IXE Q2W, IXE Q4W, or PBO. In both trials, participants initially assigned to IXE treatment were randomly

assigned in a 1:1 ratio to receive a starting dose of either 80 mg IXE or 160 mg IXE (two 80 mg injections) for the first dose at Week 0. Patients completing Week 16 entered a double-blind Extended Treatment Period (ETP; Week 16 to Week 52). During this period, patients originally randomized to PBO or ADA (COAST-V only) were re-randomized 1:1 to IXE Q2W or IXE Q4W (160 mg starting dose for patients switching from PBO, 80 mg starting dose for patients switching from ADA). Patients originally randomized to IXE Q2W or IXE Q4W continued these regimens. All doses were administrated subcutaneously using masked pre-filled manual syringes.

Outcomes

Self-reported functioning and health as assessed by generic and disease specific measures

The effects of IXE on HRQoL were assessed using 2 secondary major endpoints, SF-36 questionnaire and ASAS HI. Assessments were recorded at Week 0 (baseline), 4, 8, 16, 36, and 52. SF-36 is a 36-item patient-administered measure designed as a short, generic assessment of HRQoL including the following domains: physical and social functioning, physical and emotional roles, bodily pain, general health, vitality, and mental health. The domain scores range from 0 to 100 with higher scores indicating better levels of function and/or better health. The 2 physical (PCS) and mental component summary (MCS) scores are calculated based on differential weighting of the 8 domains having been normalized to t-scores. Items were answered based on Likert scales of 3 to 5. SF-36 version 2 (acute version), which utilizes a 1 week recall period was used in COAST-V and COAST-W studies (20).The scaled scores (0 to 100) were used in the spydergrams (21), and the least square mean (LSM) changes from baseline in t-scores were cited in the table. The 1998 norms were used in previous publications reporting values of SF-36 for week 0-16 described in this manuscript (18, 19), so the current data for week 0-16 is analyzed with this norm for consistency. The data after week 16 have

since been analyzed using the updated 2009 norms, which are used in the latest version of the SF-36 manual. The 1998 and 2009 norms are minimally different. The calculation of age/gender-matched norms for each domain in the spydergram in Figure 1 is based on 1998 US population norms and matched for the age and gender distribution of the protocol population.

The ASAS HI is a disease-specific health-index designed to assess effect of the disease on patients and covers areas of physical, emotional, and social functioning. This 17-item instrument has sum scores ranging from 0 (good health) to 17 (poor health) (22). The clinically meaningful change is defined as ≥3, and a good health status is defined by a score ≤5 (23, 24).

The EQ-5D-5L provides societal preferences for health states (health utilities) based on 5 dimensions of health: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The patient-complete EQ-5D-5L descriptive system was converted into a societal utility value using the available UK Population based algorithm to produce a patient-level index score between -0.59 and 1.0 (continuous variable) (25).

Statistical Analyses

Analyses were conducted on the intent-to-treat (ITT) population for patients initially randomized to IXE (from Week 0 to 52), ADA, or PBO (from Week 0 to 16). The analysis of the ETP (from Week 16 to 52) for patients initially assigned to ADA or PBO were conducted on ETP patients. For comparisons between each IXE treatment group (Q2W or Q4W) and PBO up to Week 16, the primary analysis method for continuous outcomes (SF-36 domains and component scores, ASAS HI and EQ-5D-5L) was mixed-effects model for repeated measures (MMRM) with treatment, geographic region, baseline CRP status (non-elevated or elevated; elevated defined as >5.00 mg/L), number of prior anti-TNFi used (COAST-W only), baseline value, visit, baseline value-by-visit, and treatment-by-visit interaction as fixed factors. Treatment comparisons for

categorical outcomes (improvement in ASAS HI ≥3 points obtained, and ASAS HI good health state achieved) were performed using logistic regression with treatment, geographic region, baseline CRP status non-elevated or elevated; elevated defined as >5.00 mg/L), and the number of prior anti-TNFi used (COAST-W only) in the model. For the ETP (from Week 16 to 52), no treatment group comparisons were conducted. For SF-36 outcomes and EQ-5D-5L, no imputation for missing data was done when using MMRM modeling up to Week 16, while descriptive statistics were provided for patients initially randomized to IXE (from Week 0 to 52) and for ETP population using the modified baseline observation carried forward imputation approach for missing data. For categorical ASAS HI outcomes, missing data were imputed as 'improvement <3' points and 'ASAS HI>5' using non-responder imputation. The statistical analyses were performed using SAS® software version 9.3 or higher.

Results

Of the 341 (COAST-V) and 316 (COAST-W) patients included in this analysis, sample sizes were PBO, n=87; IXE Q4W, n=81; IXE Q2W, n=83; and ADA, n=90 (COAST-V); and PBO, n=104; IXE Q4W, n=114; and IXE Q2W, n=98 (COAST-W) (Table 1). Sample sizes were balanced between treatment groups. Demographics and baseline clinical characteristics for the ETP populations were similar between treatment groups within each study (Table 1) and similar to those in the ITT populations (18, 19). SF-36, ASAS HI, and EQ-5D-5L baselines were also balanced between treatment arms within each trial.

Ixekizumab improves functioning and health as assessed by generic measure SF-36.

