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Long-Term Safety and Efficacy of Ixekizumab in Patients With Axial Spondyloarthritis: 3-year Data From the COAST Program

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ABSTRACT. ***Objective.*** To report safety and efficacy of ixekizumab (IXE) from the COAST program at 3 years, including 1 year from the originating studies (COAST-V, COAST-W, and COAST-X), and 2 years from COAST-Y.

Methods. In COAST-Y, patients continued with the dose received at the end of the originating study at week 52: 80 mg IXE either every 4 weeks (Q4W) or every 2 weeks (Q2W). Placebo-treated patients from COAST-X received IXE Q4W in COAST-Y. Starting at week 116 (week 64 of COAST-Y), patients receiving IXE Q4W could be escalated to Q2W. Safety for patients receiving ≥ 1 dose of IXE and efficacy for patients receiving ≥ 1 dose of IXE Q4W was assessed. Data are summarized as observed.

Results. For the 932 patients who received ≥ 1 dose of IXE (Q2W or Q4W) through 3 years, treatment-emergent adverse events (TEAEs) occurred at an incidence rate (IR) of 38.0 per 100 patient-years (PYs). The most frequently reported were infections (IR 25.7 per 100 PYs) and injection site reactions (IR 7.4 per 100 PYs); the majority of TEAEs were mild or moderate in severity. In total, 7.1% of TEAEs led to discontinuation (IR 3.1 per 100 PYs). All patient groups receiving IXE Q4W assessed through 3 years saw sustained improvements in Ankylosing Spondylitis Disease Activity Score, clinically important improvement, and other efficacy end points.

Conclusion. The 3-year safety profile of IXE in the COAST program is consistent with the previously established long-term safety profile. IXE Q4W provided sustained improvement of disease activity in patients who received treatment through 3 years. (ClinicalTrials.gov: NCT02696785 [COAST-V], NCT02696798 [COAST-W], NCT02757352 [COAST-X], and NCT03129100 [COAST-Y])

Key Indexing Terms: biological therapy, clinical trials, disease activity, interleukins, spondyloarthropathy

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Axial spondyloarthritis (axSpA) is a chronic inflammatory disease affecting the axial skeleton and sacroiliac joints. It comprises 2 subtypes based on the presence or absence of definitive radiographic sacroiliitis, termed radiographic axSpA (r-axSpA) and nonradiographic axSpA (nr-axSpA).[1,2] The primary goal of axSpA treatment is maximization of long-term health-related quality of life through control of symptoms and inflammation, prevention of progressive structural damage, and preservation/normalization of function and social participation.[3]

Ixekizumab (IXE) is a high-affinity monoclonal antibody that selectively targets interleukin (IL)-17A. It has demonstrated efficacy at week 16, which was maintained through 2 years, in patients with r-axSpA and nr-axSpA in the COAST program.[4-7] The safety profile of IXE in patients with axSpA has also been previously described, with no new safety signals reported through 2 years.[8] Determining the safety profile of a biologic from multiple studies and long-term extension studies is of the utmost importance for patients receiving longstanding treatment. An integrated safety analysis of IXE in patients with psoriasis, psoriatic arthritis, and axSpA was consistent with what has been reported in individual studies with IXE[9]; however, this integrated safety analysis presented data based on a March 2019 database lock.

COAST-Y is a long-term extension study following the 3 originating studies, COAST-V, COAST-W, and COAST-X. Here, we report the safety and efficacy of IXE treatment in patients with r-axSpA and nr-axSpA for up to 156 weeks (July 2021 database lock).

METHODS

Patients. Eligible patients with axSpA who completed either of the 2 originating studies in r-axSpA (COAST-V, ClinicalTrials.gov: NCT02696785; COAST-W, ClinicalTrials.gov: NCT02696798), or the 1 originating study in nr-axSpA (COAST-X, ClinicalTrials.gov: NCT02757352) could enroll in COAST-Y (ClinicalTrials.gov: NCT03129100; Figure 1). Eligibility, inclusion, and exclusion criteria for these originating studies have been previously reported.[4-6] COAST-Y included patients with r-axSpA who were biologic disease-modifying antirheumatic drug (bDMARD)-naïve (COAST-V) or tumor necrosis factor inhibitor (TNFi)-experienced (COAST-W), as well as patients with nr-axSpA who were bDMARD-naïve (COAST-X). Patients could receive 80 mg IXE every 2 weeks (Q2W) or every 4 weeks (Q4W) for up to 156 weeks (52 weeks of the originating study plus 104 weeks of COAST-Y). To assess the safety and efficacy of IXE in axSpA through 3 years, we analyzed the subset of patients who received

