CLINICAL SCIENCE

Efficacy and safety of ixekizumab through 52 weeks in two phase 3, randomised, controlled clinical trials in patients with active radiographic axial spondyloarthritis (COAST-V and COAST-W)

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ABSTRACT

Objectives To investigate the efficacy and safety of ixekizumab for up to 52 weeks in two phase 3 studies of patients with active radiographic axial spondyloarthritis (r-axSpA) who were biological disease-modifying antirheumatic drug (bDMARD)-naive (COAST-V) or tumour necrosis factor inhibitor (TNFi)-experienced (COAST-W).

Methods Adults with active r-axSpA were randomised 1:1:1:1 (n=341) to 80 mg ixekizumab every 2 (IXE Q2W) or 4 weeks (IXE Q4W), placebo (PBO) or 40 mg adalimumab Q2W (ADA) in COAST-V and 1:1:1 (n=316) to IXE Q2W, IXE Q4W or PBO in COAST-W. At week 16, patients receiving ixekizumab continued their assigned treatment; patients receiving PBO or ADA were randomised 1:1 to IXE Q2W or IXE Q4W (PBO/IXE, ADA/IXE) through week 52.

Results In COAST-V, Assessment of SpondyloArthritis international Society 40 (ASAS40) responses rates (intent-to-treat population, non-responder imputation) at weeks 16 and 52 were 48% and 53% (IXE Q4W); 52% and 51% (IXE Q2W); 36% and 51% (ADA/IXE); 19% and 47% (PBO/IXE). Corresponding ASAS40 response rates in COAST-W were 25% and 34% (IXE Q4W); 31% and 31% (IXE Q2W); 14% and 39% (PBO/IXE). Both ixekizumab regimens sustained improvements in disease activity, physical function, objective markers of inflammation, QoL, health status and overall function up to 52 weeks. Safety through 52 weeks of ixekizumab was consistent with safety through 16 weeks.

Conclusion The significant efficacy demonstrated with ixekizumab at week 16 was sustained for up to 52 weeks in bDMARD-naive and TNFi-experienced patients. bDMARD-naive patients initially treated with ADA demonstrated further numerical improvements after switching to ixekizumab. Safety findings were consistent with the known safety profile of ixekizumab.

Trial registration number NCT02696785/ NCT02696798.

INTRODUCTION

Axial spondyloarthritis (axSpA) is a chronic inflammatory condition comprising non-radiographic...
axSpA and radiographic axSpA (r-axSpA). The latter, also known as ankylosing spondylitis (AS), is characterised by inflammatory back pain and radiographic evidence of damage to the sacroiliac joint. These manifestations, and peripheral musculoskeletal and extra-articular signs and symptoms, may contribute to limited mobility, progressive disability and decreased quality of life (QoL). Biological disease-modifying antirheumatic drugs (bDMARDs), including tumour necrosis factor inhibitors (TNFi) and an interleukin (IL)-17A antagonist, are recommended for managing patients with axSpA who do not respond to or tolerate non-steroidal anti-inflammatory drugs (NSAIDs). However, up to 40% of patients fail to achieve satisfactory disease control with TNFi, and treatment with TNFi may be contraindicated in other patients.

The IL-17 signalling pathway plays a key role in the pathogenesis of axSpA. Ixekizumab, a high-affinity monoclonal antibody that selectively targets IL-17A, is approved for treating active psoriatic arthritis and moderate-to-severe plaque psoriasis and has demonstrated efficacy in two phase 3 trials in patients with r-axSpA who were bDMARD-naive (COAST-V) or TNFi-experienced (prior inadequate response or intolerance to TNFi; COAST-W). In both studies, ixekizumab resulted in significantly greater improvement versus placebo (PBO) at week 16 for measures of disease activity (including the primary endpoint of Assessment of SpondyloArthritis international Society 40 response (ASAS40)), function, QoL, and spinal inflammation. Here, we evaluated the sustainability of improvements observed at week 16 for treatment of r-axSpA with ixekizumab 80 mg every 4 or 2 weeks (IXE Q4W or IXE Q2W) up to week 52 in COAST-V and COAST-W. We also evaluated the safety of ixekizumab for up to 52 weeks, with a specific focus on overall safety, including events of special interest such as injection site reactions (ISRs) and candidiasis, and extra-articular manifestations such as inflammatory bowel disease (IBD), anterior uveitis (AU) and psoriasis.

MATERIALS AND METHODS

Study design

COAST-V\(^{10}\) and COAST-W\(^{11}\) are phase 3, multicentre, randomised, double-blind, active-controlled (COAST-V only) and PBO-controlled, 52-week trials, followed by an optional 2-year extension study.

All patients provided written informed consent.

Patient and public involvement

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

Patients

Patient eligibility criteria have been described previously.\(^{10}\) Patients were to be ≥18 years of age, have an established diagnosis of r-axSpA and meet ASAS criteria (with central reading of radiographic sacroiliitis). Patients in COAST-W were required to have discontinued one or two TNFi because of intolerance or inadequate response; COAST-V only included bDMARD-naive patients.

Treatment protocol

Study procedures for COAST-V and COAST-W have been described elsewhere.\(^{10}\) Patients in COAST-V were randomised 1:1:1:1 to PBO, adalimumab 40 mg (ADA) Q2W, IXE Q2W or IXE Q4W. ADA represents an active reference group; the study was not powered to test equivalence/non-inferiority of the active treatment groups to each other, including ixekizumab versus ADA. Patients in COAST-W were randomised 1:1:1 to PBO, IXE Q2W or IXE Q4W. In both trials, patients assigned ixekizumab were further randomised 1:1 to a 160 mg or 80 mg starting dose.

Patients completing week 16 entered a dose double-blind extended treatment period (ETP; weeks 16 to 52). During this period, patients originally randomised to PBO or ADA (COAST-V only) were rerandomised 1:1 to IXE Q2W or IXE Q4W (160 mg starting dose for patients switching from PBO, 80 mg starting dose for patients switching from ADA). Patients originally randomised to IXE Q2W or IXE Q4W continued these regimens.

Assessments

Efficacy

Efficacy assessments were made at weeks 20, 24, 28, 32, 36, 44 and 52 in the ETP except where specified below.