Improvement in SF-36 PCS for IXE versus PBO were significantly larger throughout the 16 weeks assessed (Fig. 1a and 1b). Improvements in the PCS scores with IXE were consistent between bDMARD-naïve and TNFi-experienced patients, with significant improvements

reported as early as Week 4. Both IXE dose groups showed sustained improvement on the SF-36 PCS through Week 52 (Fig. 1c and 1d). BDMARD-naïve patients treated with the active reference ADA also showed significant improvement in PCS treatment response score versus PBO up to 16 weeks (Fig. 1a). Interestingly, patients treated with ADA and re-randomized at Week 16 to IXE demonstrated continued improvement in the PCS, and reached a similar level at Week 52 compared with patients who received IXE from Week 0 (Fig. 1e). Patients initially assigned to the PBO arm and received IXE starting at Week 16 reported a rapid improvement throughout the ETP (Fig. 1e-f). In the bDMARD-naïve patients, non-significant differences between groups in the improvements of MCS were observed (Supplementary Figure 1). Statistically significant improvements in the MCS were reported at Week 4 (IXE Q4W only), and Week 8 in TNFi-experienced patients.

The effects of IXE on the SF-36 domains at Week 16 and Week 52 compared with baseline in the bDMARD-naïve and TNFi-experienced patients are shown in Figure 2. Improvements in all SF-36 domains were reported up to Week 52 in bDMARD-naïve and TNFi-experienced patients treated with IXE. Both bDMARD-naïve and TNFi-experienced patients treated with IXE reported larger improvements compared with PBO in SF-36 domains at Week 16 and sustained benefits through Week 52. By Week 52, the largest improvements (scaled score) among patients treated with IXE were observed in the Bodily Pain and Physical Functioning category (bDMARD-naïve [+24.7 points from baseline for Q4W, +23.5 for Q2W, +18.0 for Q4W, +20.7 for Q2W, respectively] and TNFi-experienced patients [+22.1 points from baseline for Q4W, + 21.3 for Q2W; +15.9 for Q4W, and + 19.6 for Q2W, respectively]. Patients treated with the active reference ADA also showed consistent improvement in all SF-36 domains throughout the 16 weeks assessed in the Blinded Treatment Dosing Period.

Actual scores of SF-36 domains and components at baseline and mean changes at Weeks 16 and 52 the bDMARD-naïve and TNFi-experienced patients are presented in Supplementary

Table 1. In general, bDMARD-naïve patients reported numerically higher numbers for all SF-36 baseline measures compared with TNFi-experienced, indicating better functioning health. Significant improvement of some SF-36 domains were already observed at the first assessment (Week 4, data not shown).

Ixekizumab improves functioning and health measured by the disease specific ASAS HI. At Week 16, bDMARD-naïve patients receiving IXE reported a significantly larger improvement from baseline on ASAS HI versus PBO (-2.36 for Q4W (p=0.01), -2.74 for Q2W (p<0.001) vs -1.25 for PBO). These improvements with IXE treatment were seen as early as Week 4, remained higher than PBO through Week 16, and sustained through Week 52. IXE Q4W bDMARD-naïve patients achieved numerically similar ASAS HI mean change from baseline as patients who received IXE Q2W (-2.7 vs -3.3, at Week 52). Patients treated with the active reference ADA also showed consistent significant improvement in ASAS HI mean change from baseline throughout the 16 weeks assessed (Fig. 3a). Patients who received ADA or PBO during Blinded Treatment Dosing Period and switched to IXE at Week 16 demonstrated continued numeric improvements in ASAS HI through Week 52 (Fig. 3e). Both IXE regimens (Q2W and Q4W) sustained similar improvements through Week 52. Patients in the bDMARD-naïve arm experienced a numerically greater improvement of ASAS HI mean change versus TNFi-experienced patients when treated with IXE Q4W (-2.4 vs -1.9 at Week 16 and -2.7 vs -2.3 at Week 52) or IXE Q2W (-2.7 vs -1.6 at Week 16 and -3.3 vs -2.5 at Week 52) (Fig. 3a-d).

The proportion of patients achieving an improvement in ASAS HI ≥3 points change from baseline were also analysed (Figure 4). At baseline, the proportion of bDMARD-naïve patients with ASAS HI ≥3 ranged from 95.2% to 98.9%, and from 99.0% to 100% among TNFi-experienced patients (Table 1). Compared with PBO, the improvement in ASAS HI ≥3 at Week 16 was achieved by a higher proportion of bDMARD-naïve patients treated with IXE Q4W (34.5% vs 41.8%, p=0.31) or and significantly higher proportion treated with Q2W (34.5% vs 50.6%, p=0.033), and improvements were consistent through Week 52 (Q4W 43.0% and Q2W 53.2%). The proportion of patients treated with IXE achieving improvement in ASAS HI ≥3 throughout the 52 weeks were 53.2% for Q2W and 43.0% for Q4W (bDMARD-naïve patients), and 43.3% and 36.8% (TNFi-experienced patients) (Fig. 4a and 4b). The proportion of patients

achieving improvement in ASAS HI ≥3 in the ADA arm was also significantly greater than the PBO arm (Fig. 4a). TNFi-experienced patients achieved ASAS HI ≥3 more often than those on PBO, with significant differences at Week 16 (22.1% for PBO vs 37.1%for IXE Q2W , p=0.032), and 36.0%for IXE Q4W, p=0.026). At Week 52, 43.3% of IXE Q2W, and 36.8% of IXE Q4W TNFi-experienced patients achieved an improvement in ASAS HI ≥3 (Fig. 4b).