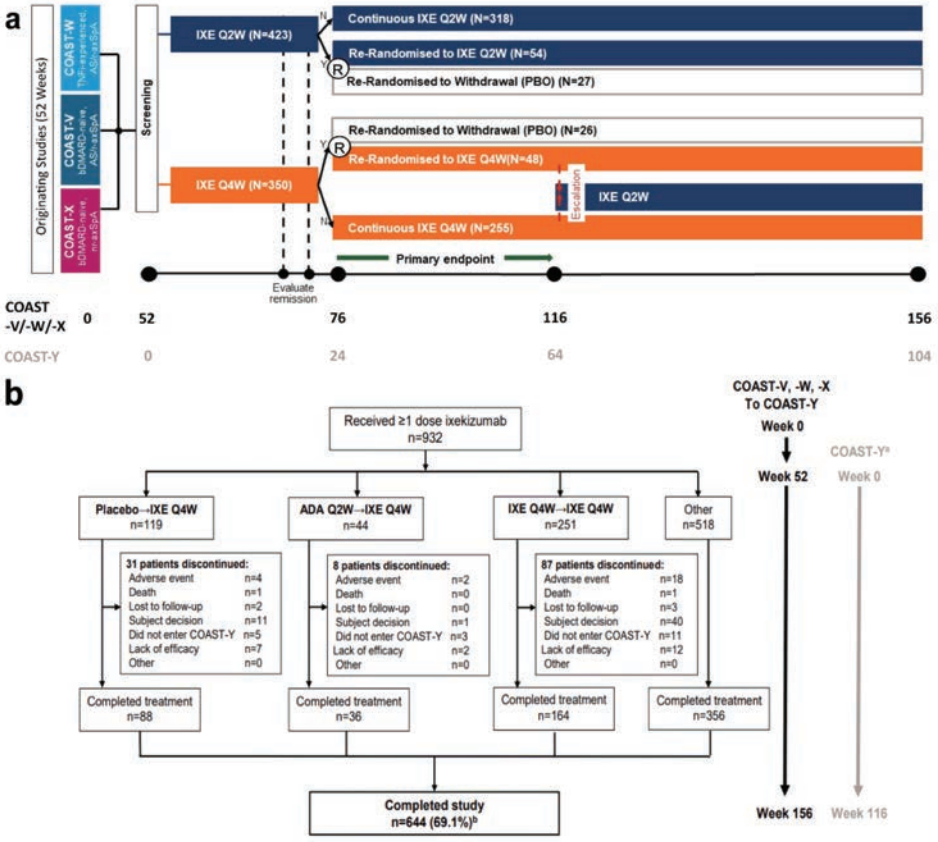

Figure 1. COAST-Y study design (A) and patient disposition diagram (B) through 3 years. In the randomized withdrawal and retreatment period, dose escalation was also permitted for patients who have been retreated for ≥ 12 weeks following a flare. [a] Seven hundred seventy-three of 932 (82.9%) patients reconsented and entered COAST-Y after completing their original study. [b] Six hundred thirty-one of 932 (67.7%) patients completed 156 weeks of treatment and 12 weeks of follow-up. ADA: adalimumab; AS: ankylosing spondylitis; bDMARD: biologic disease-modifying antirheumatic drug; IXE: ixekizumab; n/N: number of patients; nr-axSpA: nonradiographic axial spondyloarthritis; PBO: placebo; Q2W: every 2 weeks; Q4W: every 4 weeks; r-axSpA: radiographic axial spondyloarthritis; TNFi: tumor necrosis factor inhibitor.

at least 1 dose of IXE during the 3-year COAST study (July 2021 data cut-off). Data for efficacy are reported for patients while they were receiving IXE Q4W and IXE Q2W.

Statement of ethics and consent. COAST-Y was approved by the main ethics committee, Schulman Associates Institutional Review Board (IRB #201607390), and the study was approved by the ethical review boards at each of the 127 total participating sites.

Study design. A detailed description of the COAST-Y study design has been previously published.[8] At week 16 of COAST-V and COAST-W, patients initially randomized to either placebo (PBO) or adalimumab (ADA) were rerandomized to IXE Q2W or IXE Q4W. In COAST-X, between week 16 and week 44, inadequate responders (identified by an investigator) could receive rescue therapy with open-label IXE Q2W. The COAST-Y study included a double-blind, PBO-controlled, randomized withdrawal-retreatment period (RWRP) that started at week 76 of the COAST program (week 24 of the COAST-Y study) based on the achievement of remission (defined as Ankylosing Spondylitis Disease Activity Score [ASDAS] < 1.3 at least once during study visits at weeks 16 or 20 and ASDAS < 2.1 at both visits). Patients who achieved remission were rerandomized to continue IXE (IXE Q2W or IXE Q4W) or withdraw to PBO. These results have been previously published.[10] Patients who did not achieve remission continued to receive uninterrupted IXE Q2W or IXE Q4W. Starting at week 116 of the COAST program (week 64 of COAST-Y), patients receiving IXE Q4W with inadequate response, based on investigator opinion, could have their dose escalated to IXE Q2W. For the analysis presented in this manuscript, the safety population included the patients who received at least 1 dose of IXE through 156 weeks, whereas the efficacy population included patients who received at least 1 dose of IXE Q4W (Results section in main body of manuscript; Supplementary Material, available with the online version of this article) or IXE Q2W (Supplementary Material) through 156 weeks.

Outcomes. Safety outcomes reported through week 156 include instances of treatment-emergent adverse events (TEAEs), death, adverse events (AEs) leading to discontinuation, and serious AEs (SAEs). AEs of interest that will be reported include instances of injection site reactions, allergic reactions or hypersensitivities, infections, inflammatory bowel disease (IBD), uveitis, major adverse cardiac events (MACEs), malignancies, depression, and cytopenias.

Secondary efficacy outcomes of COAST-Y that are also reported in this analysis include the proportion of patients achieving a 20% and 40% improvement in the Assessment of SpondyloArthritis international Society criteria (ASAS20 and ASAS40), and ASAS partial remission, ASDAS inactive disease (ID) or low disease activity (LDA), ASDAS clinically important improvement (CII) or ASDAS major improvement, and 50% improvement in the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI50). We also report the mean (SD) change from baseline at 52, 116, and 156 weeks for ASDAS, BASDAI, BASDAI inflammation, Bath Ankylosing Spondylitis Functional Index (BASFI), ASAS Health Index (ASAS HI), 36-item Short Form Health Survey (SF-36) physical component summary (PCS), and SF-36 mental component summary (MCS).

Statistical analysis. Safety analyses through 156 weeks were performed on the population of patients who received at least 1 dose of IXE (IXE Q4W and IXE Q2W) between week 0 of the originating study and week 156. Safety data were analyzed as observed. Observed data while patients were on PBO or ADA were excluded. Data while patients were on IXE Q4W were reported in the IXE Q4W group, and data while patients were on IXE Q2W were reported in the IXE Q2W group. Efficacy analyses through 156 weeks were performed on the patients who received at least 1 dose of IXE Q4W between week 0 of the originating study and week 156 (week 104 of COAST-Y). For clinical practice, categorical responses are summarized as observed and are reported in the Results section in the main manuscript text and are also summarized with missing data imputed by nonresponder imputation (NRI) in the Supplementary Material (available with the online version of this article), whereas continuous responses are summarized as observed. Observed data while patients were on the open-label IXE Q2W escalated dose are excluded and considered missing from the as-observed analysis. Under the NRI analysis, patients who had a missing response, early discontinuation from either an originating study or COAST-Y, or had their dose escalated from IXE Q4W to open-label IXE Q2W in COAST-Y were considered nonresponders. In a separate analysis, ASAS40 and ASDAS LDA < 2.1 are reported as observed for patients who were escalated from IXE Q4W to IXE Q2W at week 156.

RESULTS

Patients. A total of 932 patients received at least 1 dose of IXE between week 0 of the originating study and week 156. Of these, 773/932 (82.9%) patients entered COAST-Y after completing the originating studies, and 631/932 (67.7%) patients completed 3 years of the COAST program. In total, 414 patients received at least 1 dose of IXE Q4W and 288 (67.9%) of these patients completed 3 years of the COAST program (PBO→IXE Q4W, 88/119 [71.4%]; ADA→IXE Q4W, 36/44 [81.8%]; and IXE Q4W→IXE Q4W, 164/251 [63.7%]; Figure 1). Baseline demographics and disease characteristics for patients have been previously reported.[4-6] In COAST-X, 40 patients had their dose escalated from IXE Q4W to IXE Q2W, whereas in COAST-Y, 86 patients had their dose escalated from IXE Q4W to IXE Q2W. Therefore, in the safety analyses, these 126 patients were counted in both the IXE Q4W and IXE Q2W groups but were only counted once in the total safety population.