Categorical efficacy endpoints assessed included the proportion of patients achieving ASAS40, \(^{13}\) ASAS20, ASAS partial remission, Ankylosing Spondylitis Disease Activity Score (ASDAS) \(^{14}\) low disease activity (score <2.1), ASDAS inactive disease (score <1.3), ASDAS clinically important improvement (≥1.1 change from baseline), ASDAS major improvement (≥2.0 change from baseline or reached a minimal ASDAS score of 0.6361) and ≥50% improvement in Bath Ankylosing Spondylitis Disease Activity Index (BASDAI50).\(^{15}\) Continuous endpoints included changes from baseline in ASDAS, BASDAI, Bath Ankylosing Spondylitis Functional Index (BASFI),\(^{16}\) Medical Outcomes Study Short Form 36 (SF-36) health survey Physical Component Score (PCS),\(^{17}\) ASAS Health Index (ASAS HI),\(^{18}\) \(^{19}\) Spondyloarthritis Research Consortium of Canada (SPARCC) MRI\(^{20}\) of the spine and sacroiliac joint (the latter in COAST-V only) and serum C reactive protein (CRP) concentrations. After week 16, SF-36 PCS and ASAS HI assessments were performed at weeks 36 and 52; MRI assessments were performed at week 16 in both studies and at week 52 in COAST-V only. MRI from baseline, week 16 and week 52 were read in a single campaign. Concomitant NSAID use and ASAS-NSAID\(^{21}\) scores were assessed.

Safety

Safety assessments included the evaluation of adverse events (AEs; per the Medical Dictionary for Regulatory Activities) and treatment-emergent antidrug antibodies (TE-ADAs).\(^{16}\) Cerebro-cardiovascular events and suspected IBD were adjudicated by an independent clinical event committee. All AEs were adjudicated by an external committee following EPIMAD criteria.\(^{22}\)

At each visit, patients were evaluated for any symptoms of AU; AU events were confirmed by an ophthalmologist. Psoriasis and IBD were not proactively evaluated, but new onset or flares were recorded as AEs.

Statistical analysis

Efficacy analyses through 52 weeks were performed on the intent-to-treat population (ITT; IXE Q4W, IXE Q2W), which included all patients initially randomised to ixekizumab, and the ETP population, which included all patients who received ≥1 dose of ixekizumab during the ETP. Considering the consistent performance of the IXE Q4W and IXE Q2W regimens, data for patients in the ETP who were initially randomised to PBO or ADA were analysed as single groups (PBO/IXE or ADA/IXE), regardless of which ixekizumab dose they received during the ETP. Safety analyses were performed on the ETP population and on the all ixekizumab exposure safety population (IXE Q4W, IXE Q2W), which included all patients who received ≥1 dose of ixekizumab at any time during the 52-week study period.

No between-treatment group comparisons were made for ETP data. For primary analyses of the ITT and ETP populations, the most conservative approach was followed, where missing data
were imputed using non-responder imputation (NRI) for categorical variables and modified baseline observation carried forward (mBOCF, a more stringent method of analysis than last observation carried forward) for continuous variables. For secondary analyses of ITT data, missing data were imputed using modified NRI for categorical variables and multiple imputation for continuous variables. ITT data were also analysed as observed. SF-36 PCS data are reported as t-scores, based on 2009 US general population norms.

Statistical analyses were performed using SAS V9.2 or higher (SAS Institute).

RESULTS

Patients
The majority of patients in COAST-V (309/329; 93.9%) and COAST-W (250/281; 89.0%) who entered the ETP completed week 52 (figure 1). Of the patients initially randomised to ixekizumab, 146/164 (89.0%) in COAST-V and 169/212 (79.7%) in COAST-W completed week 52. The most common reason for discontinuation was patient withdrawal (n=11; 3.3%) in COAST-V and lack of efficacy (n=11; 3.9%) in COAST-W.

Demographics and baseline clinical characteristics for the ETP populations were similar between treatment groups within each study (online supplementary table S1) and similar to those of the ITT populations. Baseline and historical peripheral/extra-articular manifestations of axSpA are summarised in online supplementary table S2.

Efficacy
Among patients continuously treated with ixekizumab, week 16 ASAS40 response rates were sustained for up to 52 weeks (figure 2, table 1). Week 52 ASAS40 response rates were 53.1% (IXE Q4W) and 50.6% (IXE Q2W) in COAST-V and 34.2% (IXE Q4W) and 30.6% (IXE Q2W) in COAST-W. Patients randomised to PBO and rerandomised to ixekizumab at week 16 (PBO/IXE) showed...
Figure 2 Proportion of patients achieving ASAS40, ASAS20 and ASDAS <2.1 responses through 52 weeks in COAST-V (A, C, E) and COAST-W (B, D, F). ITT population. Missing data were imputed using NRI. ADA represents an active reference group; the study was not powered to test equivalence or non-inferiority of the active treatment groups to each other, including ixekizumab versus ADA. *ASDAS <2.1 indicates low disease activity. ADA, adalimumab; ASAS, Assessment of SpondyloArthritis international Society; ASDAS, Ankylosing Spondylitis Disease Activity Score; bDMARD, biological disease-modifying antirheumatic drug; ITT, intent to treat; IXE Q4W, ixekizumab 80 mg every 4 weeks; IXE Q2W, ixekizumab 80 mg every 2 weeks; NRI, non-responder imputation; PBO, placebo; TNFi, tumour necrosis factor inhibitor.

Consistent with the ASAS40 findings, week 16 improvements in ASAS20 response rates were sustained for up to 52 weeks among patients continuously treated with ixekizumab in both studies (figure 2C and D). Week 16 improvements in other measures of disease activity were sustained for up to 52 weeks, including changes from baseline in ASDAS and BASDAI, and achievement of ASAS partial remission, ASDAS improvement categories (low disease activity (figure 2), inactive disease, clinically important improvement and major improvement) and BASDAI50 (table 1). Improvements in patient function at week 16 (change from baseline in BASFI) were sustained for up to 52 weeks in patients continuously treated with ixekizumab, as were improvements in measures of QoL (change from baseline in SF-36 PCS) and health functioning (change from baseline in ASAS HI) (table 1). Week 16 improvements in spinal MRI and objective inflammation were sustained for up to 52 weeks per SPARCC spine and sacroiliac joint scores (assessed beyond week 16 in COAST-V only) and changes from baseline in CRP (table 1).