At baseline, the proportion of patients with 'no good health status' ranged from 66.7% to 81.9% in bDMARD-naïve patients and from 80.8% to 88.8% in TNFi-experienced patients (Table 1). In general, numerically similar improvements in the proportion of patients reaching 'good health status' were reported in both IXE dose groups (Fig. 4c and 4d). At Week 16, 'good health status' was achieved by 46.3% and 45.6% of the bDMARD-naïve patients treated with IXE Q4W and Q2W respectively compared with PBO (25.0%, $p<0.05$ for both doses). 'Good health status' was achieved by 24.2% and 17.2% of the TNFi-experienced patients treated with IXE Q4W and Q2W respectively compared with PBO (15.5%) at Week 16. Also, at Week 16, 40.3% of bDMARD-naïve patients who received ADA reached 'good health status' (Fig. 4c). The proportion of patients achieving 'good health status' was sustained through 52 weeks with 51.9% and 48.5% of bDMARD-naïve patients treated with IXE Q4W and Q2W respectively, and by 27.3% and 25.3% of TNFi-experienced patients treated with IXE Q4W and Q2W respectively.

Ixekizumab improves health utility assessed by EQ-5D-5L

The results for EQ-5D-5L health utilities are provided in Figure 5. Each IXE treatment group compared to the PBO group had significantly larger improvements at Week 16 in both bDMARD-naïve (0.19 for IXE Q4W and 0.19 for IXE Q2W vs 0.10 for PBO), and TNFi-experienced patients (0.16 for IXE Q4W and 0.16 for IXE Q2W vs 0.08 for PBO). Additionally, the active reference ADA treatment group had a significantly greater proportion of patients with improvements in EQ-5D-5L at Week 16 compared with PBO. Effects were sustained throughout

Week 52 in both ixekizumab treatment groups (bDMARD-naïve: 0.18 Q4W, 0.20 Q2W; TNFi-experienced: 0.21 Q4W, 0.20 Q2W). Patients who received ADA and were switched to IXE demonstrated continued numeric improvements in EQ-5D-5L (from 0.16 at Week 16 to 0.20 at Week 52). All Patients who received PBO from Week 0 to 16 and switched to IXE showed rapid improvements and reached a similar score at Week 52 as patients who received IXE from Week 0. In bDMARD-naïve patients this improvement was 0.20 for PBO/IXE versus 0.18 IXE Q4W, and 0.20 for IXE Q2W and in TNFi-experienced patients this improvement was 0.19 for PBO/IXE versus 0.21 for IXE Q4W and 0.20 for IXE Q2W.

Discussion

In the present analysis, we demonstrate IL-17A inhibitor IXE significantly improved self-reported functioning and health as well as societal health utilities through Week 0-16 among both bDMARD-naïve and TNFi-experienced patients with active r-axSpA, and sustained through Week 16 to Week 52. Significant improvements compared with PBO were observed at Week 16 in bDMARD-naïve patients treated with both IXE Q4W or IXE Q2W for all outcomes (expect for ASAS HI ≥3 with IXE Q4W). In these patients, improvements were observed as early as the first assessment at Week 4 for mean change from baseline in SF-36 PCS and ASAS HI and proportion experiencing a meaningful improvement in ASAS HI or reaching a ‘good’ ASAS HI (IXE Q4W only). Similarly, TNFi-experienced patients treated with IXE reported a significant improvement versus PBO at Week 16 for societal health utility values as well as most generic and disease specific measures of function and health outcomes except the proportion of patients reaching a ‘good’ ASAS HI ≤5, where non-significant difference in the advantage of the IXE treated patients were observed. At baseline, SF-36 MCS were within the normal range, therefore, ranges of improvement were limited in both bDMARD-naïve and TNFi-experienced

patients. There was no meaningful difference in responses based on IXE dosing regimen (Q2W or Q4W).

Patients in the bDMARD-naïve arm had a numerically higher response to IXE treatment compared with TNFi-experienced patients, however statistical analysis comparing these groups have not been conducted. At baseline, the duration of symptoms since the onset of r-axSpA were higher in the TNFi-experienced patients versus the bDMARD-naïve patients (18.4 vs 16.0 years on average among the arms). These data could indicate bDMARD naïve patients may have more opportunity for improvement because they have more reversible physical impairment. This data could also indicate axial pain reported by TNFi-experienced patients may partly have other sources than inflammation. Further analysis aimed to investigate inflammation outcomes could be conducted to test this hypothesis.

The improvements in overall health or health related QoL outcomes observed in r-axSpA patients in this 52-week placebo-controlled trial are consistent with the SF-36 and/or EQ-5D results from the Phase 3 placebo-controlled studies with other IL-17A inhibitor, secukinumab (26), or anti-TNF agents (27-29). However, COAST-V and COAST-W were the first trials to report ASAS HI outcome to assess disease-specific functioning and health. Due to difference in patient population and study design, direct comparison between studies and agents is challenging, even when analysis on individual data would be performed as contextual factors, which are relevant for appraisal of self-reported overall health which are usually not measured in trials. Despite the tremendous interest to evaluate the efficacy and safety of IXE through 52 weeks, the design of the EPT (Weeks 16-52) presents some limitations. The interpretation of data in an extended treatment period without a control arm (PBO) is challenging. Therefore, the long-term superiority of IXE versus PBO from Week 16 to 52 cannot be established. The main strength of the present analysis is the comparison of 2 separate trials with 2 independent populations of patients. This combined analysis provides valuable information regarding the

efficacy of IXE on self-reported functioning and health outcomes in both bDMARD-naïve and TNFi-experienced patients.