Safety outcomes. TEAEs through 156 weeks (52 weeks of the originating studies plus 104 weeks of COAST-Y) of treatment were analyzed for the 932 patients with axSpA who received at least 1 dose of IXE, with 454 patients who received IXE Q4W and 604 patients who received IXE Q2W, representing a total of 2097.7 patient-years (PYs; 878.2 PYs for IXE Q4W and 1219.5 PYs for IXE Q2W). Safety outcomes for patients who received either IXE Q4W or IXE Q2W were analyzed separately. Overall, the safety profile of IXE through 3 years was consistent with what has been previously reported.[8,9] The incidence rates (IRs) for TEAEs for IXE Q4W and IXE Q2W were 43.3 and 37.9 per 100 PYs, respectively (Table 1). AEs leading to discontinuation were reported at a rate of 3.0 per 100 PYs for IXE Q4W and 3.3 per 100 PYs for IXE Q2W. The majority of TEAEs were mild or moderate in severity (Table 1). A total of 3 deaths occurred, 2 while patients were receiving IXE Q4W and 1 while the patient was receiving IXE Q2W (Table 1). One patient died by homicide, 1 patient died by suicide, and the third patient developed sepsis (probable pneumonia with multiorgan failure). These data have been reported and no additional events of death occurred since the previous study report.[8] The IRs for SAEs for IXE Q4W and IXE Q2W were 5.0 and 4.7 per 100 PYs, respectively, and 4.8 per 100 PYs in total.

AEs of special interest. Of the AEs of interest, injection site reactions were most frequent (IXE Q4W, IR 6.0 per 100 PYs; IXE Q2W, IR 8.8 per 100 PYs), the majority of which were mild or moderate in severity (Table 2). Of the patients who reported injection site reaction, 6 discontinued treatment, all of whom were receiving IXE Q2W (IR 0.5 per 100 PYs). There were 17 cases of IBD in total (IR 1.3 per 100 PYs for IXE Q4W and

Table 1. Safety outcomes at week 156 for the safety population, all patients who received ≥ 1 dose of IXE.

	Safety Population, N = 932					
	IXE Q4W, N = 454		IXE Q2W, N = 604		Total IXE, N = 932[a]	
	n (%)	IR (95% CI), PYs = 878.2	n (%)	IR (95% CI), PYs = 1219.5	n (%)	IR (95% CI), PYs = 2097.7
TEAEs[b]	380 (83.7)	43.3 (39.1-47.8)	462 (76.5)	37.9 (34.6-41.5)	798 (85.6)	38.0 (35.5-40.8)
Mild	141 (31.1)	16.1 (13.6-18.9)	161 (26.7)	13.2 (11.3-15.4)	276 (29.6)	13.2 (11.7-14.8)
Moderate	198 (43.6)	22.5 (19.6-25.9)	238 (39.4)	19.5 (17.2-22.2)	419 (45)	20.0 (18.2-22.0)
Severe	41 (9)	4.7 (3.4-6.3)	63 (10.4)	5.2 (4.0-6.6)	103 (11.1)	4.9 (4.0-6.0)
Death	2 (0.4)	0.2 (0.1-0.9)	1 (0.2)	0.1 (0.0-0.6)	3 (0.3)	0.1 (0.0-0.4)
AEs leading to discontinuation (including death)	26 (5.7)	3.0 (2.0-4.3)	40 (6.6)	3.3 (2.4-4.5)	66 (7.1)	3.1 (2.5-4.0)
SAEs[c]	44 (9.7)	5.0 (3.7-6.7)	57 (9.4)	4.7 (3.6-6.1)	101 (10.8)	4.8 (4.0-5.9)

Observed data while on placebo or adalimumab are excluded. Percentage is calculated by n/N × 100%. CIs of incidence rates are from likelihood ratio test of treatment effect from the Poisson regression. N represents the number of patients in the analysis population, and n represents the number of patients with ≥ 1 TEAE in the specified category. [a] One hundred twenty-six patients were switched from IXE Q4W to IXE Q2W and were counted in both the IXE Q4W and IXE Q2W columns. [b] Patients with multiple occurrences of the same event are counted under the highest severity. [c] The data collection for the clinical trial database does not contain specification on when events become serious; the numbers may represent more events considered serious than what was actually serious during the treatment period. Data while patients were on IXE Q4W are reported in the IXE Q4W group; data while patients were on IXE Q2W are reported in the IXE Q2W group. AE: adverse event; IR: incidence rate per 100 patient-years; IXE: ixekizumab; PY: patient-year; Q2W: every 2 weeks; Q4W: every 4 weeks; SAE: serious adverse event; TEAE: treatment-emergent adverse event.

Table 2. Selected AEs of interest through 156 weeks among all patients who received ≥ 1 dose of IXE.

