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CLINICAL SCIENCE

Continuing versus withdrawing ixekizumab treatment in patients with axial spondyloarthritis who achieved remission: efficacy and safety results from a placebo-controlled, randomised withdrawal study (COAST-Y)

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ABSTRACT

Objectives The objective of COAST-Y was to evaluate the effect of continuing versus withdrawing ixekizumab (IXE) in patients with axial spondyloarthritis (axSpA) who had achieved remission.

Methods COAST-Y is an ongoing, phase III, long-term extension study that included a double-blind, placebo (PBO)-controlled, randomised withdrawal-retreatment period (RWRP). Patients who completed the originating 52-week COAST-V, COAST-W or COAST-X studies entered a 24-week lead-in period and continued either 80 mg IXE every 2 (Q2W) or 4 weeks (Q4W). Patients who achieved remission (an Ankylosing Spondylitis Disease Activity Score (ASDAS)<1.3 at least once at week 16 or week 20, and <2.1 at both visits) were randomly assigned equally at week 24 to continue IXE Q4W, IXE Q2W or withdraw to PBO in a blinded fashion. The primary endpoint was the proportion of flare-free patients (flare: ASDAS≥2.1 at two consecutive visits or ASDAS>3.5 at any visit) after the 40-week RWRP, with time-to-flare as a major secondary endpoint.

Results Of 773 enrolled patients, 741 completed the 24-week lead-in period and 155 entered the RWRP. Forty weeks after randomised withdrawal, 83.3% of patients in the combined IXE (85/102, p<0.001), IXE Q4W (40/48, p=0.003) and IXE Q2W (45/54, p=0.001) groups remained flare-free versus 54.7% in the PBO group (29/53). Continuing IXE significantly delayed time-to-flare versus PBO, with most patients remaining flare-free for up to 20 weeks after IXE withdrawal.

Conclusions Patients with axSpA who continued treatment with IXE were significantly less likely to flare and had significantly delayed time-to-flare compared with patients who withdrew to PBO.

Key messages

What is already known about this subject?

- Results from randomised withdrawal studies of tumour necrosis factor inhibitors (TNFi) in patients with axial spondyloarthritis (axSpA) suggest that discontinuation of TNFi leads to flare in most patients and continuous treatment may be important for maintaining disease control.
- However, no studies have evaluated the effect of continuing versus withdrawing an interleukin (IL)-17A antagonist in patients with axSpA.
- Ixekizumab (IXE), a high-affinity monoclonal antibody that selectively targets IL-17A, is an efficacious treatment for the management of axSpA, including radiographic and non-radiographic axSpA.

What does this study add?

- COAST-Y is the first study to compare the maintenance of disease control in patients with axSpA who continued versus those who withdrew an IL-17A antagonist (IXE) after having achieved remission.
- In patients with axSpA, continuous IXE treatment was associated with a higher likelihood of maintaining optimal disease control compared with IXE withdrawal.
- A substantial proportion of patients remained flare-free through 40 weeks of IXE withdrawal and most patients remained flare-free for up to 20 weeks of IXE withdrawal.

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INTRODUCTION

Axial spondyloarthritis (axSpA) is a chronic inflammatory disease that predominantly affects the axial skeleton.[1] AxSpA is categorised as radiographic (r-axSpA, also known as ankylosing spondylitis) or non-radiographic (nr-axSpA) axSpA by the presence or absence of definite radiographic sacroiliitis, respectively.[2] AxSpA carries a high disease burden and generally requires long-term therapy to maintain disease control.[3 4]

Biologic disease-modifying antirheumatic drugs (bDMARDs), such as tumour necrosis factor inhibitors (TNFi) and interleukin (IL)-17A antagonists, are recommended for patients with persistently high disease activity refractory to, or intolerant of, conventional treatment with at least two non-steroidal anti-inflammatory drugs.[4] Inactive disease/remission or low disease activity has been proposed as a treatment target for axSpA.[5] There is considerable interest in the durability of bDMARDs' efficacy following withdrawal or dose reduction in patients who have achieved stable disease control. Previous

Key messages

How might this impact on clinical practice or future developments?

- The findings of COAST-Y show that continuous IXE treatment is important for the maintenance of optimal disease control.
- A substantial proportion of patients remained flare-free for a prolonged period following IXE withdrawal, which may be important in situations where temporary treatment interruption is necessary or preferred.

randomised withdrawal studies of TNFi indicated that complete withdrawal of TNFi significantly increased the likelihood of flare.[6–9] However, a reduced dosing frequency of certolizumab pegol resulted in maintenance of disease control with no significantly greater chance of flare.[6] In contrast, the maintenance of disease control following withdrawal of IL-17A antagonists has not yet been evaluated.

Ixekizumab (IXE), a high-affinity monoclonal antibody that selectively targets IL-17A, is approved for r-axSpA and nr-axSpA. In three phase III studies, IXE provided sustained improvements in the signs and symptoms of r-axSpA and nr-axSpA through 52 weeks of treatment.[10–13] The primary objective at week 64 of the current extension study was to compare the maintenance of disease control in patients who continued IXE versus those who withdrew IXE following achievement of axSpA clinical remission.

METHODS

Patients

COAST-Y (NCT03129100) included participants from two originating studies in r-axSpA (COAST-V, NCT02696785; and COAST-W, NCT02696798) and one originating study in nr-axSpA (COAST-X, NCT02757352). Eligibility criteria for the originating studies are published.[10 13] Patients eligible for COAST-Y must have completed the final week-52 visit in the originating study without permanently discontinuing investigational product. Patients with a significant uncontrolled safety concern that had developed during the originating study were excluded if the investigator considered it an unacceptable risk to the patient to continue investigational product. However, the investigational product could be resumed and the patient could be enrolled into COAST-Y if the patient recovered from the safety concern within 12 weeks of completing the originating study. Complete eligibility criteria are provided in the online supplemental appendix.

Study design

COAST-Y is an ongoing, 104-week, phase III, multicentre, long-term extension study that included an open-label lead-in period and a double-blind, placebo-controlled, randomised withdrawal-retreatment period (RWRP) (figure 1A). Patients entered a 24-week lead-in period (weeks 0–24) and continued either 80 mg IXE every 2 weeks (Q2W) or every 4 weeks (Q4W). Patients who completed COAST-X and who were receiving blinded placebo were assigned to IXE Q4W.

Patients completing the lead-in period entered a 40-week (weeks 24–64) extension period, which included the RWRP. At week 24, patients who achieved remission, defined as an Ankylosing Spondylitis Disease Activity Score (ASDAS) of <1.3 at least once at week 16 or week 20 and <2.1 at both visits, were randomly assigned in equal proportions to continue IXE Q4W, continue IXE Q2W or withdraw to placebo. Specifically, patients in each treatment group (IXE Q4W or IXE Q2W) were randomised in a 2:1 ratio to continue their assigned IXE dosing regimen or to withdraw to placebo, respectively, resulting in an overall 1:1:1 randomisation ratio. Visits during the RWRP occurred every 4 weeks from week 24 to week 64.

Patients who experienced a flare (ASDAS≥2.1 at two consecutive visits or ASDAS>3.5 at any visit) were retreated at the next visit with the same IXE dosing regimen received during the lead-in period but in an open-label fashion, except for patients originally from COAST-X, who received blinded retreatment until the COAST-X week-52 database lock. Additional details on the study design are summarised in the online supplemental appendix.

Study participants provided written informed consent prior to starting study procedures.

Outcomes

The primary outcome at week 64 was the proportion of flare-free patients during the RWRP in the combined IXE group (Q4W and Q2W combined) versus the withdrawn to placebo group. Major secondary outcomes at week 64 included the proportion of flare-free patients in the IXE Q4W group versus withdrawn to placebo group and, in the combined IXE and IXE Q4W groups, the time-to-flare versus the withdrawn to placebo group.

Other secondary outcomes included the proportion of patients at week 64 who maintained response as measured by Assessment of Spondyloarthritis International Society (ASAS) criteria, ASDAS and the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI). Categorical outcomes included ASAS20, ASAS40, ASAS Partial Remission, ASAS 5/6, ASDAS inactive disease (ID), ASDAS low disease activity (LDA) and BASDAI 50.[14–19] Continuous outcomes included the mean change from baseline in ASDAS, BASDAI, Bath Ankylosing Spondylitis Functional Index (BASFI), high sensitivity C-reactive protein (CRP) in mg/L and the Medical Outcomes Study 36-Item Short Form Health Survey Physical Component Summary. Secondary outcomes also included the proportion of patients who achieved ASDAS LDA within 16 weeks of retreatment.