In COAST-V, patients randomised to ADA showed further numerical improvements in most efficacy endpoints on switching to ixekizumab (table 2). Results from secondary analyses (online supplementary table S3 and S4) were consistent with the primary analyses (NRI and mBOCF). Concomitant NSAID and ASAS-NSAID findings are summarised in online supplementary table S5.

Safety
ETP population (weeks 16 to 52)
Overall, 201 (61.1%) patients in COAST-V and 179 (63.7%) patients in COAST-W reported treatment-emergent adverse events (TEAEs) during the ETP (table 3). Most TEAEs were of mild or moderate severity. Eight (2.4%) patients in COAST-V and 10 (3.6%) patients in COAST-W discontinued treatment because of an AE. The most common TEAEs were nasopharyngitis, ISRs and upper respiratory tract infection. Serious adverse events (SAEs) occurred in 18 (5.5%) patients in COAST-V and 9 (3.2%) patients in COAST-W; the frequency of SAEs was similar between ixekizumab regimens. The only SAE reported by more than one patient was bradycardia (n=2 patients; neither SAE
Table 1  Weeks 16* and 52 efficacy endpoints for patients treated continuously with ixekizumab: COAST-V and COAST-W (ITT population: NRI, modified baseline observation carried forward)

|                           | COAST-V (bDMARD-naive) | COAST-W (TNFi-experienced) |
|---------------------------|-------------------------|-----------------------------|
|                           | IXE Q4W (n=81)          | IXE Q2W (n=83)              | IXE Q4W (n=114) | IXE Q2W (n=98) |
| Patients achieving response, n (%) |                       |                             |                 |                  |
| NRI                       | Week 16 | Week 52 | Week 16 | Week 52 | Week 16 | Week 52 | Week 16 | Week 52 |
| ASAS40                    | 39 (48.1) | 43 (53.1) | 43 (51.8) | 42 (50.6) | 29 (25.4) | 39 (34.2) | 30 (30.6) | 30 (30.6) |
| ASAS20                    | 52 (64.2) | 53 (65.4) | 57 (68.7) | 59 (71.1) | 55 (48.2) | 60 (52.6) | 46 (46.9) | 47 (48.0) |
| ASAS partial remission    | 12 (14.8) | 22 (27.2) | 12 (14.5) | 20 (24.1) | 7 (6.1) | 13 (11.4) | 5 (5.1) | 8 (8.2) |
| ASDAS clinically important improvement | 50 (61.7) | 51 (63.0) | 50 (60.2) | 51 (61.4) | 51 (44.7) | 53 (46.5) | 48 (49.0) | 44 (44.9) |
| ASDAS major improvement   | 24 (29.6) | 30 (37.0) | 19 (22.9) | 29 (34.9) | 18 (15.8) | 27 (23.7) | 21 (21.4) | 26 (25.9) |
| ASDAS ≤<2.1 (low disease activity) | 35 (43.2) | 43 (53.1) | 35 (42.2) | 43 (51.8) | 20 (17.5) | 27 (23.7) | 16 (16.3) | 24 (24.5) |
| ASDAS ≤<1.3 (inactive disease) | 13 (16.0) | 18 (22.2) | 9 (10.8) | 16 (19.3) | 4 (3.5) | 10 (8.8) | 5 (5.1) | 4 (4.1) |
| BASDAI50                  | 34 (42.0) | 40 (49.4) | 36 (43.4) | 37 (44.6) | 25 (21.9) | 31 (27.2) | 23 (23.5) | 27 (26.6) |
| Mean change from baseline (SD) |                       |                             |                 |                  |
| mBOCF†                    | Week 16 | Week 52 | Week 16 | Week 52 | Week 16 | Week 52 | Week 16 | Week 52 |
| ASDAS                     | −1.4 (1.2) | −1.6 (1.1) | −1.4 (1.0) | −1.6 (1.0) | −1.1 (1.0) | −1.2 (1.1) | −1.2 (1.1) | −1.3 (1.2) |
| BASDAI                    | −3.0 (2.4) | −3.3 (2.5) | −2.7 (2.1) | −3.1 (2.3) | −2.1 (2.0) | −2.4 (2.4) | −2.1 (2.3) | −2.4 (2.4) |
| BASFI                     | −2.4 (2.3) | −2.8 (2.5) | −2.5 (2.2) | −2.8 (2.4) | −1.6 (2.1) | −2.1 (2.5) | −1.9 (2.3) | −2.1 (2.3) |
| SF-36 PCS‡                | 7.6 (8.4) | 8.3 (9.5) | 7.8 (7.0) | 8.1 (7.5) | 6.3 (7.5) | 6.5 (8.5) | 6.0 (7.7) | 7.1 (7.6) |
| ASAS Health Index         | −2.3 (3.3) | −2.7 (3.3) | −2.8 (3.2) | −3.3 (3.6) | −2.0 (3.1) | −2.3 (3.7) | −1.8 (3.9) | −2.5 (3.5) |
| SPARCC MRI spine score§   | −8.9 (16.2) | −8.8 (17.3) | −8.7 (16.5) | −8.5 (15.9) | −3.2 (8.3) | NA | −5.1 (11.9) | NA |
| SPARCC MRI sacroiliac joint score¶ | −3.4 (7.6) | −3.3 (8.7) | −4.1 (7.3) | −4.2 (7.5) | NA | NA | NA | NA |
| CRP, mg/L                 | −6.8 (16.7) | −9.2 (12.4) | −8.4 (15.7) | −9.6 (14.5) | −11.5 (30.1) | −10.4 (31.1) | −10.3 (19.3) | −10.0 (18.5) |