	Safety Population, N = 932					
	IXE Q4W, N = 454		IXE Q2W, N = 604		Total IXE, N = 932	
	n (%)	IR (95% CI), PYs = 878.2	n (%)	IR (95 CI), PYs = 1219.5	n (%)	IR (95% CI), PYs = 2097.7
Injection site reactions[a]	53 (11.7)	6.0 (4.6-7.9)	107 (17.7)	8.8 (7.3-10.6)	156 (16.7)	7.4 (6.4-8.7)
Mild	40 (8.8)	4.6 (3.3-6.2)	79 (13.1)	6.5 (5.2-8.1)	115 (12.3)	5.5 (4.6-6.6)
Moderate	12 (2.6)	1.4 (0.8-2.4)	23 (3.8)	1.9 (1.3-2.8)	35 (3.8)	1.7 (1.2-2.3)
Severe	1 (0.2)	0.1 (0.0-0.8)	5 (0.8)	0.4 (0.2-1.0)	6 (0.6)	0.3 (0.1-0.6)
Allergic reactions/ hypersensitivities	39 (8.6)	4.4 (3.2-6.1)	52 (8.6)	4.3 (3.2-5.6)	88 (9.4)	4.2 (3.4-5.2)
Infections	248 (54.6)	28.2 (24.9-32.0)	309 (51.2)	25.3 (22.7-28.3)	540 (57.9)	25.7 (23.7-28.0)
Serious	9 (2)	1.0 (0.5-2.0)	14 (2.3)	1.1 (0.7-1.9)	23 (2.5)	1.1 (0.7-1.6)
Herpes zoster	6 (1.3)	0.7 (0.3-1.5)	6 (1)	0.5 (0.2-1.1)	12 (1.3)	0.6 (0.3-1.0)
Candida infections						
Oral candidiasis	3 (0.7)	0.3 (0.1-1.1)	2 (0.3)	0.2 (0.0-0.7)	5 (0.5)	0.2 (0.1-0.6)
Vulvovaginal candidiasis[b]	3 (2.3)	0.3 (0.1-1.1)	4 (2.1)	0.3 (0.1-0.9)	7 (2.5)	0.3 (0.2-0.7)
Skin candidiasis	0 (0)	0.0 (0.0-0.9)	2 (0.3)	0.2 (0.0-0.7)	2 (0.2)	0.1 (0.0-0.4)
Genital candidiasis	0 (0)	0.0 (0.0-0.9)	1 (0.2)	0.1 (0.0-0.6)	1 (0.1)	0.0 (0.0-0.3)
Esophageal candidiasis	2 (0.4)	0.2 (0.1-0.9)	2 (0.3)	0.2 (0.0-0.7)	4 (0.4)	0.2 (0.1-0.5)
IBD[c]	11 (2.4)	1.3 (0.7-2.3)	6 (1)	0.5 (0.2-1.1)	17 (1.8)	0.8 (0.5-1.3)
Crohn disease	5 (1.1)	0.6 (0.2-1.4)	2 (0.3)	0.2 (0.0-0.7)	7 (0.8)	0.3 (0.2-0.7)
Ulcerative colitis	6 (1.3)	0.7 (0.3-1.5)	4 (0.7)	0.3 (0.1-0.9)	10 (1.1)	0.5 (0.3-0.9)
Uveitis	28 (6.2)	3.2 (2.2-4.6)	30 (5)	2.5 (1.7-3.5)	58 (6.2)	2.8 (2.1-3.6)
MACE[c]	2 (0.4)	0.2 (0.1-0.9)	4 (0.7)	0.3 (0.1-0.9)	6 (0.6)	0.3 (0.1-0.6)
Malignancies	3 (0.7)	0.3 (0.1-1.1)	6 (1)	0.5 (0.2-1.1)	9 (1)	0.4 (0.2-0.8)
Depression	6 (1.3)	0.7 (0.3-1.5)	13 (2.2)	1.1 (0.6-1.8)	19 (2)	0.9 (0.6-1.4)
Cytopenia	8 (1.8)	0.9 (0.5-1.8)	21 (3.5)	1.7 (1.1-2.6)	28 (3)	1.3 (0.9-1.9)

Observed data while on placebo or adalimumab are excluded. Percentage is calculated by n/N × 100%. CIs of incidence rates are from likelihood ratio test of treatment effect from the Poisson regression. N represents the number of patients in the analysis population, and n represents the number of patients with ≥ 1 TEAE in the specified category. [a] Patients with multiple occurrences of the same event are counted under the highest severity. [b] Denominator adjusted because this is a gender-specific event for females: IXE Q4W, N = 128; IXE Q2W, N = 195. [c] Confirmed by adjudication. Data while patients were on IXE Q4W are reported in the IXE Q4W group; data while patients were on IXE Q2W are reported in the IXE Q2W group. AE: adverse event; IBD: inflammatory bowel disease; IR: incidence rate per 100 patient-years; IXE: ixekizumab; MACE: major adverse cerebro-cardiovascular event; PY: patient-year; Q2W: every 2 weeks; Q4W: every 4 weeks; TEAE: treatment-emergent adverse event.

0.5 per 100 PYs for IXE Q2W, confirmed by adjudication). Of these, there were 7 cases of Crohn disease (IR 0.3 per 100 PYs), 6 of which were new onset, and 10 cases of ulcerative colitis (IR 0.5 per 100 PYs), 6 of which were new onset. There were 58 patients with anterior uveitis (IR 2.8 per 100 PYs), the majority of which were mild (IR 1.2 per 100 PYs) or moderate (IR 1.5 per 100 PYs). Of the 173 patients who had a previous history of anterior uveitis, 41 patients had an episode of flare (IR 2.0 per 100 PYs), whereas 17 patients were new onset (0.8 per 100 PYs). IRs for MACE (confirmed by adjudication) and malignancies were both ≤ 0.5 per 100 PYs (Table 2). There were no latent cases that presented any sign of active tuberculosis.

Of the reported cases of candidiasis, the majority were mild (12/19) to moderate (7/19) in severity. There was a total of 5 cases of oral candidiasis, 3 of which were mild (IR 0.1 per 100 PYs) and 2 of which were moderate (0.1 per 100 PYs) in severity. Of the 4 cases of esophageal candidiasis reported, 2 were mild (0.1 per 100 PYs) and 2 were moderate (0.1 per 100 PYs) in severity. The 2 cases of skin candida reported were mild in severity (IR 0.1 per 100 PYs), and there was 1 mild case of genital candidiasis (IR 0.0 per 100 PYs). There were 7 reported cases of vulvovaginal candidiasis; 4 were mild (IR 0.2 per 100 PYs) and 3 were moderate in severity (IR 0.1 per 100 PYs). There were 12 cases of herpes zoster, all of which were either mild or moderate. There were no recorded cases of systemic candidiasis.

Efficacy outcomes. ASDAS statuses at week 156 among patients who received ≥ 1 dose of IXE Q4W are shown by treatment arm and by originating study in Figure 2. Of the patients from COAST-V who received IXE Q4W→IXE Q4W, a total of 75% (33/44) achieved either ASDAS ID or ASDAS LDA at week 156 (Figure 2A). Thirty-nine percent (16/41) of patients from COAST-W who received IXE Q4W→IXE Q4W achieved either ASDAS ID or ASDAS LDA at week 156 (Figure 2B), whereas a total of 66% (19/29) of patients from COAST-X who received IXE Q4W→IXE Q4W achieved either ASDAS ID or ASDAS LDA at week 156 (Figure 2C).