Post hoc assessments were conducted to evaluate predictors of flare during the RWRP. MRI of the sacroiliac joint and spine was conducted at week 24 for patients who qualified for the RWRP to evaluate residual inflammation on MRI as a predictive variable for flare. A post hoc assessment was also conducted to evaluate the proportion of patients who did not meet the ASAS definition of clinically important worsening (ASDAS worsening of ≥0.9) since week 24.[20]

Safety evaluations included laboratory tests, vital signs, physical examination findings and adverse events (AEs), including treatment-emergent AEs (TEAEs), serious AEs (SAEs) and AEs of special interest. Data associated with cerebrocardiovascular events or suspected inflammatory bowel disease were adjudicated by an external clinical events committee. Additional details regarding efficacy and safety outcomes are provided in the online supplemental appendix.

Statistical analysis

Efficacy analyses were conducted on the randomised withdrawal intent-to-treat (RW ITT) population, defined as all patients who achieved remission and entered the RWRP. Categorical efficacy variables were analysed using logistic regression with treatment group, geographic region and originating study as factors with non-responder imputation used for handling missing data.

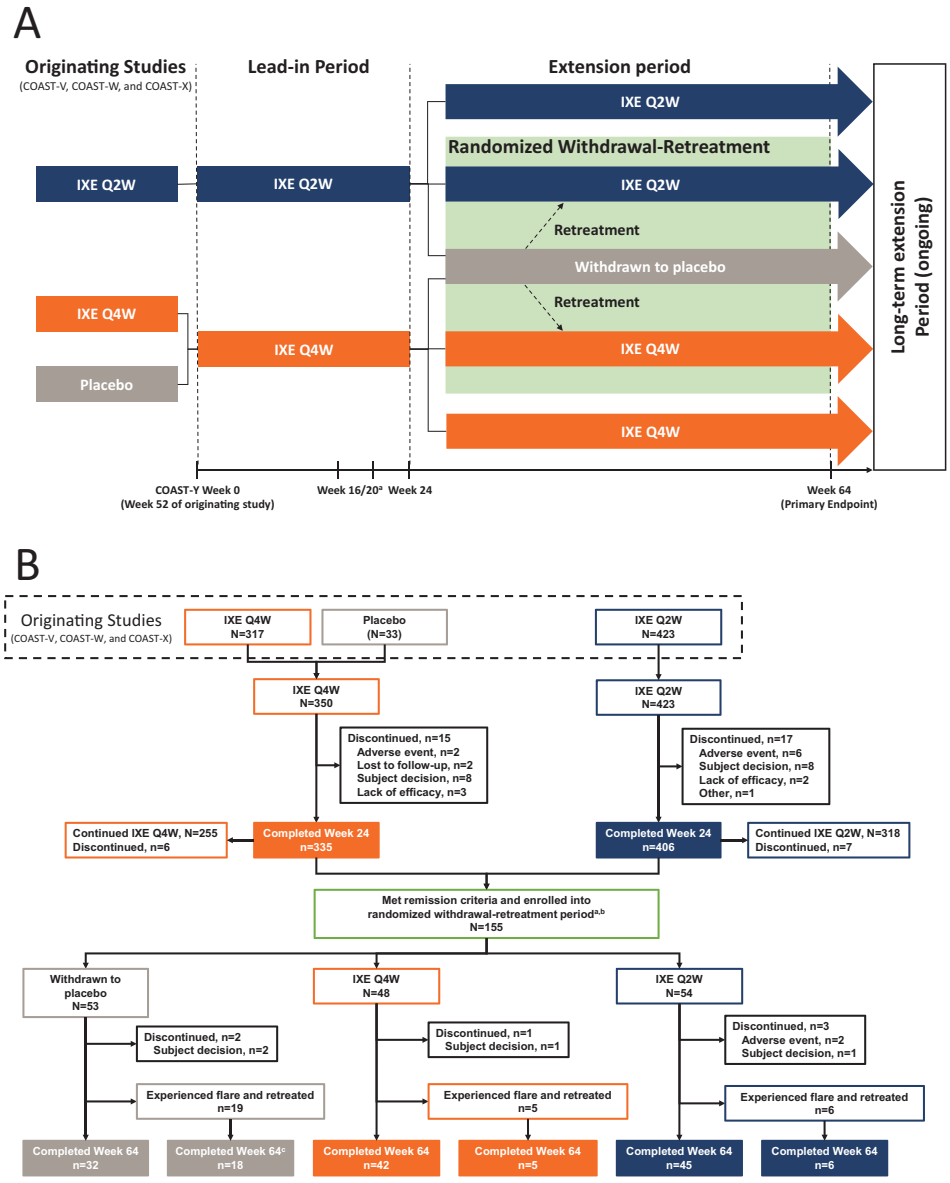


Figure 1 COAST-Y study design (A) and patient flow diagram through week 64 of COAST-Y (B). Treatment groups from the originating studies indicate the assigned treatments at the final visit (week 52) of the originating studies. In addition, patient numbers from the originating studies include only those who entered the lead-in period of COAST-Y. The 33 patients receiving placebo at week 52 of the originating studies were from COAST-X. [a]Patients were eligible for entering the randomised withdrawal-retreatment period at week 24 if they achieved an Ankylosing Spondylitis Disease Activity Score (ASDAS) of <1.3 at least once during study visits at week 16 or week 20 and <2.1 at both visits. [b]A total of 157 patients met the remission criteria at week 20, but 2 patients discontinued prior to randomisation at week 24. [c]One patient in the withdrawn to placebo group who experienced a flare and was retreated discontinued for reason of 'subject decision'. IXE, ixekizumab; Q2W, every 2 weeks; Q4W, every 4 weeks.

Continuous efficacy variables were analysed using analysis of covariance with treatment, COAST-Y week-24 value, baseline (week 0 of the originating study) value, geographical region and originating study included in the model with modified baseline observation carried forward used for handling missing data. Type III sums of squares for the least squares means were used for treatment group comparisons of continuous variables. Baseline for efficacy and health outcomes analyses was defined as the last available value before the first dose of study treatment from the originating study and, in most cases, was the value recorded at week 0 from the originating study.

The Kaplan-Meier product limit method was used to estimate the survival curves for time-to-flare and the log-rank test with strata of geographical region and originating study was used for treatment group comparisons. Flare-free patients who completed the treatment period were censored at the date of completion of the analysis period and patients who discontinued were censored at the date of the last dose or the date of the last attended visit in the treatment period (whichever was later).

Among patients who experienced a flare and were retreated with open-label IXE, the proportion of patients who achieved ASDAS LDA within 16 weeks after retreatment are reported using descriptive statistics. Post hoc analyses were conducted to evaluate potential predictors of flare. Due to a small number of patients experiencing flare with continuous IXE treatment, the two IXE treatment groups (IXE Q4W and IXE Q2W) were pooled into a combined IXE group. Additional details of analyses