To conclude, the present analyses demonstrate IXE significantly improved functioning and health outcomes (as assessed by generic and disease specific measures) as well as societal health utility values as early as Week 4, and sustained through Week 52 among patients with r-axSpA who are bDMARD naïve or have had a prior inadequate response or intolerance to TNFi.

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Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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Compliance with Ethics Guidelines. 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 and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the studies.

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Table 1. Baseline demographics, disease characteristics. COAST-V and COAST-W (intent-to-treat population).

	COAST-V (bDMARD Naïve)				COAST-W (TNFi Experienced)		
	PBO	ADA	IXE Q4W	IXE Q2W	PBO	IXE Q4W	IXE Q2W
	N=87	N=90	N=81	N=83	N=104	N=114	N=98
Age (years), mean (SD)	42.7 (12.0)	41.8 (11.4)	41.0 (12.1)	41.3 (11.2)	46.6 (12.7)	47.4 (13.4)	44.2 (10.8)
Male, n (%)	71 (82.6)	73 (81.1)	68 (84.0)	64 (77.1)	87 (83.7)	91 (79.8)	75 (76.5)
BMI (kg/m^2), mean (SD)	27.6 (5.7)	26.6 (5.6)	25.8 (4.0)	25.9 (6.9)	28.9 (5.6)	29.4 (7.3)	27.5 (5.4)
Race, n (%)							
Asian	28 (32.6)	29 (32.2)	25 (30.9)	25 (30.1)	13 (12.5)	14 (12.4)	13 (13.3)
White	52 (60.5)	57 (63.3)	52 (64.2)	52 (62.7)	85 (81.7)	91 (80.5)	78 (79.6)
Age of onset of r-axSpA (years), mean (SD)	26.4 (8.4)	26.5 (8.6)	25.4 (7.7)	25.8 (8.2)	27.1 (8.8)	28.9 (9.6)	28.1 (10.0)
Duration of symptoms (years), mean (SD)	16.6 (10.1)	15.6 (9.3)	15.8 (11.2)	15.8 (10.6)	19.9 (11.6)	18.8 (11.6)	16.5 (9.6)
CRP level at baseline (mg/L), means (SD)	16.0 (21.0)	12.5 (17.6)	12.2 (13.3)	13.4 (15.3)	16.0 (22.3)	20.2 (34.3)	17.0 (19.8)
BASDAI baseline, mean (SD)	6.8 (1.2)	6.7 (1.5)	6.8 (1.3)	6.7 (1.6)	7.3 (1.3)	7.5 (1.3)	7.5 (1.3)
ASDAS baseline, mean (SD)	3.9 (0.7)	3.7 (0.8)	3.7 (0.7)	3.8 (0.8)	4.1 (0.8)	4.2 (0.9)	4.2 (0.8)
SF-36 PCS baseline, mean (SD)	32.0 (8.3)	33.5 (8.3)	34.0 (7.5)	34.1 (7.6)	30.6 (7.8)	27.5 (8.3)	27.9 (7.3)
SF-36 MCS baseline, mean (SD)	49.8 (10.8)	48.4 (12.4)	50.4 (12.3)	46.3 (12.6)	46.2 (12.6)	45.9 (12.3)	44.5 (12.7)
ASAS HI baseline, mean (SD)	8.1 (3.5)	8.2 (3.7)	7.5 (3.3)	8.4 (3.6)	9.0 (3.5)	10.0 (3.7)	10.1 (3.6)
ASAS HI >5 baseline, n (%)	64 (73.6)	67 (74.4)	54 (66.7)	68 (81.9)	84 (80.8)	99 (86.8)	87 (88.8)

EQ-5D-5L UK population index score, mean (SD)	0.52 (0.22)	0.53 (0.22)	0.57 (0.19)	0.52 (0.21)	0.45 (0.22)	0.38 (0.24)	0.39 (0.23)

Abbreviations: ASAS HI = assessment of spondyloarthritis international society health index; BMI = body mass index; bDMARD = biologic disease-modifying anti-rheumatic drugs; EQ-5D-5L= European Quality of Life-5 Dimensions 5-Level; HLA-B27 = human leukocyte antigen B27; IXE Q2W = IXE dosed every 2 weeks; IXE Q4W = IXE dosed every 4 weeks; MCS = mental component score; PCS = physical component score; r-axSpA = radiographic axial spondyloarthritis; SD = standard deviation; SF-36 = short-form-36 questionnaire; TNFi = tumor necrosis factor inhibitors