Over half of patients from COAST-V, COAST-W, and COAST-X achieved ASDAS CII by week 52 and sustained that response through week 156 (Figure 3; Supplementary Table S1, available with the online version of this article). In COAST-V, the observed proportions of patients who achieved ASDAS CII who received PBO→IXE Q4W, ADA→IXE Q4W, and IXE Q4W→IXE Q4W were 83%, 62%, and 80%, respectively,

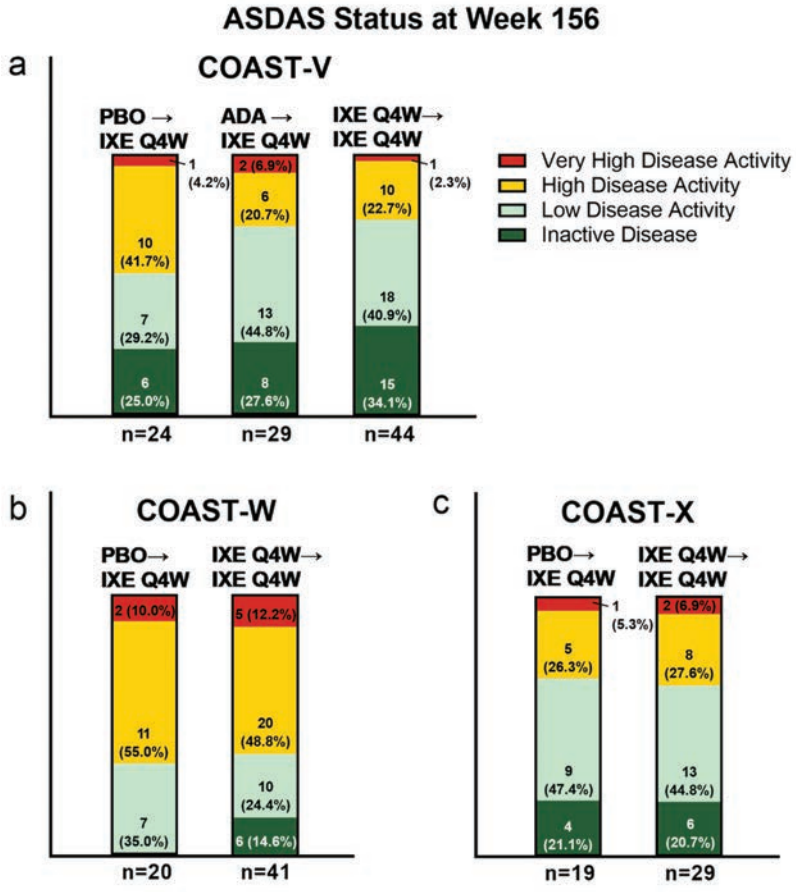

Figure 2. ASDAS status (as observed) at week 156 among patients from (A) COAST-V, (B) COAST-W, and (C) COAST-X, who received ≥ 1 dose of IXE Q4W. Data are presented as the number and proportion (n [%]) of patients in each category, and the number (n) of patients with ASDAS data available at week 156. ADA: adalimumab; ASDAS: Ankylosing Spondylitis Disease Activity Score; IXE: ixekizumab; PBO: placebo; Q4W: every 4 weeks.

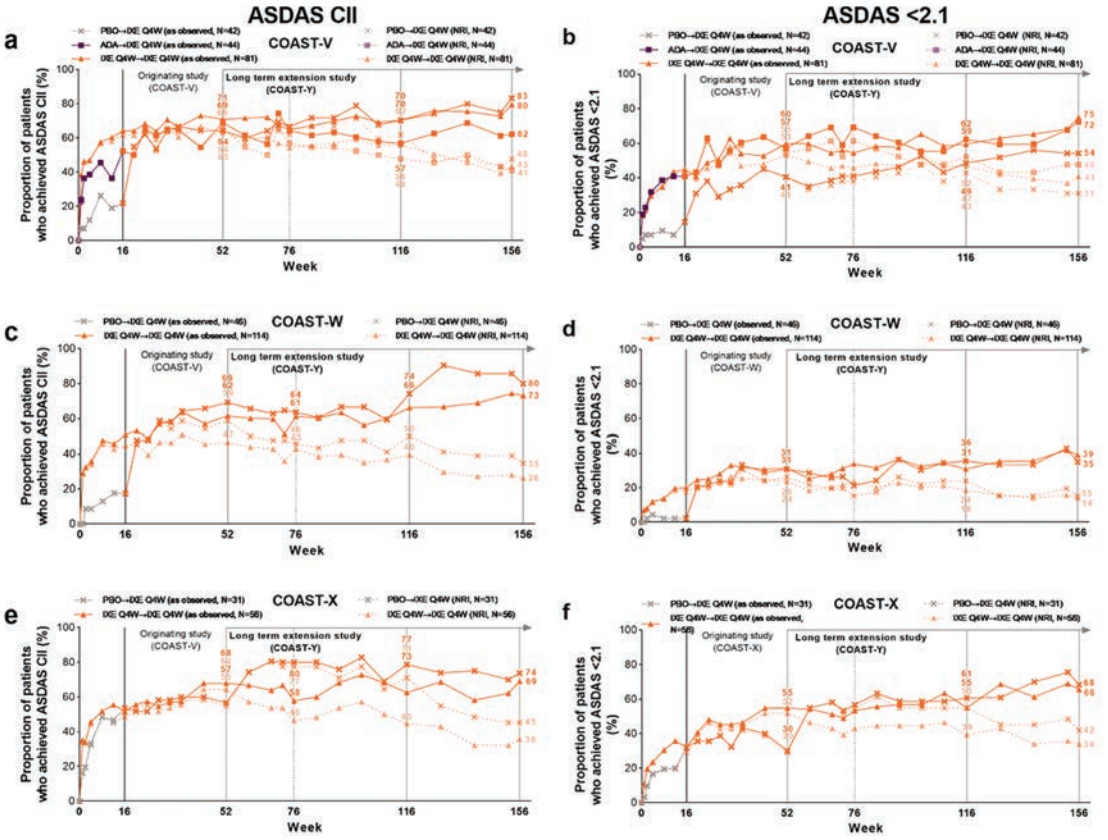

Figure 3. The proportion (%, as observed and NRI) of patients achieving ASDAS CII and ASDAS < 2.1 through 156 weeks in patients who received ≥ 1 dose of IXE Q4W from COAST-V (A and B), COAST-W (C and D), and COAST-X (E and F). Data are presented as observed (solid line) and NRI (dotted line). Observed data while on IXE Q2W escalated dose are excluded. At week 16, patients receiving either PBO (gray) or ADA (purple) were switched to IXE Q4W (orange). ADA→IXE Q4W are patients who were on washout period from weeks 14 to 20 and started the first injection of IXE Q4W at week 20. ADA: adalimumab; ASDAS: Ankylosing Spondylitis Disease Activity Score; CII: clinically important improvement; IXE: ixekizumab; NRI: nonresponder imputation; PBO: placebo; Q2W: every 2 weeks; Q4W: every 4 weeks.

at week 156 (Figure 3A, Supplementary Table S1 for IXE Q4W→IXE Q4W only). In patients from COAST-W, the observed proportions who achieved ASDAS CII who received PBO→IXE Q4W and IXE Q4W→IXE Q4W were 80% and 73%, respectively, at week 156 (Figure 3C, Supplementary Table S1 for IXE Q4W→IXE Q4W only). In COAST-X, the observed proportions of patients who achieved ASDAS CII who received PBO→IXE Q4W and IXE Q4W→IXE Q4W were 74% and 69%, respectively, at week 156 (Figure 3E, Supplementary Table S1 for IXE Q4W→IXE Q4W only).