* Except for ASAS partial remission (both studies), ASDAS clinically important improvement (both studies), ASDAS major improvement (both studies), ASAS ≤<1.3 (COAST-W) and BASDAI50 (COAST-W), all week 16 data have been previously reported.10 11
† For patients who discontinued study drug because of an adverse event, the baseline observation was carried forward to the corresponding time point for evaluation. For patients discontinuing study drug for any other reason, the last non-missing observation before discontinuation was carried forward to the corresponding time point for evaluation.
‡ SF-36 PCS data are reported as t-scores, based on 2009 US general population norms.
§ Observed data only (not assessed after week 16 in COAST-W). COAST-V: week 16, n=78 (IXE Q4W) and n=74 (IXE Q2W); week 52, n=72 (IXE Q4W) and n=68 (IXE Q2W). COAST-W: week 16, n=49 (IXE Q4W) and n=45 (IXE Q2W).
¶ Observed data only (not assessed in COAST-W). COAST-V: week 16, n=78 (IXE Q4W) and n=75 (IXE Q2W); week 52, n=72 (IXE Q4W) and n=69 (IXE Q2W).
ASAS, Assessment of SpondyloArthritis International Society; ASDAS, Ankylosing Spondylitis Disease Activity Score; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; bDMARD, biological disease-modifying antirheumatic drug; CRP, C reactive protein; ITT, intent to treat; IXE Q2W, ixekizumab 80 mg every 2 weeks; IXE Q4W, ixekizumab 80 mg every 4 weeks; mBOCF, modified baseline observation carried forward; NA, not applicable; NRI, non-responder imputation; SF-36 PCS, Medical Outcomes Study 36-item Short-Form Health Survey Physical Component Score; SPARCC, Spondyloarthritis Research Consortium of Canada; TNFi, tumour necrosis factor inhibitor.
Figure 3  Proportion of patients initially randomised to PBO or ADA achieving ASAS40 responses on treatment with ixekizumab from week 16 through week 52 in COAST-V (A) and COAST-W (B). ETP population. Missing data were imputed using NRI. ADA, adalimumab; ASAS, Assessment of SpondyloArthritis international Society; bDMARD, biological disease-modifying antirheumatic drug; ETP, dose double-blind extended treatment period; IXE, ixekizumab; NRI, non-responder imputation; PBO, placebo; TNFi, tumour necrosis factor inhibitor.

Table 2  Week 16* and 52 efficacy endpoints for PBO and ADA patients rerandomised to ixekizumab at week 16: COAST-V and COAST-W (ETP population: NRI, modified baseline observation carried forward)

|                              | COAST-V (bDMARD-naive) | COAST-W (TNFi-experienced) |
|------------------------------|-------------------------|----------------------------|
|                              | PBO/IXE (n=86)          | ADA/IXE (n=86)             | PBO/IXE (n=93) |
| Patients achieving response, n (%) |                         |                            |               |
| NRI                          | Week 16                 | Week 52                    | Week 16       | Week 52       | Week 16                  | Week 52                  |
| ASAS40                       | 16 (18.6)               | 40 (46.5)                  | 31 (36.0)     | 44 (51.2)     | 13 (14.0)                | 36 (38.7)                |
| ASAS20                       | 35 (40.7)               | 58 (67.4)                  | 52 (60.5)     | 58 (67.4)     | 31 (33.3)                | 50 (53.8)                |
| ASAS partial remission       | 7 (8.1)                 | 16 (18.6)                  | 13 (15.1)     | 18 (20.9)     | 1 (1.1)                  | 9 (9.7)                  |
| ASDAS clinically important improvement | 20 (23.3)               | 55 (64.0)                  | 48 (55.8)     | 55 (64.0)     | 18 (19.4)                | 49 (52.7)                |
| ASDAS major improvement      | 4 (4.7)                 | 27 (31.4)                  | 21 (24.4)     | 28 (32.6)     | 4 (4.3)                  | 25 (26.9)                |
| ASDAS<2.1 (low disease activity) | 11 (12.8)               | 35 (40.7)                  | 33 (38.4)     | 41 (47.7)     | 5 (5.4)                  | 27 (29.0)                |
| ASDAS<1.3 (inactive disease) | 2 (2.3)                 | 14 (16.3)                  | 14 (16.3)     | 15 (17.4)     | 1 (1.1)                  | 6 (6.5)                  |
| BASDAI50                     | 15 (17.4)               | 40 (46.5)                  | 28 (32.6)     | 39 (45.3)     | 10 (10.8)                | 35 (37.6)                |
| Mean change from baseline (SD) |                         |                            |               |
| mBOCF†                       | Week 16                 | Week 52                    | Week 16       | Week 52       | Week 16                  | Week 52                  |
| ASDAS                        | −0.6 (0.8)              | −1.6 (1.0)                 | −1.3 (1.2)    | −1.5 (1.1)    | −0.2 (1.1)               | −1.4 (1.3)               |
| BASDAI                       | −1.5 (1.7)              | −2.9 (2.1)                 | −2.4 (2.3)    | −3.0 (2.3)    | −1.0 (2.1)               | −2.7 (2.6)               |
| BASFI                        | −1.3 (1.8)              | −2.4 (2.2)                 | −2.2 (2.2)    | −2.7 (2.3)    | −0.7 (2.1)               | −2.2 (2.7)               |
| SF-36 PCS§                   | 4.2 (6.3)               | 7.7 (8.0)                  | 6.6 (7.2)     | 7.7 (8.0)     | 1.0 (7.2)                | 6.2 (8.7)                |
| ASAS Health Index            | −1.4 (2.5)              | −2.5 (3.3)                 | −2.4 (3.1)    | −2.9 (3.6)    | −0.9 (3.2)               | −2.4 (3.6)               |
| SPARRC MRI spine score¶      | −1.1 (5.9)              | −8.5 (14.6)                | −12.6 (21.4)  | −13.9 (21.2)  | NA                       | NA                       |
| SPARRC MRI sacroiliac joint score¶ | 0.76 (5.4)            | −2.7 (6.2)                 | −2.8 (8.4)    | −3.0 (9.0)    | NA                       | NA                       |
| CRP, mg/L                    | −1.0 (22.9)             | −11.2 (22.3)               | −8.4 (17.3)   | −9.4 (17.0)   | 6.8 (29.9)               | −9.7 (25.8)              |