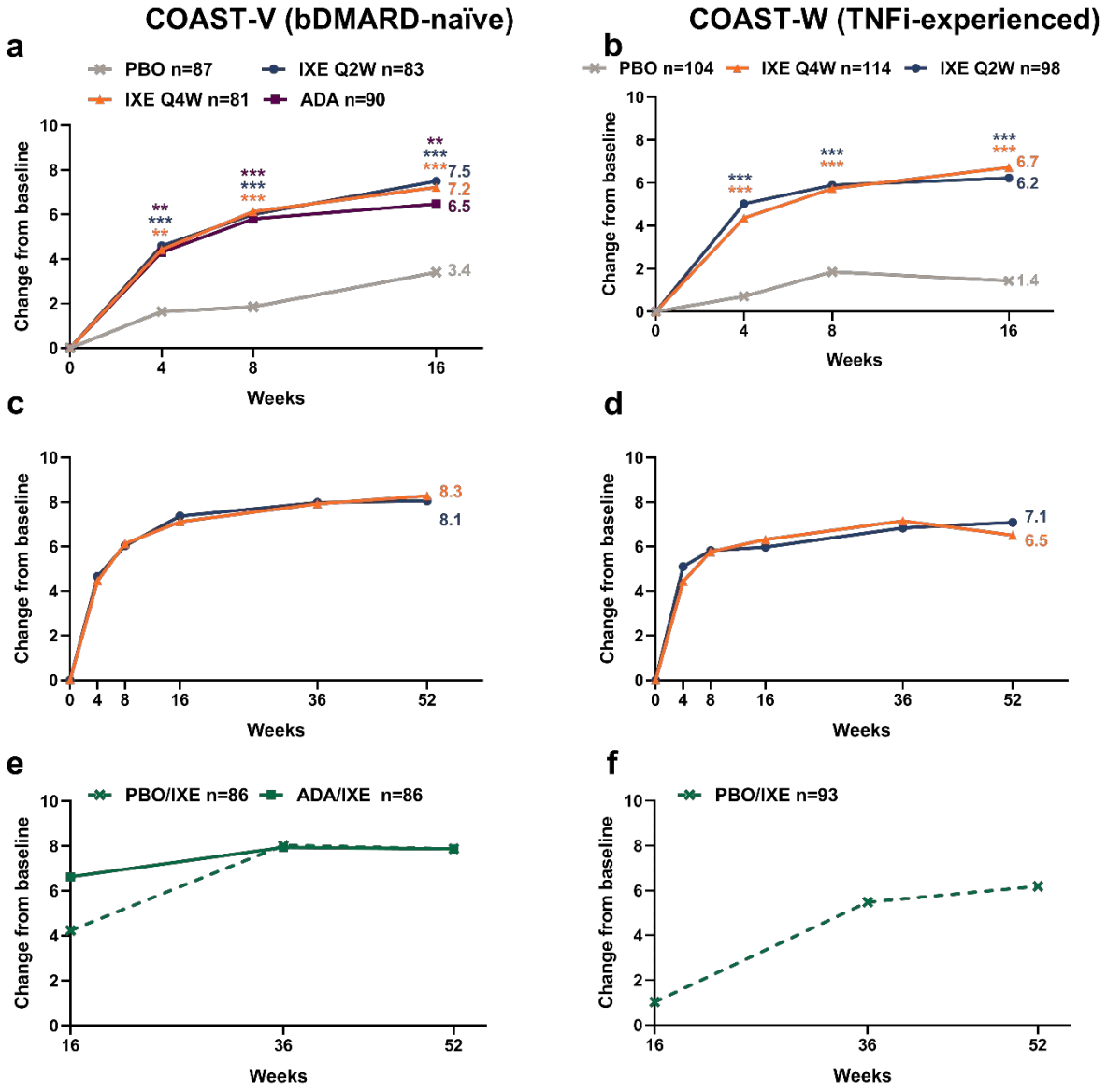

Figure 1. SF-36 Physical Component Scores change from baseline COAST-V and COAST-W (Intent-to-Treat Population). Comparisons with PBO were made using a mixed-effects model for repeated measures up to Week 16 (least-squares means for **a** and **b**). Descriptive statistics were provided using mBOCF for missing data imputation approach (**c-f**). Week 0-16 data are based on 1998 general US population (norm 1998) as norms (**a** and **b**) and reports after Week 16 are based on 2009 general US population (norm 2009) as norms (**c-f**).
**p<0.01
***p<0.001
Abbreviations: ADA = adalimumab 40mg every 2 weeks; bDMARD = biologic disease-modifying anti-rheumatic drugs; IXE Q2W = IXE dosed every 2 weeks; IXE Q4W = IXE dosed every 4 weeks; mBOCF = modified baseline observation carried forward; n = number of patients in analysis population; PBO = placebo; PCS= physical component score; SF-36 = short-form-36 questionnaire; TNFi = tumor necrosis factor inhibitors.