Table 1 Demographics and disease characteristics for patients in COAST-Y

	Lead-in period (N=773)	Randomised withdrawal-retreatment period (N=155)			
	All entered patients N=773	Withdrawn to placebo N=53	IXE Q4W N=48	IXE Q2W N=54	Combined IXE N=102
Baseline demographics at week 0					
Age (years)	43.2 (12.3)	38.5 (12.7)	36.5 (9.7)	38.4 (10.8)	37.5 (10.3)
Sex, n (%)					
Male	551 (71%)	38 (72%)	38 (79%)	40 (74%)	78 (76%)
Race, n (%)					
White	562 (73%)	35 (66%)	31 (65%)	31 (57%)	62 (61%)
Asian	155 (20%)	13 (25%)	15 (31%)	15 (28%)	30 (29%)
Other	54 (7%)	5 (9%)	2 (4%)	8 (15%)	10 (10%)
BMI (kg/m^2)	27.5 (5.4)	25.5 (3.9)	25.9 (4.5)	25.9 (4.7)	25.9 (4.6)
axSpA symptom duration (years)	15.5 (10.3)	12.6 (9.6)	12.6 (7.5)	12.9 (8.6)	12.7 (8.0)
axSpA diagnosis duration (years)	8.3 (8.0)	6.6 (7.5)	7.1 (7.0)	7.6 (8.4)	7.4 (7.7)
HLA-B27 positive, n (%)	643 (84%)	45 (85%)	43 (90%)	49 (91%)	92 (90%)
csDMARDs use, n (%)	275 (36%)	21 (40%)	18 (38%)	24 (44%)	42 (41%)
NSAID use, n (%)	682 (88%)	50 (94%)	44 (92%)	51 (94%)	95 (93%)
Prior TNFi use, n (%)*					
0	537 (70%)	44 (83%)	39 (81%)	46 (85%)	85 (83%)
1	158 (20%)	9 (17%)	3 (6%)	8 (15%)	11 (11%)
2	78 (10%)	0	6 (13%)	0	6 (6%)
Originating study, n (%)					
COAST-V (r-axSpA, bDMARD-naïve)	291 (38%)	24 (45%)	25 (52%)	22 (41%)	47 (46%)
COAST-W (r-axSpA, TNFi-experienced)	236 (31%)	9 (17%)	9 (19%)	8 (15%)	17 (17%)
COAST-X (nr-axSpA, bDMARD-naïve)	246 (32%)	20 (38%)	14 (29%)	24 (44%)	38 (37%)
Disease characteristics at week 0					
C-reactive protein (mg/L)	4.5 (6.1)	3.5 (8.8)†	2.9 (5.8)	2.1 (2.2)	2.5 (4.3)
≤5 mg/L, n (%)	548 (71%)	45 (85%)	43 (90%)	48 (89%)	91 (89%)
>5 mg/L, n (%)	225 (29%)	8 (15%)	5 (10%)	6 (11%)	11 (11%)
ASDAS score	2.3 (0.9)	1.3 (0.5)	1.3 (0.6)	1.3 (0.5)	1.3 (0.5)
ASDAS LDA (<2.1), n (%)	344 (45%)	48 (91%)	44 (92%)	52 (96%)	96 (94%)
ASDAS ID (<1.3), n (%)	123 (16%)	36 (68%)	30 (63%)	31 (57%)	61 (60%)
BASDAI score	3.9 (2.3)	1.3 (1.1)	1.4 (1.1)	1.6 (1.2)	1.5 (1.1)
BASDAI spinal pain‡	4.2 (2.5)	1.5 (1.2)	1.7 (1.5)	1.7 (1.3)	1.7 (1.4)
BASDAI morning stiffness§	3.5 (2.4)	1.1 (1.1)	1.1 (1.1)	1.2 (1.3)	1.2 (1.2)
PatGA	4.1 (2.5)	1.6 (1.9)	1.6 (1.6)	1.6 (1.3)	1.6 (1.4)
BASFI score	3.8 (2.5)	1.1 (1.1)	1.2 (1.1)	1.2 (1.2)	1.2 (1.1)
BASMI score	3.5 (1.6)	2.7 (1.2)	2.7 (1.3)	2.7 (1.4)	2.7 (1.3)
Disease characteristics at week 24					
C-reactive protein (mg/L)	–	2.0 (2.4)	3.1 (4.0)	2.1 (1.8)	2.6 (3.1)
≤5 mg/L, n (%)	–	46 (87%)	38 (79%)	49 (91%)	87 (85%)
>5 mg/L, n (%)	–	7 (13%)	10 (21%)	5 (9%)	15 (15%)
ASDAS score	–	1.2 (0.5)	1.3 (0.5)	1.2 (0.4)	1.2 (0.5)
ASDAS LDA (<2.1), n (%)	–	50 (94%)	43 (90%)	54 (100%)	97 (95%)
ASDAS ID (<1.3), n (%)	–	37 (70%)	32 (67%)	34 (63%)	66 (65%)
BASDAI score	–	1.2 (1.1)	1.2 (1.0)	1.3 (1.1)	1.2 (1.0)
BASDAI spinal pain†	–	1.5 (1.7)	1.4 (1.5)	1.4 (1.2)	1.4 (1.4)
BASDAI morning stiffness‡	–	1.1 (1.3)	0.8 (1.0)	0.9 (0.9)	0.8 (0.9)
PatGA	–	1.3 (1.4)	1.5 (1.4)	1.3 (1.2)	1.4 (1.3)
BASFI score	–	1.1 (1.1)	1.2 (1.2)	1.0 (1.1)	1.1 (1.2)
BASMI score	–	2.5 (1.3)	2.7 (1.3)	2.8 (1.4)	2.8 (1.3)

Data are presented as mean (SD), unless otherwise specified.
*Excludes adalimumab taken as study drug in COAST-V.
†One patient in the withdrawn to placebo group had a high CRP of 61.5 mg/L at week 0, resulting in an increased mean CRP for this treatment group (maximum CRP level was 32.3 for IXE Q4W and 12.3 for IXE Q2W).
‡BASDAI Question 2.
§Mean of BASDAI Questions 5 and 6.
ASDAS, Ankylosing Spondylitis Disease Activity Score; axSpA, axial spondyloarthritis; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; BASMI, Bath Ankylosing Spondylitis Metrology Index; bDMARD, biologic disease-modifying antirheumatic drug; BMI, body mass index; csDMARD, conventional synthetic disease-modifying antirheumatic drug; HLA-B27, human leucocyte antigen B27; IXE, ixekizumab; nr-axSpA, non-radiographic axial spondyloarthritis; NSAID, non-steroidal anti-inflammatory drug; PatGA, Patient Global Assessment of Disease Activity; Q2W, every 2 weeks; Q4W, every 4 weeks; r-axSpA, radiographic axial spondyloarthritis; TNFi, tumour necrosis factor inhibitor.

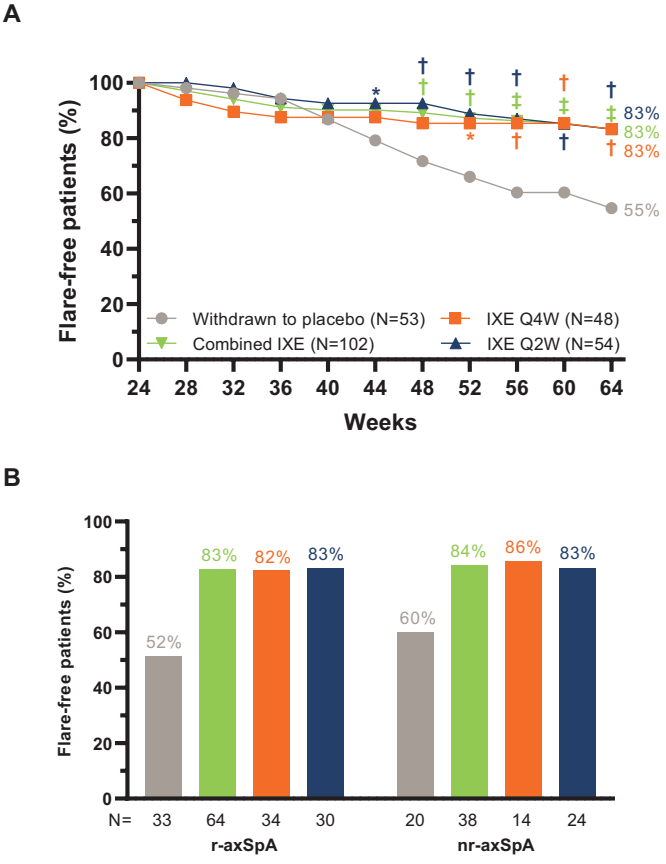


Figure 2 (A) Proportion of flare-free patients through week 64. P value vs withdrawn to placebo: *p<0.05, †p<0.01, ‡p<0.001. (B) Proportion of flare-free patients at week 64 in patient subgroups with radiographic axial spondyloarthritis (r-axSpA) and non-radiographic axial spondyloarthritis (nr-axSpA).

of the flare population with retreatment and for predictors of flare are described in the online supplemental appendix.

Safety analyses were conducted on the randomised withdrawal safety population, defined as all patients who were randomly assigned in the RWRP at week 24 and received at least one dose of study treatment after randomisation. Safety data are summarised from week 24 to week 64. Data after retreatment due to flare were excluded. Baseline was defined as the last non-missing assessment prior to the first injection of study treatment in the RWRP.

Patient and public involvement

Patients were not involved in the design or conduct of the study, development of outcomes or dissemination of study results.

RESULTS

Patients

Of 773 enrolled patients, 741 completed the 24-week lead-in period and 155 entered the RWRP (figure 1B). At week 24, patients in the RW ITT population had received up to 76 weeks of treatment with IXE and 93.5% (145/155) had received at least 52 weeks of IXE treatment.

Baseline demographics and disease characteristics in the RW ITT population were well balanced across treatment arms (table 1). Mean (SD) age and symptom duration were 37.9 (11.1) and 12.7 (8.6) years, respectively. Most (n=97, 63%) patients had r-axSpA and 37% (n=58) had nr-axSpA. Most patients (n=129, 83%) were bDMARD-naïve and 17% (n=26) had prior failure (inadequate response or intolerance) to one or two TNFi. Compared with the overall enrolled patient population at week 0 of COAST-Y, patients in the RW ITT population had lower disease activity (CRP, ASDAS, BASDAI, and Patient Global Assessment of Disease Activity) and better function and mobility (BASFI and Bath Ankylosing Spondylitis Metrology Index) at week 24; patients in the RW ITT population were also more likely to be younger, bDMARD-naïve and had shorter symptom duration.