The majority of patients from COAST-V and COAST-W achieved ASDAS < 2.1 by week 52, responses which were sustained through week 156 (Figure 3; Supplementary Table S1, available with the online version of this article). In COAST-V, the observed proportions of patients who achieved ASDAS < 2.1 who received PBO→IXE Q4W, ADA→IXE Q4W, and IXE Q4W→IXE Q4W were 54%, 72%, and 75%, respectively, at week 156 (Figure 3B, Supplementary Table S1 for IXE Q4W→IXE Q4W only). In COAST-W, the observed proportions of patients who achieved ASDAS < 2.1 who received PBO→IXE Q4W and IXE Q4W→IXE Q4W were 35% and 39%, respectively, at week 156 (Figure 3D, Supplementary Table S1 for IXE Q4W→IXE Q4W only). In COAST-X, the observed proportions of patients who achieved ASDAS < 2.1 who received PBO→IXE Q4W and IXE Q4W→IXE Q4W were 68% and 66%, respectively, at week 156 (Figure 3F, Supplementary Table S1 for IXE Q4W→IXE Q4W only). Of the 86 patients who had their dose escalated from IXE Q4W to open-label IXE Q2W during COAST-Y, at the last visit prior to escalation, the observed proportions of patients who achieved ASDAS < 2.1 who received PBO→IXE Q4W (RWRP) or IXE Q4W→IXE Q4W were 75% (3/4) and 24% (20/82), respectively. The proportion of patients who achieved ASDAS < 2.1 at least once after dose escalation was 100% (4/4) for patients who received PBO→IXE Q4W (RWRP) and were escalated to open-label IXE Q2W, and 39% (32/82) for patients who received IXE Q4W→IXE Q4W and were escalated to open-label IXE Q2W.

Among the patients with r-axSpA from COAST-V who were bDMARD-naïve, observed ASAS40 responses for patients who received PBO→IXE Q4W, ADA→IXE Q4W, and IXE Q4W→IXE Q4W were 54%, 62%, and 68%, respectively, at week 156 (Figure 4A; Supplementary Table S1 for IXE Q4W→IXE Q4W only, available with the online version of this article). Among the patients with r-axSpA from COAST-W

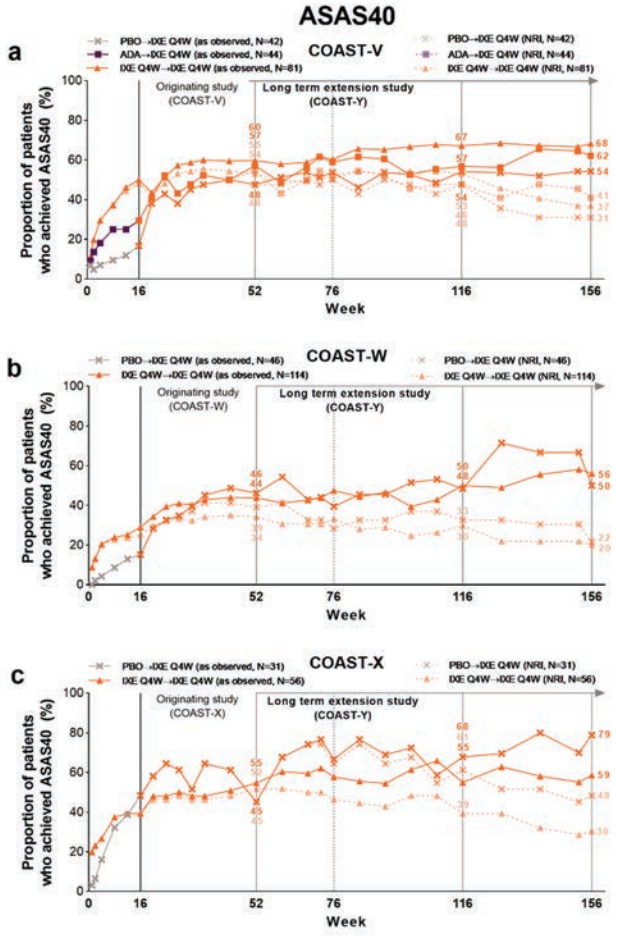

Figure 4. The proportion (NRI and as observed) of patients who achieved ASAS40 through 156 weeks in patients who received ≥ 1 dose of IXE Q4W from (A) COAST-V, (B) COAST-W, and (C) COAST-X. Data are presented as observed (solid line) and NRI (dotted line). Observed data while on IXE Q2W escalated dose are excluded. At week 16, patients receiving either PBO (gray) or ADA (purple) were switched to IXE Q4W (orange). ADA→IXE Q4W are patients who were on washout period from weeks 14 to 20 and started the first injection of IXE Q4W at week 20. ADA: adalimumab; ASAS40: 40% improvement in the Assessment of Spondyloarthritis international Society criteria; IXE: ixekizumab; NRI: nonresponder imputation; PBO: placebo; Q2W: every 2 weeks; Q4W: every 4 weeks.

who were TNFi-experienced, observed ASAS40 response rates for patients who received PBO→IXE Q4W and IXE Q4W→IXE Q4W were 50% and 56%, respectively, at week 156 (Figure 4B, Supplementary Table S1 for IXE Q4W→IXE Q4W only). Observed ASAS40 response rates for patients with nr-axSpA from COAST-X who were bDMARD-naïve and who received PBO→IXE Q4W and IXE Q4W→IXE Q4W were 79% and 59%, respectively, at week 156 (Figure 4C, Supplementary Table S1 for IXE Q4W→IXE Q4W only). A total of 86 patients had their dose escalated from IXE Q4W to open-label IXE Q2W during COAST-Y. At the last visit prior to dose escalation, the observed proportions of patients who achieved ASAS40 who received PBO→IXE Q4W (RWRP) and IXE Q4W→IXE Q4W were 50% (2/4) and 41.5% (34/82), respectively. The proportion of patients who achieved ASAS40 at least once after dose escalation was 75% (3/4) for patients who received PBO→IXE Q4W (RWRP) and were escalated to open-label IXE Q2W, and 58.5% (48/82) for patients who received IXE Q4W→IXE Q4W and were escalated to open-label IXE Q2W.