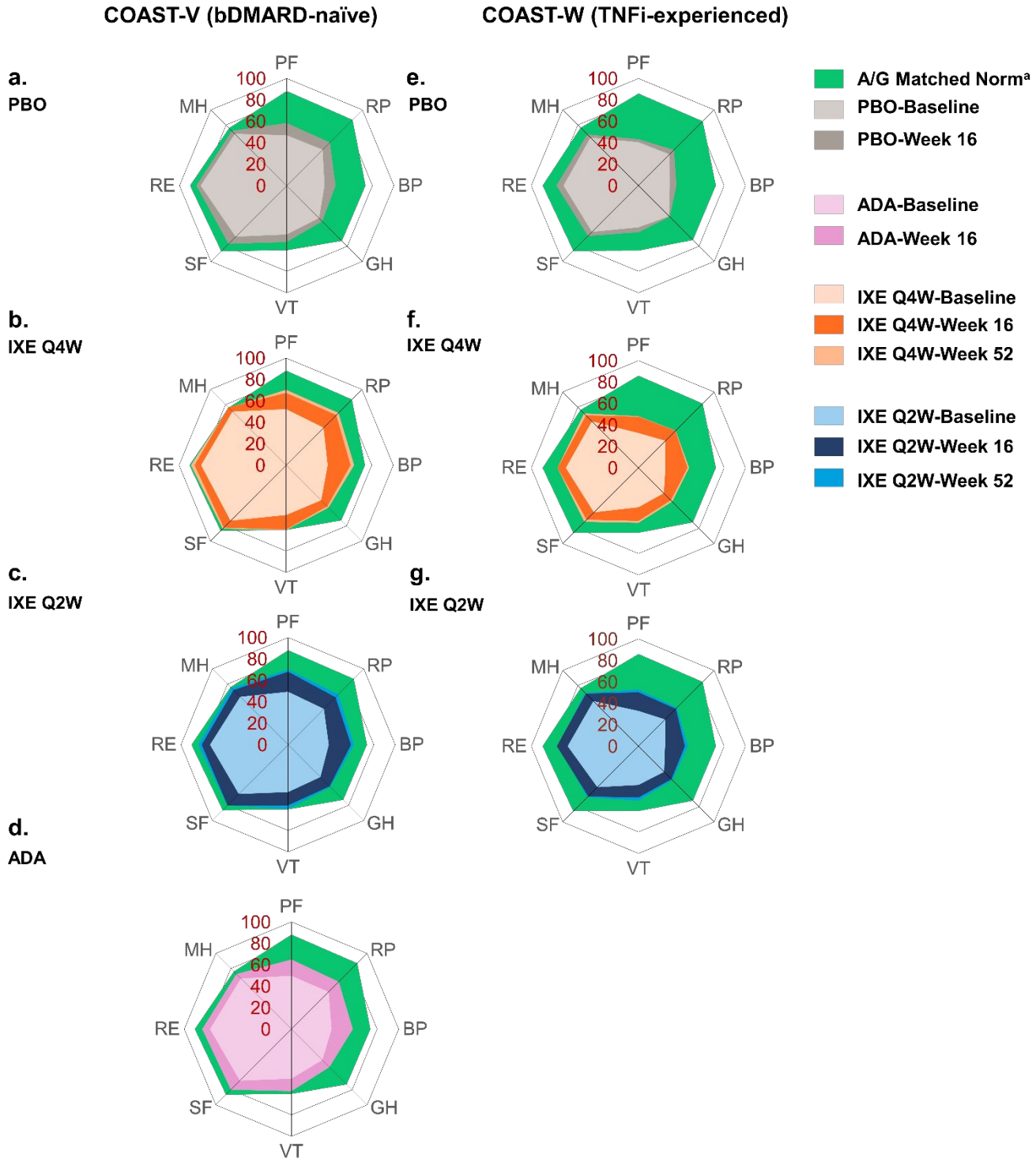

Figure 2. SF-36 Domain Scores at baseline, 16 and 52 Weeks COAST-V and COAST-W (intent-to-treat Population). The spydergrams depict mBOCF SF-36 domain scores (scale 0-100) and US A/G matched normative values. SF-36 A/G-matched norms are based on 1998 US population norms and patient counts for each age and gender distribution of the protocol population. [a]1998 US population

Abbreviations: A/G = age/gender; BP = bodily pain; bDMARD = biologic disease-modifying anti-rheumatic drugs; GH = general health; IXE Q2W = 80 mg ixekizumab every 2 weeks; IXE Q4W = 80 mg ixekizumab every 4 weeks; MH = mental health; mBOCF = modified baseline observation carried forward; PBO = placebo; PF = physical functioning; RE = role-emotional; RP = role-physical; SF = social functioning; SF-36 = Medical Outcomes Survey Short Form-36; TNFi = tumor necrosis factor inhibitors; VT = vitality.