*Except for ASAS partial remission (both studies), ASDAS clinically important improvement (both studies), ASDAS major improvement (both studies), ASDAS <1.3 (COAST-W) and BASDAI50 (COAST-W), all week 16 data have been previously reported.10 11
† For patients who discontinued study drug because of an adverse event, the baseline observation was carried forward to the corresponding timepoint for evaluation. For patients discontinuing study drug for any other reason, the last non-missing observation before discontinuation was carried forward to the corresponding time point for evaluation.
§ Observed data only (not assessed after week 16 in COAST-W). COAST-V: week 16, n=81 (PBO/IXE) and n=80 (ADA/IXE); week 52, n=76 (PBO/IXE) and n=76 (ADA/IXE). COAST-W: week 16, n=49 (IXE Q4W) and n=45 (IXE Q2W).
¶ Observed data only (not assessed in COAST-W). COAST-V: week 16, n=81 (PBO/IXE) and n=80 (ADA/IXE); week 52, n=76 (PBO/IXE) and n=76 (ADA/IXE).
ADA, adalimumab; ASAS, Assessment of SpondyloArthritis international Society; ASDAS, Ankylosing Spondylitis Disease Activity Score; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; bDMARD, biological disease-modifying antirheumatic drug; CRP, C reactive protein; ETP, dose double-blind extended treatment period; mBOCF, modified baseline observation carried forward; NA, not applicable; NRI, non-responder imputation; PBO, placebo; SF-36 PCS, Medical Outcomes Study 36-item Short-Form Health Survey Physical Component Score; IXE Q2W, ixekizumab 80 mg every 2 weeks; IXE Q4W, ixekizumab 80 mg every 4 weeks; TNFi, tumour necrosis factor inhibitor.
was considered related to treatment). There were no deaths during the ETP in either study.

Malignancy (bladder cancer) was reported by one patient (ADA/IXE) in COAST-V; the event was rated severe and led to study discontinuation. Depression was reported by two patients in COAST-W (both continued treatment); there were no events of suicide or attempted suicide in the ETP (one event of suicide occurred during the placebo-controlled period in a patient (IXE Q2W) with a history of depression). There were no events of grade 3/4 neutropenia in either study.

Cerebrocardiovascular events were reported by one patient in COAST-TV and two patients in COAST-W. One patient (PBO/IXE) in COAST-W reported a major adverse cerebrocardiovascular event of acute myocardial infarction; the event was severe, resolved and did not lead to study nor treatment discontinuation. Allergic reactions/hypersensitivities were reported by 14 (4.3%) patients in COAST-V and 12 (4.3%) patients in COAST-W.

Infections were reported by 103 (31.3%) patients in COAST-V and 94 (33.5%) patients in COAST-W; most were mild or moderate in severity. Serious infections were reported by three patients (cellulitis, pneumonia and tonsillitis; all n=1 patient) in COAST-V and three patients (gastroenteritis, pneumonia and sinusitis; all n=1 patient) in COAST-W; one of these patients discontinued the study. Candida infection was reported by two patients (oesophageal candidiasis and fungal oesophagitis; both n=1 patient) in COAST-TV and two patients (oesophageal...
candidiasis and oral candidiasis; both n = 1 patient) in COAST-W (all were mild or moderate in severity); one of these patients discontinued the study. Three Candida infection events resolved and the other was resolving at the time of patient discontinuation. ISRs were reported by 42 (12.8%) patients in COAST-V and 18 (6.4%) patients in COAST-W. Most were mild or moderate in severity; two were severe. One patient discontinued study drug due to an ISR.

AU was reported by 17 patients, 6 (1.8%) in COAST-V and 11 (3.9%) in COAST-W; none were SAEs and 14 had a history of AU. One patient in COAST-W (IXE Q4W/IXE Q4W) discontinued the study because of AU.

In COAST-V, two patients (with no prior diagnosis) reported Crohn’s disease and two patients with a prior diagnosis of ulcerative colitis reported a flare (online supplementary table S6). All events were mild or moderate in severity; one patient discontinued treatment. All events, except one, were adjudicated as ‘probable’; one event of Crohn’s disease (ADA/IXE) was adjudicated as ‘definitive’. There were no events of Crohn’s disease or ulcerative colitis in COAST-W.

All ixekizumab exposure safety population (weeks 0 to 52)

During the 52-week study periods of COAST-V and COAST-W (n=641), the pooled exposure-adjusted incidence rate per 100 patient years (EAIR) of serious infections was 2.0 among patients treated with ixekizumab (table 3). Pooled EAIRs of Candida infection and grade 3/4 neutropenia were 1.0 and 0.2, respectively. Corresponding EAIRs for Crohn’s disease, ulcerative colitis and IBD not otherwise specified (NOS) were 0.8, 0.4 and 0.4, respectively (total IBD EAIR: 1.6). The EAIR for AU was 3.9; 15/20 (75%) patients had a history of AU and 14/20 (70%) patients were from COAST-W. The pooled EAIR for psoriasis was 1.0. One patient had a major adverse cerebrocardiovascular event (acute myocardial infarction) and two malignancies were reported (acute promyelocytic leukaemia and bladder cancer).

Fewer ISRs were reported with IVE Q4W (9.2%) versus IVE Q2W (17.2%). The number of patients reporting an ISR decreased over time. Specifically, 6.4%, 3.8% and 3.4% of patients on IVE Q4W and 14.3%, 8.6% and 5.2% of patients on IVE Q2W reported an ISR from weeks 0–12, weeks 12–24 and weeks 24–36, respectively. Few patients (IVE Q4W ≤1%; IVE Q2W approximately 3%) reported an ISR beyond week 36.

Treatment-emergent antidrug antibodies

TE-ADAs were detected during the 52-week study period in 23 (6.9%) patients in COAST-V and 27 (8.9%) patients in COAST-W. Most TE-ADA-positive patients had low titres (COAST-V, 18 (78%); COAST-W, 23 (85%)) and four patients (COAST-V, 1 (0.3%); COAST-W, 3 (1.0%)) were neutralising antibody positive. There were no associations between TE-ADA positivity and ASAS40 response, ISRs or allergic reaction/hyper-sensitivity events.