Among the patients from COAST-V who were bDMARD-naïve with r-axSpA, observed BASDAI50 response rates for patients who received PBO→IXE Q4W, ADA→IXE Q4W, and IXE Q4W→IXE Q4W were 62.5%, 62.1%, and 70.5%, respectively, at week 156 (Supplementary Table S1 for IXE Q4W→IXE Q4W only, Supplementary Figure S1A, available with the online version of this article). Among the patients from COAST-W who were TNFi-experienced, observed BASDAI50 response rates for patients who received PBO→IXE Q4W and IXE Q4W→IXE Q4W were 45% and 48.8%, respectively, at week 156 (Supplementary Table S1 for IXE Q4W→IXE Q4W only, Supplementary Figure S1C). In COAST-X, the observed BASDAI50 response rates for patients who received PBO→IXE Q4W and IXE Q4W→IXE Q4W were 63.2% and 55.2%, respectively, at week 156 (Supplementary Table S1 for IXE Q4W→IXE Q4W only, Supplementary Figure S1E).

Baseline BASDAI scores for patients from COAST-V who received PBO→IXE Q4W, ADA→IXE Q4W, and IXE Q4W→IXE Q4W were 6.9, 6.4, and 6.8, respectively. The mean (observed) change from baseline for patients who received PBO→IXE Q4W, ADA→IXE Q4W, and IXE Q4W→IXE Q4W were −3.9, −3.5, and −4.0, respectively, at week 156 (Supplementary Table S1 for IXE Q4W→IXE Q4W only, Supplementary Figure S1B, available with the online version of this article). Baseline BASDAI scores for patients from COAST-W who received PBO→IXE Q4W and IXE Q4W→IXE Q4W were 7.5 and 7.5, respectively. Mean (observed) change from baseline for patients who received PBO→IXE Q4W and IXE Q4W→IXE Q4W was −3.7 and −3.4, respectively, at week 156 (Supplementary Table S1 for IXE Q4W→IXE Q4W only, Supplementary Figure S1D). Baseline BASDAI scores for patients from COAST-X who received PBO→IXE Q4W and IXE Q4W→IXE Q4W were 7.0 and 7.0, respectively. Mean (observed) change from baseline for patients who received PBO→IXE Q4W and IXE Q4W→IXE Q4W was −4.4 and −3.4, respectively, at week 156 (Supplementary Table S1 for IXE Q4W→IXE Q4W only, Supplementary Figure S1F).

Efficacy outcomes analyzed using NRI are reported in Supplementary Tables S2, S3, and S4 (available with the online version of this article) for patients who were assigned to either IXE Q2W or IXE Q4W at entry; data are presented by the originating study.

Patient-reported outcomes assessed through week 156 include SF-36 PCS (SF-36 MCS data are shown in Supplementary Table S1, available with the online version of this article), BASFI, and the ASAS HI (Supplementary Table S1, Supplementary Figures S2 and S3). Baseline SF-36 PCS scores and improvements from baseline are shown in Supplementary Figure S2. In COAST-V, the mean (observed) changes from baseline in SF-36 PCS among patients who received PBO→IXE Q4W, ADA→IXE Q4W, and IXE Q4W→IXE Q4W were 11.0, 8.3, and 9.4, respectively, at week 156 (Supplementary Table S1 for IXE Q4W→IXE Q4W only, Supplementary Figure S2A). In COAST-W, the mean

(observed) changes from baseline in SF-36 PCS among patients who received PBO→IXE Q4W and IXE Q4W→IXE Q4W were 7.2 and 9.7, respectively, at week 156 (Supplementary Table S1 for IXE Q4W→IXE Q4W only, Supplementary Figure S2C). In COAST-X, the mean (observed) changes from baseline in SF-36 PCS among patients who received PBO→IXE Q4W and IXE Q4W→IXE Q4W were 12.5 and 10.0, respectively, at week 156, respectively (Supplementary Table S1 for IXE Q4W→IXE Q4W only, Supplementary Figure S2E). Similar patterns of improvement were noted for the BASFI and ASAS HI, with the majority of patients achieving improvements from baseline at week 52, which were sustained through week 156 (Supplementary Table S1 for IXE Q4W→IXE Q4W only, Supplementary Figures S2 and S3).

DISCUSSION

These results provide additional evidence to support the fact that patients with axSpA receiving IXE experience long-term safety and sustained improvements in efficacy and patient-reported outcomes at 3 years.

Safety is of the utmost importance to patients receiving any long-term therapy. Here, we report that through 3 years of the COAST program, the safety profile is consistent with what has been previously published for IXE with up to 2 years of exposure.[9] There were no new or unexpected safety concerns through 3 years of COAST. TEAEs were generally mild or moderate in severity. AEs leading to discontinuation were low, in line with what has been reported previously for all pooled patients treated with IXE through 2 years of exposure.[9] Candida infections also remained low through 3 years of IXE treatment. Similarly, incidences of MACE and malignancies also remained low for patients who received IXE through 3 years. In addition, in the present safety population, rates of IBD are low. In a population of patients with ankylosing spondylitis (AS)/nr-axSpA from a large US administrative claims data set, a significantly higher proportion of patients with AS were diagnosed with comorbid IBD compared to matched controls.[11]

Improvements in clinical efficacy outcomes were sustained through 3 years in all study populations studied: bDMARD-naïve patients with r-axSpA, TNFi-experienced patients with r-axSpA, and bDMARD-naïve patients with nr-axSpA. These results are consistent with what has been previously published at 2 years in patients from the COAST program,[8] and long-term studies of other biologics.[12-17]

Strengths of this study include the presence of the ADA→IXE Q4W and PBO→IXE Q4W arms, which allowed for the comparison of outcomes among patients who were originally randomized to different treatments. A limitation of this study is the escalation of patients receiving IXE Q4W to IXE Q2W, which was done solely at the investigator's discretion and without any specific or predefined criteria to guide the decision. Specifically, between weeks 116 and 156, patients could have their dose escalated if the investigator determined that they may benefit from the change. Consequently, patients who were switched from IXE Q4W to IXE Q2W were considered nonresponders. A further limitation is that the observed data while patients were receiving the IXE Q2W escalated dose were excluded from the main results and obscured definitive analysis of IXE Q4W efficacy, as switching to IXE Q2W placed Q4W responders in the NRI category. However, ASDAS LDA, and ASAS40 response rates prior to and following dose escalation for these 86 patients who were escalated from IXE Q4W to open-label IXE Q2W during COAST-Y have also been reported herein.