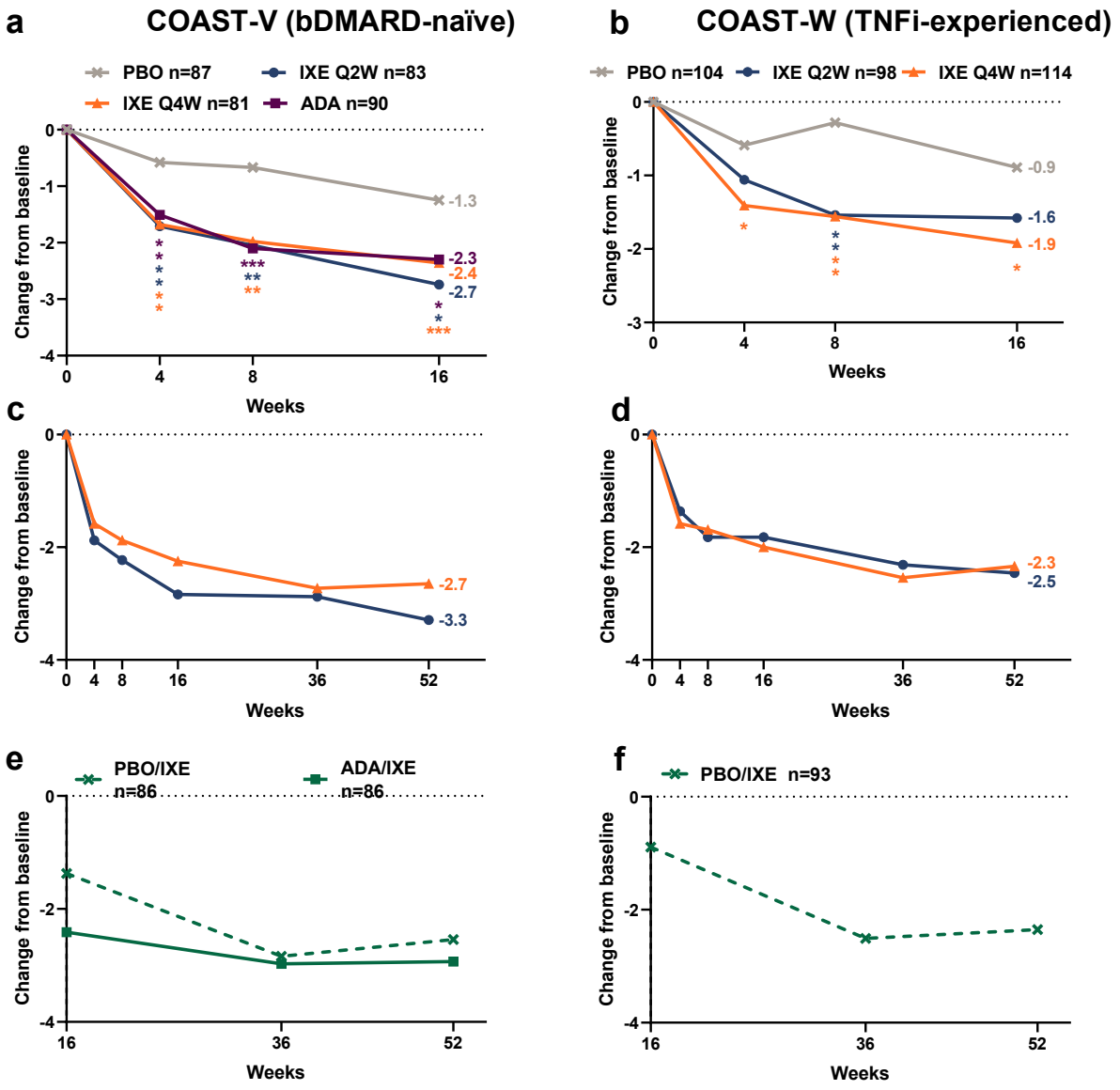

Figure 3. ASAS HI Least-squares mean change from baseline COAST-V and COAST-W (intent-to-treat population). Comparisons with PBO were made using a mixed-effects model for repeated measures up to Week 16 (**a** and **b**). Descriptive statistics were provided for Week 36 to 52 using mBOCF for missing data imputation approach (**c-f**).

*p<0.05

**p<0.01

***p<0.001

Abbreviations: ADA = adalimumab 40mg every 2 weeks; ASAS HI = Assessment of Spondyloarthritis international Society Health Index; bDMARD = biologic disease-modifying anti-rheumatic drugs; IXE Q2W = IXE dosed every 2 weeks; IXE Q4W = IXE dosed every 4 weeks; mBOCF = modified baseline observation carried forward; n = number of patients in analysis population; PBO = placebo; TNFi = tumor necrosis factor inhibitors.

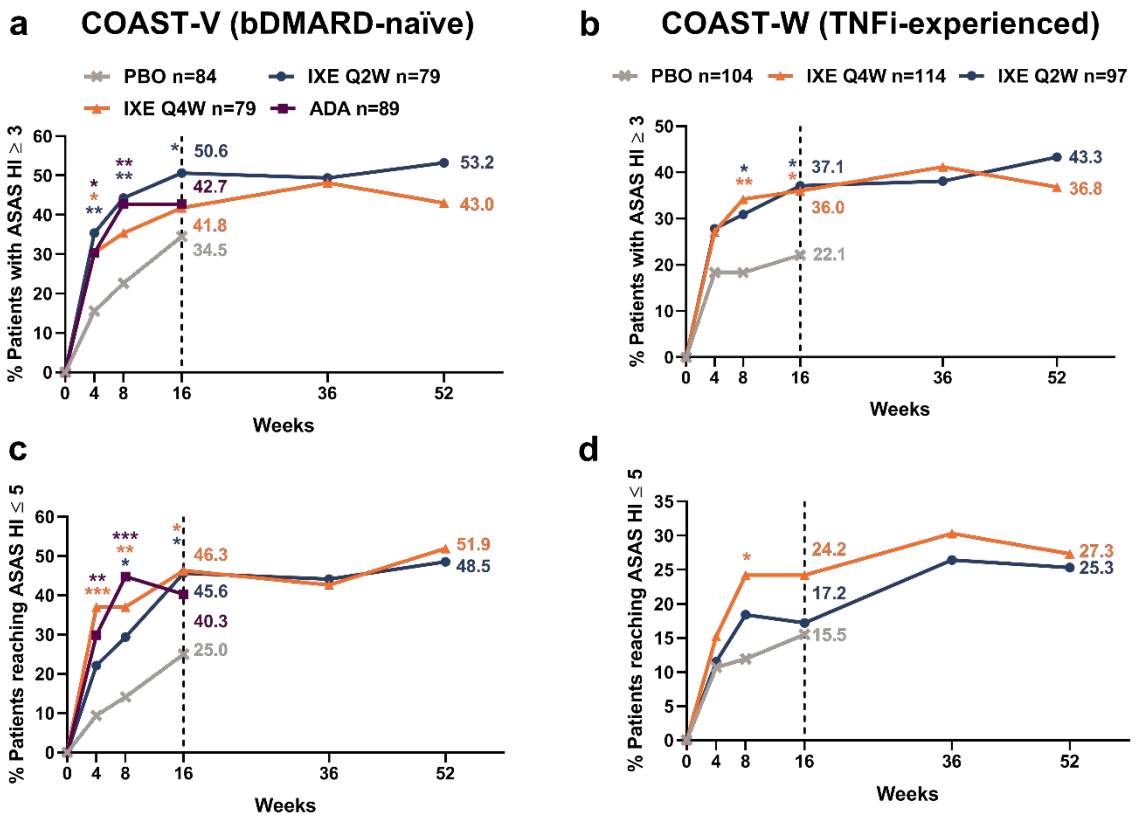

Figure 4. Proportion of patients with ASAS HI improvement ≥3 and achieving ASAS HI ≤5 ('good health' status) COAST-V and COAST-W (intent-to-treat population). Missing data were imputed using NRI. Comparisons with PBO were made using logistic regression model up to Week 16. Descriptive statistics were provided for Week 36 to 52.