Maintenance of disease control when continuing versus withdrawing ixekizumab

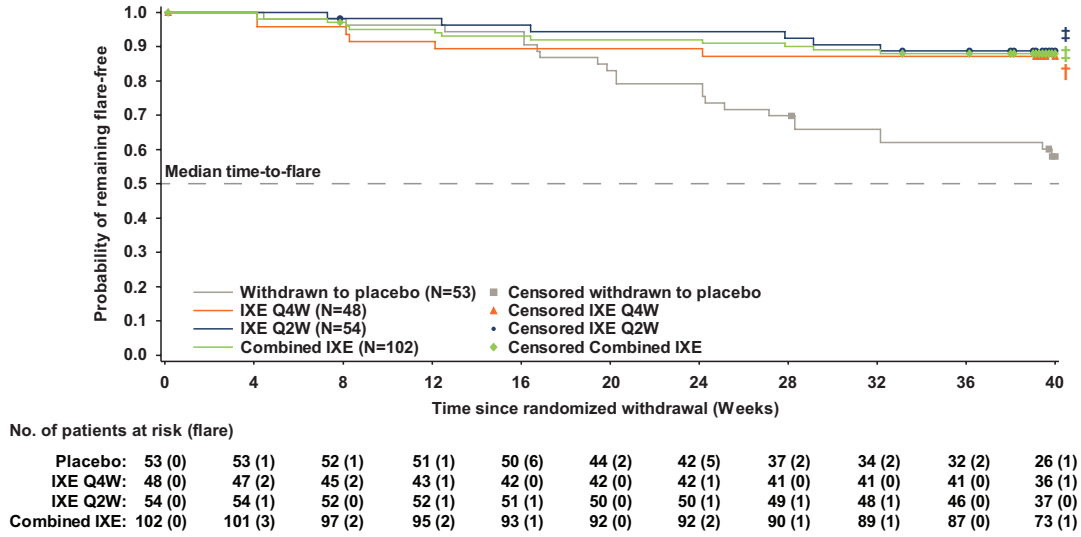
The primary and all major secondary objectives were achieved at week 64. During the RWRP, 83.3% of patients (n=85, p<0.001) in the combined IXE treatment group (IXE Q4W: 83.3%, n=40, p=0.003; IXE Q2W 83.3%, n=45, p=0.001) remained flare-free versus 54.7% (n=29) in patients who withdrew to placebo (figure 2A, table 2). The proportion of flare-free patients was similar between patient subgroups with r-axSpA and nr-axSpA (figure 2B). The proportion of flare-free rates in additional patient subgroups are presented in online supplemental table 1.

Continuing IXE treatment significantly delayed time-to-flare versus withdrawal to placebo for the combined IXE (p<0.001), IXE Q4W (p=0.004) and IXE Q2W (p<0.001)

Table 2 Summary of efficacy outcomes at week 64 in the randomised withdrawal intent-to-treat population

	Withdrawn to placebo N=53	IXE Q4W N=48			IXE Q2W N=54			Combined IXE N=102		
	Response n (%)	Response n (%)	Difference vs placebo (95% CI)	P value vs placebo	Response n (%)	Difference vs placebo (95% CI)	P value vs placebo	Response n (%)	Difference vs placebo (95% CI)	P value vs placebo
Flare-free patients*	29 (54.7%)	40 (83.3%)	28.6%(11.6% to 45.7%)	0.003	45 (83.3%)	28.6% (11.9% to 45.3%)	0.001	85 (83.3%)	28.6% (13.4% to 43.8%)	<0.001
Patients without clinically important worsening (ASDAS worsening ≥0.9 per ASAS definition)†	16 (30.2%)	35 (72.9%)	42.7% (25.1% to 60.4%)	<0.001	40 (74.1%)	43.9% (26.9% to 60.9%)	<0.001	75 (73.5%)	43.3% (28.3% to 58.4%)	<0.001
ASDAS										
ASDAS LDA (<2.1)	24 (45.3%)	40 (83.3%)	38.1% (21.0% to 55.1%)	<0.001	44 (81.5%)	36.2% (19.3% to 53.1%)	<0.001	84 (82.4%)	37.1% (21.8% to 52.4%)	<0.001
ASDAS ID (<1.3)	13 (24.5%)	29 (60.4%)	35.9% (17.8% to 53.9%)	<0.001	29 (53.7%)	29.2% (11.5% to 46.8%)	0.003	58 (56.9%)	32.3% (17.3% to 47.4%)	<0.001

*Flare was defined as an ASDAS≥2.1 at two consecutive visits or an ASDAS>3.5 at any visit.
†Assessment of ASDAS worsening of ≥0.9 was conducted as a post hoc analysis and was not the prespecified definition of flare nor a criterion for retreatment after flare. Six patients (IXE Q4W: n=4, IXE Q2W: n=1, and withdrawn to placebo: n=1) were censored due to retreatment after meeting the prespecified definition of flare. As a result, response is slightly underestimated using non-responder imputation.
ASAS, Assessment of Spondyloarthritis International Society criteria; ASDAS, Ankylosing Spondylitis Disease Activity Score; ID, inactive disease; IXE, ixekizumab; LDA, low disease activity; Q2W, every 2 weeks; Q4W, every 4 weeks.



No. of patients at risk (flare)

Placebo:	53 (0)	53 (1)	52 (1)	51 (1)	50 (6)	44 (2)	42 (5)	37 (2)	34 (2)	32 (2)	26 (1)
IXE Q4W:	48 (0)	47 (2)	45 (2)	43 (1)	42 (0)	42 (0)	42 (1)	41 (0)	41 (0)	41 (0)	36 (1)
IXE Q2W:	54 (0)	54 (1)	52 (0)	52 (1)	51 (1)	50 (0)	50 (1)	49 (1)	48 (1)	46 (0)	37 (0)
Combined IXE:	102 (0)	101 (3)	97 (2)	95 (2)	93 (1)	92 (0)	92 (2)	90 (1)	89 (1)	87 (0)	73 (1)

Figure 3 Time-to-flare. P value vs withdrawn to placebo: †p<0.01, ‡p<0.001. IXE, ixekizumab; Q2W, every 2 weeks; Q4W, every 4 weeks.

groups (figure 3). Separation between the continuous IXE and withdrawn to placebo groups first occurred 20 weeks after withdrawal from IXE treatment.

In post hoc analyses, the proportion of patients who did not experience a clinically important worsening (ASDAS worsening ≥0.9) since week 24 was significantly greater in the IXE groups versus patients who withdrew to placebo (table 2).

Predictors of flare

Post hoc analysis for the pooled RW ITT population was conducted to identify patient characteristics associated with flare, which are presented in online supplemental tables 2-4. Multivariate model analysis identified IXE withdrawal, non-normal body mass index (BMI) (non-normal BMI: <18.5 or ≥25 kg/m^2), antidrug antibody positive status at any time between week 0 of the originating study and week 24 of COAST-Y, higher CRP level at baseline of the originating study, and larger ASDAS area under the curve as being associated with flare (online supplemental table 3). In addition, when the interaction of treatment by the potential predictors of flare was examined, IXE withdrawal, non-normal BMI and higher CRP at baseline of the originating study were identified as predictors of flare (online supplemental table 4). A significant interaction of IXE withdrawal by BASDAI pain score at week 24 was identified, indicating that higher BASDAI pain score at week 24 was significantly associated with flare in patients who continued IXE treatment; this association was not significant in patients who withdrew to placebo.

Efficacy following retreatment with ixekizumab

The mean (SD) ASDAS at the time of flare was 2.9 (1.1) for IXE Q4W, 2.8 (0.6) for IXE Q2W and 3.5 (0.9) for patients who withdrew to placebo. In addition, a greater proportion of patients who withdrew to placebo (48%) had ASDAS very high disease activity (>3.5) than patients who continued IXE treatment (IXE Q4W: 29%, IXE Q2W: 17%) (online supplemental table 5). Among patients who flared and received at least 16 weeks of retreatment with open-label IXE, ASDAS LDA and ASDAS ID were recaptured within 16 weeks of retreatment for 93% (n=14/15) and 44% (n=8/18) of those who had withdrawn to placebo, respectively; 50% (n=2/4) of those who had continued IXE recaptured ASDAS LDA and 30% (3/10) recaptured ASDAS ID within 16 weeks of retreatment.