DISCUSSION

In COAST-V and COAST-W, the significant improvements observed at week 16 were sustained for up to 52 weeks with ixekizumab treatment as measured by ASAS40 responses and other efficacy outcomes assessing disease activity, function, subjective inflammation, QoL, health status and overall functioning. The results for IVE Q4W and IVE Q2W were similar across endpoints. ASAS40 response rates in patients rerandomised from PBO rapidly increased to levels consistent with those seen with continuous ixekizumab treatment. Patients rerandomised from ADA to ixekizumab at week 16 achieved numerically greater response rates for ASAS40 and other efficacy outcomes at week 52 than at week 16. Collectively, the data from COAST-V and COAST-W demonstrate that ixekizumab is an effective treatment in patients with active r-axSpA who are bDMARD-naive or TNFi-experienced.

In general, treatment responses were numerically smaller in TNFi-experienced (COAST-W) versus bDMARD-naive (COAST-V) patients, reflecting a more difficult to treat population with prior treatment failure and more long-standing disease.

Currently approved biological therapies for axSpA include several TNFi and one IL-17A antagonist. Although only head-to-head trials can fully assess the relative efficacy and safety of different treatments, the week 52 ASAS40 findings reported herein are consistent with those reported for TNFi in patients who were bDMARD-naive and for secukinumab in subgroups of patients who were bDMARD-naive or had previously failed TNFi treatment.

The safety profile of ixekizumab during the ETP (week 16 to 52) in both COAST-V and COAST-W is consistent with that observed during weeks 0 to 16. Discontinuation due to AEs was <4% in both studies, whereas <6% of patients reported SAEs. Most infections and ISRs were mild or moderate in severity and did not result in study discontinuation. ISRs were more frequent with IVE Q2W than IVE Q4W. Furthermore, ISRs were most frequently reported during the first 4 weeks of treatment and decreased in frequency over time. During the 52-week study period, pooled EAIRs for Crohn’s disease, ulcerative colitis, IBD NOS, Candida infection and grade 3/4 neutropenia were ≤ 1 event/100 patient-years among patients treated with ixekizumab. Among patients who reported IBD events, most had a prior diagnosis of IBD or a gastrointestinal history potentially indicative of IBD. Fewer IBD events were reported with IVE Q2W versus IVE Q4W, and there was no apparent relationship between the length of ixekizumab exposure and IBD. Previous reports have indicated that the EAIR for AU in patients with AS ranges from 2.6 to 3.5 for patients treated with TNFi. The EAIR of AU reported herein is at the upper limit of this range, primarily driven by patients from the TNFi-experienced population. All but one patient were HLA-B27 positive, with the majority having a history of AU.

An important strength of these analyses is the use of the most conservative methods of missing data imputation (NRI and mBOCF) for the primary analyses. Furthermore, as COAST-V and COAST-W exclusively enrolled bDMARD-naive and TNFi-experienced patients, respectively, both studies were fully powered for analyses in these populations. Notably, patients in COAST-W had very active disease (baseline ASDAS ≥4) and more than 30% had failed two prior TNFi. Another strength is the use of objective measures of inflammation, including MRI at week 52 (COAST-V only); to date, ixekizumab is the only IL-17A antagonist for which short-term and long-term MRI clinical trial data are available. The ETP results are limited by the lack of any placebo or active control comparators.

In conclusion, ixekizumab provided sustained and clinically meaningful improvement in the signs and symptoms of active r-axSpA for up to 52 weeks in COAST-V and COAST-W, with a high rate of completion. The safety findings were consistent with the known safety profile of ixekizumab. These findings suggest that ixekizumab could be a treatment option for axSpA in patients who are bDMARD-naive or who have had a prior inadequate response or intolerance to TNFi.
Spondyloarthritis

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Acknowledgements
These results were presented in part at the European Congress of Rheumatology 2019, Madrid, Spain (12–15 June). Medical writing assistance was provided by Luke Carey, PhD, CMP of ProScribe – Envision Pharma Group, and was funded by Eli Lilly and Company. ProScribe’s services complied with international guidelines for Good Publication Practice (GPP3). The authors would like to thank all study participants and Emily Seem, Eli Lilly and Company, for assistance with statistical analyses.

Contributors
All authors participated in the interpretation of study results, and in the drafting, critical revision and approval of the final version of the manuscript. MD, JC-CW, JS, FvdB, WPM, AD, DvdH, XL, FZ and HC contributed to the manuscript content and/or design. JC-CW, RL, WPM, AD, DvdH, FZ, XL and HC contributed to the acquisition of study results. MD, RL, JS, XL, FZ and HC contributed to the analysis of study results.

Funding
The studies described in this manuscript were sponsored by Eli Lilly and Company, which was involved in the study design, data collection, data analysis and preparation of the manuscript.