*p<0.05

**p<0.01

***p<0.001

Abbreviations: ADA = adalimumab 40mg every 2 weeks; ASAS HI = Assessment of Spondyloarthritis international Society Health Index; bDMARD = biologic disease-modifying anti-rheumatic drugs; IXE Q2W = IXE dosed every 2 weeks; IXE Q4W = IXE dosed every 4 weeks; mBOCF = modified baseline observation carried forward; n = number of patients in analysis population; PBO = placebo; TNFi= tumor necrosis factor inhibitors.

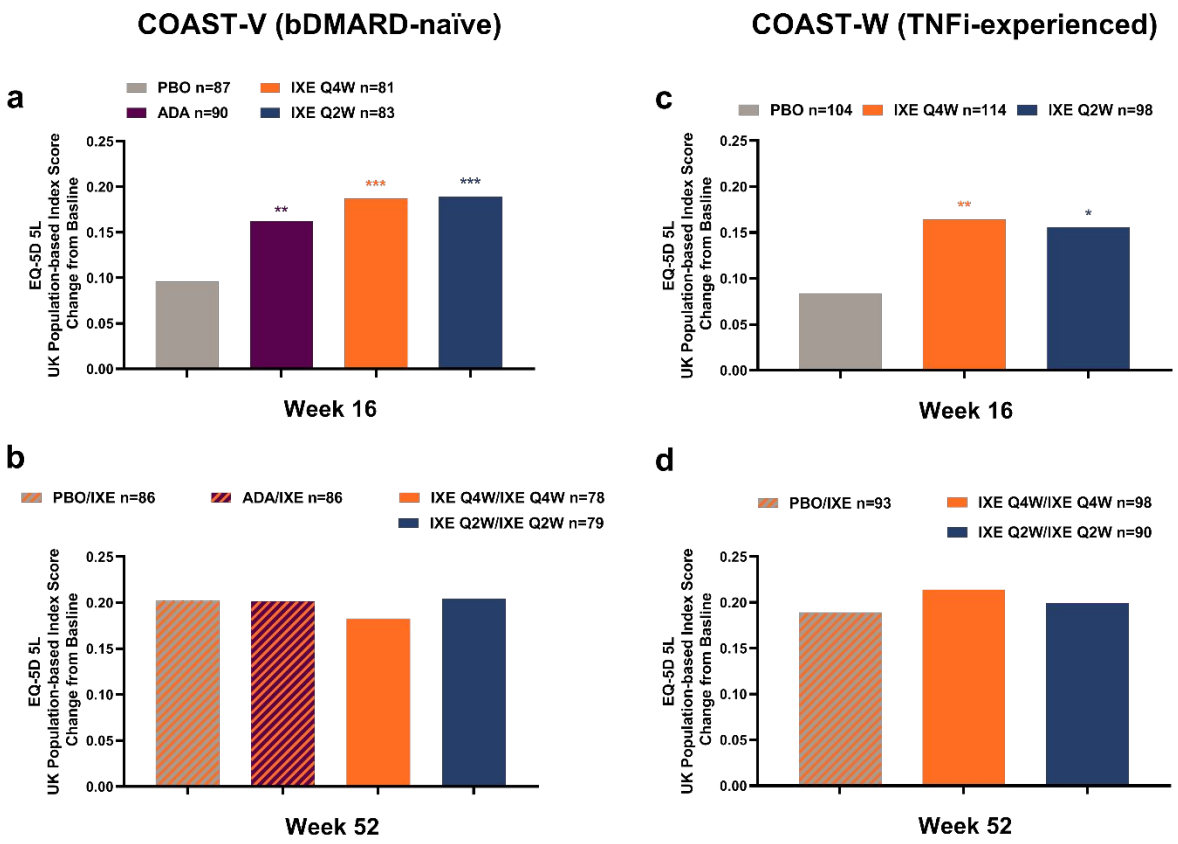

Figure 5. EQ-5D-5L UK population index score least-squares mean change from baseline COAST-V and COAST-W. Intent-to-treat population were used at Week 16, and Extended Treatment Period Population at Week 52. Missing data were imputed using NRI. Comparisons with PBO were made using logistic regression model at Week 16. Descriptive statistics were provided at Week 52 using mBOCF for missing data imputation approach.
*p<0.05
**p<0.01
***p<0.001
Abbreviations: ADA = adalimumab 40 mg every 2 weeks; bDMARD = biologic disease-modifying anti-rheumatic drugs; EQ-5D-5L = European Quality of Life-5 Dimensions 5-Level; IXE Q2W = IXE dosed every 2 weeks; IXE Q4W = IXE dosed every 4 weeks; mBOCF = modified baseline observation carried forward; n=number of patients in analysis population; PBO = placebo; TNFi = tumor necrosis factor inhibitors.