Safety

TEAEs were reported in 42.6% (IXE Q4W), 44.4% (IXE Q2W) and 52.8% (withdrawn to placebo) of patients (table 3). Two patients (IXE Q2W) discontinued the study due to AEs. SAEs were reported in two (4.3%) patients in the IXE Q4W group (benign ovarian germ cell teratoma and compression fracture), two (3.7%) patients in the IXE Q2W group (chronic tonsillitis and myelopathy in one patient and *Clostridium difficile* colitis in another) and one (1.9%) patient who withdrew to placebo (soft tissue inflammation). Only one SAE (*C. difficile* colitis) resulted in discontinuation. There were no deaths and no reports of reactivation of tuberculosis, inflammatory bowel disease, major adverse cardiovascular events (MACEs) or malignancy.

DISCUSSION

Continued IXE treatment resulted in significantly lower occurrence of flare and significantly delayed time-to-flare versus treatment withdrawal among patients with axSpA who achieved remission with IXE treatment. Most patients remained flare-free for as long as 20 weeks after IXE withdrawal. Flare-free response was similar between IXE regimens and between patients with r-axSpA and nr-axSpA.

Large randomised withdrawal studies have evaluated the effects of withdrawal or tapering of TNFi in patients with axSpA, including the ABILITY-3 study of adalimumab and the C-OPTIMISE study of certolizumab pegol.[6–9] COAST-Y is the first study to assess the effects of withdrawal of an IL-17A antagonist in patients who achieved axSpA remission. There are several differences in the study design and patient populations between COAST-Y, ABILITY-3 and C-OPTIMISE. COAST-Y included both bDMARD-naïve and TNFi-experienced patients across the axSpA spectrum with a long (12.7 years) mean symptom duration. ABILITY-3 only enrolled bDMARD-naïve patients with nr-axSpA and a mean symptom duration of 6.7 years, whereas C-OPTIMISE enrolled patients across the axSpA spectrum with a short (3.1–3.8 years) mean symptom duration.[6 7] At the time of randomised withdrawal, patients in COAST-Y had up to 76 weeks of treatment versus 28 weeks in ABILITY-3 and 48 weeks in C-OPTIMISE. Additional differences include the length of the randomised withdrawal periods, eligibility criteria for entry into the RWRP and definitions for flares.

Table 3 Summary of safety in the randomised withdrawal safety population* (weeks 24–64)

	Withdrawn to placebo N=53	IXE Q4W N=47	IXE Q2W N=54	Combined IXE N=101
TEAE	28 (52.8%)	20 (42.6%)	24 (44.4%)	44 (43.6%)
Mild	14 (26.4%)	13 (27.7%)	11 (20.4%)	24 (23.8%)
Moderate	9 (17.0%)	4 (8.5%)	13 (24.1%)	17 (16.8%)
Severe	5 (9.4%)	3 (6.4%)	0	3 (3.0%)
Serious AE	1 (1.9%)	2 (4.3%)	2 (3.7%)	4 (4.0%)
Discontinuation due to AE	0	0	2 (3.7%)	2 (2.0%)
Death	0	0	0	0
TEAEs of special interest				
Infections	18 (34.0%)	8 (17.0%)	13 (24.1%)	21 (20.8%)
Serious infections	0	0	2 (3.7%)	2 (2.0%)
Opportunistic infections	0	0	0	0
Candidiasis	0	0	0	0
Injection-site reactions	0	1 (2.1%)	3 (5.6%)	4 (4.0%)
IBD (adjudicated)†	0	0	0	0
Anterior uveitis	3 (5.7%)	2 (4.2%)	3 (5.6%)	5 (4.9%)
Allergic reactions/hypersensitivities‡	3 (5.7%)	0	2 (3.7%)	2 (2.0%)
Cytopenia	0	1 (2.1)	0	1 (1.0%)
Hepatic events	2 (3.8%)	2 (4.3%)	1 (1.9%)	3 (3.0%)
Adjudicated cerebrocardiovascular events	1 (1.9%)	0	0	0
MACE	0	0	0	0
Malignancies	0	0	0	0
Depression	0	1 (2.1%)	0	1 (1.0%)

Data are presented as n (%).
*Includes all randomly assigned patients who entered the randomised withdrawal-retreatment period and received at least one dose of study treatment after randomisation in the randomised withdrawal-retreatment period. Data after retreatment were excluded.
†Includes adjudicated Crohn's disease and ulcerative colitis. Events of suspected IBD were confirmed by adjudication by an external clinical events committee with expertise in IBD. EPIdemiologique des Maladies de l'Appareil Digestif (EPIMAD) criteria for adjudication of suspected IBD define 'probable' and 'definite' classifications as confirmed cases.
‡No anaphylaxis was reported.
AE, adverse event; IBD, inflammatory bowel disease; IXE, ixekizumab; MACE, major adverse cardiovascular event; Q2W, every 2 weeks; Q4W, every 4 weeks; TEAE, treatment-emergent adverse event.

The above methodological differences limit the comparison of results across studies; however, there are several notable similarities and differences in results. ABILITY-3 and C-OPTIMISE showed that complete withdrawal of adalimumab or certolizumab pegol, respectively, led to significantly more flares compared with continuous treatment.[6 7] Similarly, COAST-Y results suggest continuous treatment with IXE is important to maintain optimal disease control. The proportion of flare-free patients continuing IXE in COAST-Y (83.3%, all treatment groups) was similar to those seen for the certolizumab pegol 200 mg Q2W (83.7%) and 200 mg Q4W (79.0%) dosing regimens from C-OPTIMISE.[6] In ABILITY-3, a slightly lower proportion of patients (70.0%) remained flare-free.[7]

Interestingly, 54.7% of patients who withdrew to placebo in COAST-Y remained flare-free during the RWRP, which was greater than observed in ABILITY-3 (47%) and C-OPTIMISE (20.2%). The first separation between the withdrawn to placebo and IXE groups in time-to-flare was observed at approximately 20 weeks after withdrawal from IXE in COAST-Y, whereas first separation occurred earlier in ABILITY-3 (12 weeks) and C-OPTIMISE (8 weeks).

Identifying predictors of flare is important to help clinicians better understand the risk of flare for patients following treatment interruption. Post hoc analyses identified multiple characteristics associated with flare including ASDAS area under the curve, suggesting that patients with less well-controlled disease over time may have been more likely to flare than those who had stable disease control. In addition, withdrawal of IXE, a higher baseline CRP and non-normal BMI (which in most cases was ≥25 kg/m^2) were identified as being associated with flare. Higher BASDAI pain score at week 24 was also associated with flare in patients who continued IXE treatment, but not in patients who withdrew to placebo. It is difficult to compare predictors between COAST-Y, ABILITY-3 and C-OPTIMISE given differences in sample size and methodology used to identify predictors.

Among patients who flared and received at least 16 weeks of retreatment with open-label IXE, 93% in the withdrawal to placebo group and 50% of those who continued IXE treatment recaptured ASDAS LDA within 16 weeks of retreatment. These findings are consistent with findings with TNFi, as most patients who flared were able to recapture disease control with retreatment.[6 7] However, the number of patients who flared and received retreatment during the first 40 weeks of the RWRP was limited. Longer-term data from this ongoing study (with up to 80 weeks of randomised withdrawal) will likely provide additional information regarding response to retreatment with IXE, as well as predictors of flare.

There were no new or unexpected safety concerns during the RWRP of COAST-Y. TEAEs were typically mild or moderate in severity and SAEs were reported in five (3.2%) patients equally spread across arms. One SAE in the IXE Q2W arm led to discontinuation. There were no deaths and no TEAEs of opportunistic infections, reactivation of tuberculosis, *Candida* infections, positively adjudicated IBD, MACE or malignancies reported.

COAST-Y provides the first randomised withdrawal data in axSpA for an IL-17A antagonist. The RWRP of COAST-Y included patients across the axSpA spectrum with and without prior TNFi failure and with symptom duration ranging from 1.9 to 44.7 years (mean of 12.7 years). Eligibility criteria for entry into the RWRP and the definition for flare used in COAST-Y are consistent with the current recommended treatment goals of achieving inactive disease, or at least low disease activity, in patients with axSpA.[5] COAST-Y is the first randomised-withdrawal study in axSpA to include an assessment of clinically important worsening in disease activity, as defined by ASAS as an increase in ASDAS of ≥0.9 point.[20] However, clinically important worsening in disease activity was not the prespecified flare definition in COAST-Y and thus was not a criterion for retreatment after flare. An additional strength of COAST-Y was the long period of active treatment of up to 76 weeks prior to randomised withdrawal (93.5% of patients had ≥52 weeks of IXE treatment), which reflects long-term sustained treatment in clinical practice before clinicians may consider treatment withdrawal for patients with stable disease control. A limitation of COAST-Y is that the study did not assess the effect of tapering treatment.