Competing interests
MD has served as a consultant and received research grants from AbbVie, Eli Lilly and Company, Pfizer and UCB Pharma. JC-CW has served as a consultant and/or speaker and has received research grants from Abbott, Bristol-Myers Squibb, Cellgene, Chugai, Eisai, Genentech, Janssen, Novartis, Pfizer, Sanofi-Aventis, TSH Taiwan and UCB Pharma. RL has served as a consultant and/or advisor and has received research grants from AbbVie, Bristol-Myers Squibb, Cellgene, Eli Lilly and Company, Janssen, Galapagos, Merck, Novartis, Pfizer, Roche and UCB Pharma. RL is the director of Rheumatology Consultancy BV, a company that was indirectly contracted by Eli Lilly and Company to perform read services for the COAST program. JS has served as a consultant and/or speaker for AbbVie, Boehringer Ingelheim, Eli Lilly and Company, Janssen, Merck, Novartis, Pfizer, Roche and UCB Pharma. XL has served as a consultant and has received research grants from AbbVie, Bristol-Myers Squibb, Cellgene, Janssen, MSD, Novartis, Pfizer, Roche and UCB Pharma. FvdB has served as a consultant and/or speaker and has received research grants from AbbVie, Bristol-Myers Squibb, Cellgene, Eli Lilly and Company, Janssen, Merck, Novartis, Pfizer, Sanofi and UCB Pharma. WPM has served as a consultant and/or received honoraria and/or research/educational grants from AbbVie, Boehringer Ingelheim, Cellgene, Eli Lilly and Company, Galapagos, Janssen, Novartis, Pfizer and UCB Pharma. When the manuscript was written, WPM has been a consultant for AbbVie, Boehringer Ingelheim, Cellgene, Eli Lilly and Company, Galapagos, Gilead, Janssen, Merck, Novartis, Pfizer, Regeneron, Roche, Sanofi, Takeda and UCB Pharma and is the Chief Medical Officer of CARE Arthritis Limited. JE has served as a consultant and/or received research grants from AbbVie, Boehringer Ingelheim, Eli Lilly and Company, Janssen, Novartis, Pfizer, Takeda and UCB Pharma. JAw has served as a consultant and/or received research grants from AbbVie, Amgen, Cellgene, Eli Lilly and Company, Novartis, Pfizer and UCB Pharma. AD has been a consultant and/or received research support from AbbVie, Bristol-Myers Squibb, Eli Lilly and Company, Glaxo Smith & Klein, Janssen, Novartis, Pfizer and UCB Pharma. AD has been a consultant and/or received research support from AbbVie, Bristol-Myers Squibb, Eli Lilly and Company, Glaxo Smith & Klein, Janssen, Novartis, Pfizer and UCB Pharma. DvdH has been a consultant for AbbVie, Amgen, Astellas, AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Cellgene, Daiichi, Eli Lilly and Company, Galapagos, Gilead, Janssen, Merck, Novartis, Pfizer, Regeneron, Roche, Sanofi, Takeda and UCB Pharma and is a Director of Imaging Rheumatology BV. TT has been a consultant and speaker for AbbVie, Astellas, Bristol-Myers Squibb, Eisai, Eli Lilly and Company, Janssen, Mitsubishi Tanabe, Novartis, Pfizer and Takeda. XL, FZ, CCB, GG and HC are current employees and shareholders of Eli Lilly and Company. LSG has been a consultant and/or received research grants/support from AbbVie, Amgen, Eli Lilly and Company, Galapagos, Janssen, Novartis, Pfizer and UCB Pharma.

Patient consent for publication Not required.

Ethics approval Trial protocols were approved by ethics review boards at each study site. Trials were performed in accordance with the ethical principles of the Declaration of Helsinki.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Lilly provides access to all individual participant data collected during the trial after the trial has been closed to patient enrolment and after primary publication acceptance, whichever is later. No expiration date of data requests is currently set once they are made available. Access is provided after a proposal has been approved by an independent review committee identified for this purpose and after receipt of a signed data sharing agreement. Data and documents, including the study protocol, statistical analysis plan, clinical study report, blank or annotated case report forms, will be provided in a secure data sharing environment for up to 2 years per proposal. For details on submitting a request, see the instructions provided at www.clinicalstudydatarequest.com.

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| Table S1 Baseline demographics and clinical characteristics: COAST-V and COAST-W (Extended Treatment Period Population) |
|--------------------------------------------------|
| **COAST-V (bDMARD-naïve)** | **COAST-W (TNFi-experienced)** |
| PBO/IXE (N=86) | ADA/IXE (N=86) | IXE Q4W/IXE Q4W (N=78) | IXE Q2W/IXE Q2W (N=79) | PBO/IXE (N=93) | IXE Q4W/IXE Q4W (N=98) | IXE Q2W/IXE Q2W (N=90) |
| Age, mean (SD), years | 42.7 (12.0) | 41.5 (11.6) | 40.8 (11.8) | 41.2 (11.4) | 47.1 (12.7) | 47.1 (13.3) | 44.5 (10.5) |
| Male sex | 71 (82.6) | 70 (81.4) | 65 (83.3) | 61 (77.2) | 77 (82.8) | 81 (82.7) | 68 (75.6) |
| Race | | | | | | | |
| White | 52 (60.5) | 56 (65.1) | 51 (65.4) | 50 (63.3) | 77 (82.8) | 78 (80.4) | 72 (80.0) |
| Asian | 28 (32.6) | 26 (30.2) | 23 (29.5) | 23 (29.1) | 11 (11.8) | 12 (12.4) | 11 (12.2) |
| Other | 6 (7.0) | 4 (4.7) | 4 (5.1) | 6 (7.6) | 5 (5.4) | 7 (7.2) | 7 (7.8) |
| Weight, mean (SD) | 79.9 (17.1) | 78.6 (17.3) | 77.8 (14.9) | 76.8 (13.9) | 85.0 (17.5) | 86.2 (20.1) | 79.0 (17.1) |
| Duration of symptoms, mean (SD), years | 16.6 (10.1) | 15.7 (9.4) | 15.8 (11.0) | 15.7 (10.9) | 20.2 (11.8) | 18.2 (11.1) | 16.6 (9.3) |
| Time since axial SpA diagnosis, mean (SD), years | 6.8 (7.6) | 7.6 (7.5) | 8.3 (9.5) | 8.2 (9.1) | 13.1 (10.7) | 9.7 (8.0) | 11.6 (8.4) |
| HLA-B27 positive | 76 (89.4) | 78 (90.7) | 72 (92.3) | 73 (92.4) | 76 (81.7) | 81 (82.7) | 73 (81.1) |
| CRP concentration (mg/L), mean (SD) | 16.0 (21.0) | 12.8 (17.9) | 12.5 (13.5) | 13.0 (15.2) | 17.2 (23.3) | 19.5 (34.1) | 17.1 (20.4) |
| CRP >5 mg/L | 60 (69.8) | 51 (59.3) | 52 (66.7) | 51 (64.6) | 60 (64.5) | 61 (62.2) | 65 (72.2) |
| ASDAS, mean (SD) | 3.9 (0.7) | 3.7 (0.9) | 3.7 (0.7) | 3.8 (0.8) | 4.1 (0.8) | 4.2 (0.8) | 4.1 (0.8) |
| BASDAI, mean (SD) | 6.8 (1.2) | 6.6 (1.5) | 6.8 (1.3) | 6.7 (1.6) | 7.3 (1.3) | 7.4 (1.3) | 7.4 (1.2) |
| BASFI, mean (SD) | 6.4 (1.9) | 6.1 (2.0) | 6.1 (1.8) | 6.3 (2.1) | 7.0 (1.7) | 7.2 (1.8) | 7.4 (1.4) |
| BASMI linear, mean (SD) | 4.5 (1.5) | 4.2 (1.6) | 3.9 (1.5) | 4.0 (1.4) | 4.9 (1.5) | 4.6 (1.5) | 4.7 (1.5) |
| Medication use | | | | | | | |
| Methotrexate | 8 (9.3) | 8 (9.3) | 9 (11.5) | 3 (3.8) | 17 (18.3) | 11 (11.2) | 9 (10.0) |
| Sulfasalazine | 23 (26.7) | 24 (27.9) | 24 (30.8) | 24 (30.4) | 13 (14.0) | 16 (16.3) | 16 (17.8) |