This analysis of patients with axSpA in the COAST program demonstrates that the safety profile of IXE is consistent with the established long-term safety profile. Long-term IXE treatment provided sustained CII through 156 weeks. IXE Q4W demonstrated efficacy across the 3 pivotal studies and 1 long-term extension study. Almost 70% of patients in the COAST program remained on IXE treatment through 3 years.

ACKNOWLEDGMENT

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ONLINE SUPPLEMENT

Supplementary material accompanies the online version of this article.

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Correction

Long-Term Safety and Efficacy of Ixekizumab in Patients With Axial Spondyloarthritis: 3-year Data From the COAST Program

Atul Deodhar, Denis Poddubnyy, Proton Rahman, Jeorg Ermann, Tetsuya Tomita, Rebeca Bolce, Soyi Liu Leage, Andris Kronbergs, Caroline Johnson, Joana Araújo, Ann Leung, and Désirée van der Heijde

J Rheumatol 2023; doi:10.3899/jrheum.221022

Figure 1 was incomplete. The corrected Figure 1 appears here. This version contains all the reasons for discontinuation, including "lack of efficacy." The "completed study" number and percentage were also corrected, and 2 footnotes were added for clarity: "[a] Seven hundred seventy-three of 932 (82.9%) patients reconsented and entered COAST-Y after completing their original study. [b] Six hundred thirty-one of 932 (67.7%) patients completed 156 weeks of treatment and 12 weeks of follow-up." This correction applies only to the March 1 2023 First Release. The correct text appears in the print and online issues.

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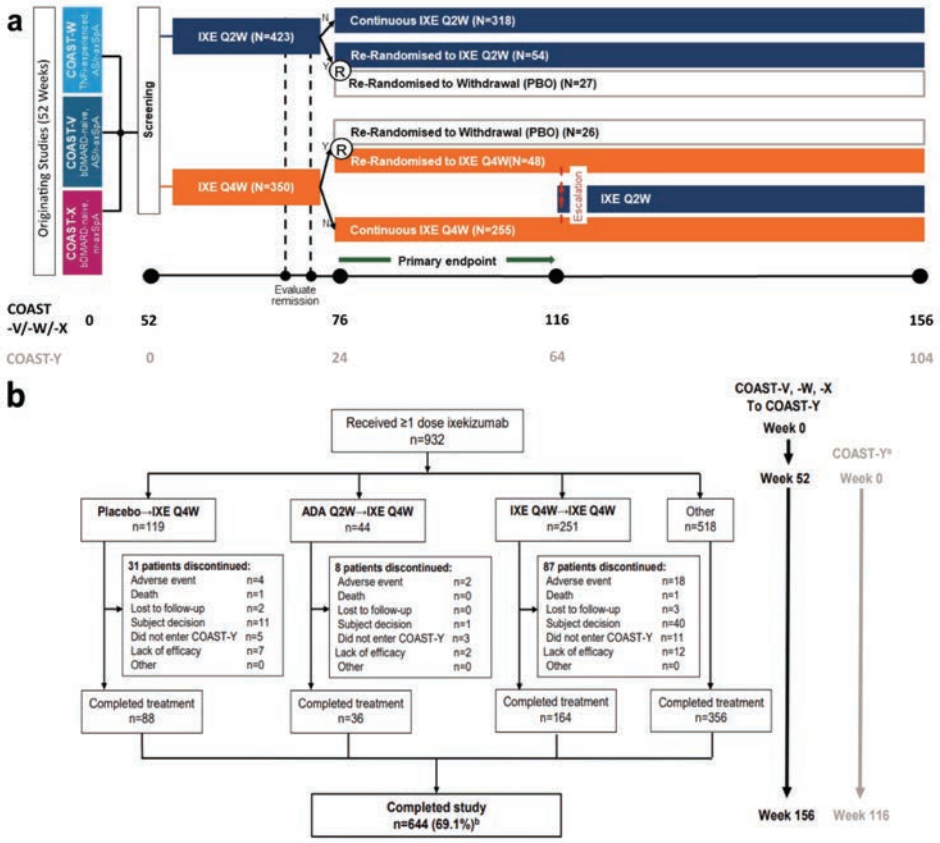

Figure 1. COAST-Y study design (A) and patient disposition diagram (B) through 3 years. In the randomized withdrawal and retreatment period, dose escalation was also permitted for patients who have been retreated for ≥ 12 weeks following a flare. [a] Seven hundred seventy-three of 932 (82.9%) patients reconsented and entered COAST-Y after completing their original study. [b] Six hundred thirty-one of 932 (67.7%) patients completed 156 weeks of treatment and 12 weeks of follow-up. ADA: adalimumab; AS: ankylosing spondylitis; bDMARD: biologic disease-modifying antirheumatic drug; IXE: ixekizumab; n/N: number of patients; nr-axSpA: nonradiographic axial spondyloarthritis; PBO: placebo; Q2W: every 2 weeks; Q4W: every 4 weeks; r-axSpA: radiographic axial spondyloarthritis; TNFi: tumor necrosis factor inhibitor.

Correction

Long-Term Safety and Efficacy of Ixekizumab in Patients With Axial Spondyloarthritis: 3-year Data From the COAST Program

Atul Deodhar, Denis Poddubnyy, Proton Rahman, Jeorg Ermann, Tetsuya Tomita, Rebeca Bolce, Soyi Liu Leage, Andris Kronbergs, Caroline Johnson, Joana Araújo, Ann Leung, and Désirée van der Heijde

J Rheumatol 2023; doi:10.3899/jrheum.221022

The following text in the Results section of the originally published manuscript contained incorrect values: "Of the 173 patients who had a previous history of anterior uveitis, 41 patients had an episode of flare (IR 2.0 per 100 PYs), whereas 17 patients were new onset (0.8 per 100 PYs)."

This has been corrected to: "Of the 173 patients who had a previous history of anterior uveitis, 41 patients had an episode of flare (IR 10.7 per 100 PYs), whereas, of the 755 patients with no anterior uveitis, 17 patients were new onset (1.0 per 100 PYs)."

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