Continuing IXE treatment resulted in significantly fewer flares and significantly delayed time-to-flare compared with patients who withdrew treatment. Interestingly, 54.7% of patients who withdrew to placebo remained flare-free for up to 40 weeks of treatment withdrawal, with most patients remaining flare-free for up to 20 weeks of withdrawal from IXE. In addition, patients who withdrew to placebo appeared to have greater disease activity at the time of flare than those who continued IXE treatment. Among those patients who did flare, most recaptured an acceptable level of disease control within 16 weeks of retreatment.

Overall, these findings suggest that continuous IXE treatment is important to maintain long-term disease control for most patients. However, the long durability of treatment response following withdrawal of IXE suggests that temporary treatment interruption, such as during infection or prior to surgical procedures, is unlikely to result in flare for most patients. These results are important for clinicians when making treatment decisions regarding treatment interruption and optimising long-term management of axSpA.

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SUPPLEMENTARY METHODS

Inclusion criteria

The study population for Study COAST-Y included patients from any of the originating studies (COAST-V, COAST-W, or COAST-X), and therefore included patients with rad-axSpA and patients with nonrad-axSpA, with or without prior use of TNF inhibitors.

For most patients, Week 52 of the originating study (COAST-V, COAST-W, or COAST-X) coincided with Week 0 (Visit 1) for Study COAST-Y. Study investigator(s) reviewed patient data from Week 52 in the respective originating study to determine if the patient met all inclusion and none of the exclusion criteria to qualify for participation in Study COAST-Y. If, at Week 52 in the originating study, a patient was not able to enter Study COAST-Y (e.g., due to unresolved safety concerns), investigational product was temporarily interrupted and the patient was evaluated in the originating study for up to 12 weeks beyond Week 52 to determine whether treatment with investigational product could resume. If, in the opinion of the investigator, restarting ixekizumab did not pose an unacceptable risk, the patient could begin participation in Study COAST-Y (Visit 1 [Week 0]).

Patients were eligible to be included in the study only if they met the following criteria:

1) Have completed the final study visit in Study COAST-V, COAST-W, or COAST-X. (Note: Patients from Study COAST-X are not eligible if they permanently discontinued ixekizumab and were receiving a TNF inhibitor).
2) Must agree to use a reliable method of birth control.
    a. If the patient is male, the patient must agree to use a reliable method of birth control during the study and for at least 12 weeks following the last dose of investigational product, whichever is longer. Methods of birth control include, but are not limited to, condoms with spermicide and male sterilization.
    b. If the patient is female and is a woman of childbearing potential who tests negative for pregnancy, the patient must agree to use a reliable method of birth control or remain abstinent during the study and for at least 12 weeks following the last dose of investigational product, whichever is longer. Methods of birth control include, but are not limited to, oral contraceptives, contraceptive patch, injectable or implantable contraceptives, intrauterine device, vaginal ring, or diaphragm with contraceptive gel. (Note: Where required by regulation, a highly effective method of birth control is required. A highly effective method of birth control is defined as one that results in a low failure rate [that is, <1% per year] when used consistently and correctly, such as male sterilization, oral contraceptives, contraceptive patch, injectable or implantable contraceptives, intrauterine device, or vaginal ring).
    c. If a female patient is a woman of nonchildbearing potential she is not required to use any method of birth control. Nonchildbearing potential is defined as:
        i. Women who have had surgical sterilization (hysterectomy, bilateral oophorectomy, or tubal ligation).
        ii. Or, women who are ≥60 years of age.
        iii. Or, women ≥40 and <60 years of age who have had a cessation of menses for ≥12 months and a follicle stimulating hormone test confirming nonchildbearing potential (≥40 mIU/mL or ≥40 IU/L).

3) Have given written informed consent approved by Lilly or its designee, and the Investigational Review Board/Ethical Review Board governing the site.

Exclusion criteria

Patients were excluded from study enrollment if they met any of the following criteria:

1) Have significant uncontrolled cerebrocardiovascular (e.g., myocardial infarction, unstable angina, unstable arterial hypertension, severe heart failure, or cerebrovascular accident), respiratory, hepatic, renal, gastrointestinal, endocrine, hematologic, neuropsychiatric disorders, or abnormal laboratory values that developed during the originating ixekizumab study (COAST-V, COAST-W, or COAST-X) that, in the opinion of the investigator, pose an unacceptable risk to the patient if investigational product continues to be administered.
2) Have a known hypersensitivity to ixekizumab or any component of this investigational product.
3) Had investigational product permanently discontinued during a previous ixekizumab study.
4) Had temporary investigational product interruption at any time during or at the final study visit of the originating ixekizumab study (COAST-V, COAST-W, or COAST-X) and, in the opinion of the investigator, restarting ixekizumab poses an unacceptable risk for the patient's participation in the study.
5) Have any other condition that, in the opinion of the investigator, renders the patient unable to understand the nature, scope, and possible consequences of the study or precludes the patient from following and completing the protocol.
6) Are currently enrolled in any other clinical trial involving an investigational product or any other type of medical research judged not to be scientifically or medically compatible with this study.

Study design

Patient enrollment for COAST-Y occurred between May 9, 2017 and March 1, 2019. Patients eligible for the RWRP were assigned to treatment groups in the RWRP using a computer-generated random sequence and an interactive web-response system. Randomization was stratified by region and originating study. Patients, study site personnel, and study team members were blinded to treatment assignment during the RWRP. Patients who entered the RWRP were requested to not have any changes to concomitant medications during the RWRP except for the defined retreatment medication or changes needing to be made for an AE or safety reasons.

Patients who were not eligible for participation in the RWRP continued the ixekizumab treatment regimen received during the lead-in period through Week 64, and during the long-term extension period. During the long-term extension period, patients who were receiving IXE Q4W could have their dose escalated to IXE Q2W if the investigator determined the patient may benefit from an increase in dosing frequency to achieve adequate disease control.

During the long-term extension period, patients who participated in the randomized withdrawal-retreatment period continued receiving the treatment they were receiving at Week 64. Patients who had not experienced a flare through Week 64 and experienced a flare during the long-term extension period were retreated with the ixekizumab dosing regimen received during the lead-in period. Patients who had been retreated with ixekizumab Q4W following a flare could have their dose escalated to IXE

Q2W if they had received retreatment for at least 12 Weeks and if the investigator determined that the patient may benefit from an increase in dosing frequency to achieve adequate disease control.

Ixekizumab and matching placebo were supplied as an injectable solution in 1-mL, single-dose, prefilled, disposable manual syringes with study specific labels. Each syringe of ixekizumab was designed to deliver 80 mg ixekizumab. The syringes and contents of ixekizumab and matching placebo were visibly indistinguishable from each other.

Outcomes

ASDAS

Flare was defined as an ASDAS≥2.1 at two consecutive visits or >3.5 at any visit during the randomized withdrawal-retreatment period. The ASDAS is a composite index that assesses disease activity in axSpA.[1-3] The components of the ASDAS are total back pain as measured by the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) question 2, the patient global assessment of disease activity, peripheral pain/swelling as measured by BASDAI question 3, duration of morning stiffness as measured by BASDAI question 6, and high sensitivity C-reactive protein in mg/L.

The ASDAS CRP is calculated using the following equation: 0.121 X total back pain + 0.110 X patient global + 0.073 X peripheral pain/swelling + 0.058 X duration of morning stiffness + 0.579 X Ln(CRP+1).[4] CRP was calculated in mg/L, the range of other variables was from 0 to 10. Ln represents the natural logarithm. ASDAS and all ASDAS components were measured at each study visit.

ASDAS inactive disease and low disease activity are defined as an ASDAS<1.3 or <2.1 respectively.[5]

ASAS

The following ASAS domains were used to determine ASAS20, ASAS40, ASAS 5/6, and ASAS Partial Remission: Patient Global (Assessment of Disease Activity), Spinal Pain, Function (BASFI), Inflammation (mean of BASDAI questions 5 and 6), CRP, and Spinal mobility (lateral spinal flexion from the Bath Ankylosing Spondylitis Metrology Index [BASMI]).[6] The ASAS20, ASAS40, and ASAS Partial Remission responses were derived from the patient-reported domains of Patient Global, Spinal Pain, Function, and Inflammation. ASAS 5/6 included assessment of all 6 ASAS domains.

An ASAS20 response is defined as a ≥20% improvement and an absolute improvement from baseline (from originating study) of ≥1 units (range 0 to 10) in ≥3 of the 4 patient-reported domains and no worsening of ≥20% and ≥1 unit (range 0 to 10) in the remaining domain. The ASAS40 is defined as a ≥40% improvement and an absolute improvement from baseline (from originating study) of ≥2 units (range 0 to 10) in ≥3 of the 4 patient-reported domains without any worsening in the remaining domain.[6-8] ASAS 5/6 represents improvement of ≥20% in at least 5 of the 6 ASAS domains. An ASAS partial remission is defined as a value not above 2 units (range 0 to 10, numeric rating scale in each of the 4 patient-reported ASAS domains.

BASDAI

The BASDAI is a patient-reported assessment consisting of 6 questions that relate to 5 major symptoms relevant to axSpA, including fatigue, spinal pain, peripheral arthritis enthesitis, intensity of morning stiffness, and duration of morning stiffness.[6,9] Each question was scored on a numerical rating scale ranging from 0 to 10 with higher score representing worse disease activity. BASDAI 50 represents an improvement of ≥50% improvement from baseline in the BASDAI. BASDAI was assessed at each study visit.

Patient Global Assessment of Disease Activity

The patient is asked to the following question: "How active was your spondylitis on average during the last week?".[6] The answer is recorded on a numerical rating scale ranging from "0" (not active) to "10" (very active). The patient Global Assessment of Disease activity was assessed at each study visit.

High sensitivity C-Reactive Protein

High sensitivity C-Reactive Protein was the measure of acute phase reactant. It was measured using a high sensitivity assay at a central laboratory to assess the effect of ixekizumab on disease activity. High sensitivity CRP was assessed at each study visit.

Spinal Pain

The patient is asked to respond to the following 2 questions (on average during the last week):

1. "How much pain of your spine due to ankylosing spondylitis do you have?"
2. "How much pain of your spine due to ankylosing spondylitis do you have at night?"

The answers are recorded on an numeric rating scale and are each rated between "0" (no pain) and "10" (most severe pain). The first question was used to derive ASAS responses. Spinal pain was assessed at each study visit.

BASFI

The BASFI is a patient-reported assessment that establishes a patient's functional baseline and subsequent response to treatment.[10] To complete the BASFI, a patient is asked to rate the difficulty associated with 10 individual basic functional activities. Patients respond to each question using an NRS (range 0 to 10), with a higher score indicating worse functioning. The patient's final BASFI score is the mean of the 10 item scores completed on an NRS. The BASFI was assessed at each study visit.

BASMI

The BASMI is a combined index comprising the following 5 clinical measurements of spinal mobility in patients with axSpA: lateral spinal flexion, tragus-to-wall distance, lumbar flexion (modified Schrober), maximal intermalleolar distance, and cervical rotation.[11] Each measurement is scaled to a score of 0 to 10 depending on the result of the assessment (BASMI linear function). The average score of the 5 assessments gives the BASMI linear result.[6,12] The BASMI was assessed by a rheumatologist or health care provider who met qualifications for study assessment. The BASMI was assessed at study visits at Weeks 0, 16, 24, 40, 56, 64, 88, and 104, and at an early termination visit when applicable.

SF-36

The SF-36 is a 36-item, patient-reported measure designed to be a short, multipurpose assessment of health in the areas of physical functioning, role – physical, role - emotional, bodily pain, vitality, social functioning, mental health, and general health. The 2 overarching domains of mental well-being and physical well-being are captured by the Mental Component Summary and Physical Component Summary scores. The summary scores range from 0 to 100; higher scores indicate better levels of function and/or better health. Items are answered on Likert scales of varying lengths. The SF-36 version 2 (acute

version), which uses a 1-week recall period, was used.[13] The SF-36 was assessed at Weeks 0, 24, 40, 64, 88, and 104, and at an early termination visit when applicable.

Safety outcomes

TEAEs were any untoward medical occurrence that either occurred or worsened at any time after treatment baseline, regardless of whether it had a causal relationship with treatment. AEs of special interest included cytopenia, clinically significant hepatic events and/or significant elevations in liver function tests/enzyme elevations, infections, injection-site reactions, allergic reactions/hypersensitivities, cerebrocardiovascular events, malignancies, inflammatory bowel disease, or depression. Data on preferred terms associated with cerebrocardiovascular events were collected and were adjudicated by an external clinical events committee which included a chairman, two cardiologists, and a neurologist. Data on suspected inflammatory bowel disease, including events possibly indicative of ulcerative colitis and Crohn's disease, were collected and adjudicated by an external clinical events committee with expertise in inflammatory bowel disease.

Statistical analysis

Approximately 750 patients were predicted to enter COAST-Y after completion of the originating studies based on the 1-year retention rates from ixekizumab psoriasis studies and from a study of secukinumab in patients with r-axSpA, which had a retention rate of approximately 85%.[14] Approximately 30% of the 750 patients were estimated to be eligible for entry into the RWRP.[15] Approximately 100 patients in each IXE treatment group (Q2W and Q4W) were anticipated for randomization in a 2:1 ratio to IXE or placebo. This sample size of 200 was determined to provide over 99% power to detect a difference between the combined ixekizumab treatment group and placebo in the proportion of flare-free patients using a 2-sided Fisher's exact test at the 0.05 level, assuming the flare rates would be 10% for ixekizumab and 70% for placebo.

Descriptive statistics were summarized as observed for the flare population with retreatment, defined as all patients who were randomly assigned at Week 24, experienced a flare after randomization, and received at least one injection of IXE retreatment after flare. Patients were retreated at the next scheduled visit after they had flared. For analyses of recapture of response after flare within 16 weeks of retreatment, patients who flared but recaptured response at the next scheduled visit (i.e. patients who regained response prior to retreatment) were excluded from the analysis so that recapture of response was not incorrectly attributed to retreatment with IXE.

Post-hoc analyses were conducted to evaluate potential predictors of flare. Variables with p-values <0.2 were entered into the multivariate logistic model for stepwise selection, with a p-value of 0.1 as a criterion for removal and stay. Interaction of each of the variables of interest with ixekizumab treatment withdrawal was also evaluated in an individual logistic regression model. Variables and their corresponding interaction were entered into the multivariate logistic regression model for variables found in the stepwise selection procedure; a backward selection was used to build the final model. Results from the univariate model and final model are presented in Supplementary Tables 1, 2, and 3.

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SUPPLEMENTARY TABLES

Supplementary Table 1. Proportion of flare-free patients at Week 64 in patient subgroups.

	Withdrawn to Placebo N=53	IXE Q4W N=48	IXE Q2W N=54	Combined IXE N=102
Radiographic diagnosis				
r-axSpA	17/33 (51.5%)	28/34 (82.4%)	25/30 (83.3%)	53/64 (82.8%)
nr-axSpA	12/20 (60.0%)	12/14 (85.7%)	20/24 (83.3%)	32/38 (84.2%)
Prior TNFi experience				
No (bDMARD-naïve)	24/44 (54.5%)	33/39 (84.6%)	39/46 (84.8%)	72/85 (84.7%)
Yes (bDMARD-experienced)	5/9 (55.6%)	7/9 (77.8%)	6/8 (75.0%)	13/17 (76.5%)
Concomitant NSAID[a] use				
No	2/6 (33.3%)	8/9 (88.9%)	4/5 (80%)	12/14 (85.7%)
Yes	28/47 (59.6%)	33/39 (84.6%)	44/49 (89.8%)	77/88 (87.5%)
Concomitant csDMARDs use				
No	19/32 (59.4%)	26/30 (86.7%)	27/30 (90%)	53/60 (88.3%)
Yes	11/21 (52.4%)	15/18 (83.3%)	21/24 (87.5%)	36/42 (85.7%)

The proportion of flare-free patients is presented as the number of responders divided by the number of patients within the subgroup.
[a]Includes COX-2 inhibitors
Abbreviations: bDMARD, biologic disease-modifying anti-rheumatic drug; COX-2, cyclooxygenase 2; csDMARDs, conventional synthetic disease-modifying anti-rheumatic drug; IXE, ixekizumab; nr-axSpA, non-radiographic axial spondyloarthrits; NSAID, non-steroidal anti-inflammatory drug; Q2W, every two weeks; Q4W, every four weeks; r-axSpA, radiographic axial spondyloarthritis; TNFi, tumor necrosis factor inhibitor

Supplementary Table 2. Patient characteristics associated with flare during the randomized withdrawal-retreatment period of COAST-Y (univariate logistic regression model)

Variable	Category	Odds ratio (95% CI)	p-value
Categorical variables			
Treatment	Placebo (n=53), IXE (n=102)	4.14 (1.95 to 8.77)	<0.001
Residual inflammation by MRI at Week 24 of COAST-Y	Yes (n=55), No (n=84)	2.43 (1.14 to 5.21)	0.022
Anti-drug antibody positive at any time between Week 0 of the originating study and Week 24 of COAST-Y	Yes (n=32), No (n=123)	2.32 (1.02 to 5.28)	0.045
BMI group at Week 0 of COAST-Y	Non-normal (n=86), Normal (n=69)[a]	2.08 (0.98 to 4.42)	0.057*
Length of IXE treatment at Week 24 of COAST-Y	24-60 weeks (n=69), 76 weeks (n=86)	1.65 (0.80 to 3.39)	0.171
Geographic region	Non-Europe (n=97), Europe (n=58)	1.63 (0.76 to 3.53)	0.211
Sustained low CRP[b]	Yes (n=136), No (n=19)	0.57 (0.21 to 1.57)	0.277
Anti-drug antibody positive at Week 24 of COAST-Y	Yes (n=10), No (n=143)	1.98 (0.53 to 7.42)	0.31
CRP group at baseline of originating study	>5 mg/L (n=96), ≤5 mg/L (n=59)	1.46 (0.68 to 3.11)	0.33
HLA-B27 status at baseline of originating study	Positive (n=137), Negative (n=18)	0.69 (0.24 to 1.97)	0.483
Symptom duration group at Week 0 of COAST-Y	≥5 years (n=123), <5 years (n=32)	1.36 (0.54 to 3.45)	0.511
Age group at Week 0 of COAST-Y	≥35 years (n=88), <35 years (n=67)	1.26 (0.61 to 2.62)	0.527
CRP group at Week 24 of COAST-Y	>5 mg/L (n=22), ≤5 mg/L (n=133)	1.36 (0.51 to 3.61)	0.539
Prior TNFi experience	Yes (n=26), No (n=129)	1.29 (0.51 to 3.25)	0.585
Symptom duration group at Week 0 of COAST-Y	≥10 years (n=85), <10 years (n=70)	0.82 (0.40 to 1.68)	0.587
AxSpA classification	r-axSpA (n=97), nr-axSpA (n=58)	1.21 (0.57 to 2.56)	0.614
Concomitant DMARD use at Week 0 of COAST-Y	Yes (n=63), No (n=92)	1.20 (0.58 to 2.47)	0.621
Sex	Male (n=116), Female (n=39)	0.89 (0.39 to 2.00)	0.774
Tobacco use group	Ever used (n=63), Never used (n=92)	1.05 (0.51 to 2.16)	0.901
Tobacco use group	Current use (n=45), Former or never used (n=110)	1.02 (0.46 to 2.23)	0.969
Continuous variables			
CRP at baseline of originating study	Continuous	1.03 (1.01 to 1.04)	0.005
ASDAS at baseline of originating study	Continuous	1.63 (1.07 to 2.49)	0.024
ASDAS area under the curve[c]	Continuous	1.06 (1.01 to 1.12)	0.024*
BASFI at baseline of originating study	Continuous	1.16 (0.97 to 1.39)	0.109
BASDAI inflammation at Week 24 of COAST-Y	Continuous	1.29 (0.93 to 1.80)	0.125*
Total back pain at Week 24 of COAST-Y	Continuous	1.19 (0.94 to 1.50)	0.146*
BASDAI at Week 24 of COAST-Y	Continuous	1.26 (0.92 to 1.73)	0.154*
Total back pain at baseline of originating study	Continuous	1.17 (0.94 to 1.46)	0.166
ASDAS at Week 24 of COAST-Y	Continuous	1.67 (0.80 to 3.51)	0.174*

BASDAI at baseline of originating study	Continuous	1.17 (0.92 to 1.49)	0.213
CRP at Week 24 of COAST-Y	Continuous	1.06 (0.95 to 1.19)	0.309
BASDAI inflammation at baseline of originating study	Continuous	1.10 (0.90 to 1.35)	0.36
PatGA at baseline of originating study	Continuous	1.10 (0.89 to 1.36)	0.383
CRP area under the curve[c]	Continuous	1.00 (1.00 to 1.01)	0.411
BASFI at Week 24 of COAST-Y	Continuous	1.10 (0.82 to 1.49)	0.52*
PatGA at Week 24 of COAST-Y	Continuous	1.02 (0.78 to 1.32)	0.895

*Indicates treatment interaction p-value of <0.05

[a]Normal BMI category is defined as ≥18.5 and <25 kg/m^2. Non-normal BMI category includes underweight (<18.5 kg/m^2), overweight (≥25 and <30 kg/m^2), obese (≥30 and <40 kg/m^2), or extremely obese (≥40 kg/m^2).

[b]Sustained low CRP is defined as CRP≤10 mg/L for all visits from Week 0 to Week 24 of COAST-Y.

[c]Area under the curve for CRP and ASDAS are defined as the area under the curve across time from Week 0 to Week 24 in COAST-Y

Abbreviations: ASDAS, Ankylosing Spondylitis Disease Activity Score; axSpA, axial spondyloarthritis; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; BMI, body mass index; CI, confidence interval; CRP, C-reactive protein; DMARD, disease-modifying anti-rheumatic drug; HLA-B27, human leukocyte antigen B27; IXE, ixekizumab; MRI, magnetic resonance imaging; nr-axSpA, non-radiographic axSpA; PatGA, Patient Global Assessment of disease activity; r-axSpA, radiographic axSpA; TNFi, tumor necrosis factor inhibitor

Supplementary Table 3. Patient characteristics associated with flare during the randomized withdrawal-retreatment period of COAST-Y (multivariate model after stepwise selection)

Variable	Category	Odds ratio (95% CI)	p-value
Categorical Variables			
Treatment	Placebo, IXE	5.12 (2.18 to 12.05)	<0.001
BMI group at Week 0 of COAST-Y	Non-normal, Normal[a]	2.46 (1.03 to 5.86)	0.043
Anti-drug antibody positive status at any time between Week 0 of originating study and Week 24 of COAST-Y	Yes, No	2.63 (1.02 to 6.79)	0.046
Continuous Variables			
CRP at baseline of originating study	Continuous	1.03 (1.01 to 1.05)	0.006
ASDAS area under the curve[b]	Continuous	1.07 (1.01 to 1.14)	0.019

[a]Normal BMI category is defined as ≥18.5 and <25 kg/m^2. Non-normal BMI category includes underweight (<18.5 kg/m^2), overweight (≥25 and <30 kg/m^2), obese (≥30 and <40 kg/m^2), or extremely obese (≥40 kg/m^2).
[b]Area under the curve for ASDAS is defined as the area under the curve across time from Week 0 to Week 24 in COAST-Y
Abbreviations: ASDAS, Ankylosing Spondylitis Disease Activity Score; BMI, body mass index; CI, Confidence interval, CRP, C-reactive protein; IXE, ixekizumab.

Supplementary Table 4. Patient characteristics associated with flare during the randomized withdrawal-retreatment period of COAST-Y (final model with interaction effect)

Variable	Estimate (SE)	p-value
Intercept	-1.9620 (0.3856)	<0.0001
IXE treatment (continued IXE versus withdrawn to placebo)	-1.3937 (0.3209)	<0.0001
CRP at baseline of originating study	0.0312 (0.0101)	0.0021
Non-normal BMI group at Week 0 of COAST-Y (non-normal versus normal)[a]	0.5215 (0.2238)	0.0198
BASDAI Pain score at Week 24 of COAST-Y	0.2649 (0.1362)	0.0517
Interaction of BASDAI Pain score at Week 24 of COAST-Y with IXE treatment (continued IXE versus withdrawal to placebo)	0.3717 (0.1358)	0.0062

[a]Normal BMI category is defined as ≥18.5 and <25 kg/m^2. Non-normal BMI category includes underweight (<18.5 kg/m^2), overweight (≥25 and <30 kg/m^2), obese (≥30 and <40 kg/m^2), or extremely obese (≥40 kg/m^2).

Abbreviations: BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BMI, body mass index; CRP, C-reactive protein; IXE, ixekizumab; SE, standard error

Supplementary Table 5. Summary of efficacy outcomes at the time of flare during the randomized withdrawal-retreatment Period of COAST-Y.

	Placebo N=23	IXE Q4W N=7	IXE Q2W N=6	Combined IXE N=13
ASDAS, mean (SD)	3.5 (0.9)	2.9 (1.1)	2.8 (0.6)	2.8 (0.9)
High disease activity[a]	12 (52%)	5 (71%)	5 (83%)	10 (77%)
Very high disease activity[b]	11 (48%)	2 (29%)	1 (17%)	3 (23%)
CRP (mg/L), mean (SD)	12.2 (12.7)	6.9 (5.5)	3.6 (2.2)	5.4 (4.5)

Values are presented as n (%) unless otherwise indicated.

[a]ASDAS high disease activity is a score of ≥2.1 and ≤3.5

[b]ASDAS very high disease activity is a score of >3.5

Abbreviations: ASDAS, Ankylosing Spondylitis Disease Activity Score; CRP, C-reactive protein; IXE, ixekizumab; Q2W, every two weeks; Q4W, every four weeks; SD, standard deviation.