Supplementary material

Dougados M, et al. Ann Rheum Dis 2019; 0:1–10. doi: 10.1136/annrheumdis-2019-216118
| Oral corticosteroid | 6 (7.0) | 9 (10.5) | 12 (15.4) | 5 (6.3) | 13 (14.0) | 9 (9.2) | 11 (12.2) |
| NSAIDs             | 78 (90.7) | 80 (93.0) | 71 (91.0) | 76 (96.2) | 75 (80.6) | 75 (76.5) | 64 (71.1) |
| 1 prior TNFi       | NA       | NA       | NA       | NA       | 58 (62.4) | 62 (63.3) | 63 (70.0) |
| 2 prior TNFi       | NA       | NA       | NA       | NA       | 35 (37.6) | 36 (36.7) | 27 (30.0) |

Data are n (%) unless otherwise indicated.
ADA, adalimumab; ASDAS, Ankylosing Spondylitis Disease Activity Score; BASFI, Bath Ankylosing Spondylitis Functional Index; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASMI, Bath Ankylosing Spondylitis Metrology Index; bDMARD, biological disease-modifying antirheumatic drug; CRP, C-reactive protein; HLA, human leucocyte antigen; IXE Q4W, ixekizumab 80 mg every 4 weeks; IXE Q2W, ixekizumab 80 mg every 2 weeks; MRI, magnetic resonance imaging; NA, not applicable; NSAID, non-steroidal anti-inflammatory drug; PBO, placebo; SD, standard deviation; SpA, spondyloarthritis; TNFi, tumour necrosis factor inhibitor.
## Table S2 Baseline and historical peripheral and extra-articular manifestations of axial spondyloarthritis: COAST-V and COAST-W (ITT population)

|                     | COAST-V (bDMARD-naïve) |          | COAST-W (TNFi-experienced) |          |
|---------------------|-------------------------|----------|-----------------------------|----------|
|                     | PBO (N=87)              | ADA (N=90)| IXE Q4W (N=81)               | IXE Q2W  |
| Arthritis           |                         |          |                             |          |
| Current             | 24 (27.9)               | 21 (23.3)| 26 (32.1)                   | 20 (24.1)| 38 (36.5)               | 39 (34.2)               | 37 (37.8)               |
| Historical only     | 5 (5.8)                 | 5 (5.6)  | 3 (3.7)                     | 4 (4.8)  | 12 (11.5)               | 10 (8.8)                | 11 (11.2)               |
| Anterior uveitis    |                         |          |                             |          |
| Current             | 2 (2.3)                 | 5 (5.6)  | 1 (1.2)                     | 4 (4.8)  | 2 (1.9)                 | 4 (3.5)                 | 1 (1.0)                 |
| Historical only     | 12 (14.0)               | 14 (15.6)| 16 (19.8)                   | 17 (20.5)| 25 (24.0)               | 17 (14.9)               | 25 (25.5)               |
| Psoriasis           |                         |          |                             |          |
| Current             | 8 (9.3)                 | 5 (5.6)  | 4 (4.9)                     | 3 (3.6)  | 13 (12.5)               | 13 (11.4)               | 8 (8.2)                 |
| Historical only     | 0                      | 1 (1.1)  | 0                            | 0        | 2 (1.9)                 | 2 (1.8)                 | 1 (1.0)                 |
| Crohn's disease or ulcerative colitis |             |          |                             |          |
| Current             | 1 (1.2)                 | 1 (1.1)  | 0                            | 1 (1.2)  | 3 (2.9)                 | 2 (1.8)                 | 0                       |
| Historical only     | 1 (1.2)                 | 0        | 1 (1.2)                     | 1 (1.2)  | 0                      | 0                       | 3 (3.1)                 |
| Dactylitis          |                         |          |                             |          |
| Current             | 2 (2.3)                 | 0        | 1 (1.2)                     | 3 (3.6)  | 6 (5.8)                 | 3 (2.6)                 | 3 (3.1)                 |
| Historical only     | 0                      | 2 (2.2)  | 0                            | 0        | 0                      | 4 (3.5)                 | 1 (1.0)                 |
| Enthesitis          |                         |          |                             |          |
| Current             | 21 (24.4)               | 18 (20.0)| 21 (25.9)                   | 15 (18.1)| 33 (31.7)               | 37 (32.5)               | 30 (30.6)               |
| Historical only     | 5 (5.8)                 | 4 (4.4)  | 3 (3.7)                     | 4 (4.8)  | 8 (7.7)                 | 4 (3.5)                 | 10 (10.2)               |

Data are n (%) and are presented for patients with non-missing values.

ADA, adalimumab; bDMARD, biological disease-modifying antirheumatic drug; ITT, intent-to-treat; IXE Q4W, ixekizumab 80 mg every 4 weeks; IXE Q2W, ixekizumab 80 mg every 2 weeks; PBO, placebo; TNFi, tumour necrosis factor inhibitor.
## Table S3 Week 16 and 52 efficacy endpoints for patients treated continuously with ixekizumab: COAST-V and COAST-W (ITT: observed data)

| Patients achieving response, n (%) | COAST-V (bDMARD-naïve) | COAST-W (TNFi-experienced) |
|-----------------------------------|-------------------------|-----------------------------|
|                                   | IXE Q4W (N=81)          | IXE Q2W (N=83)              | IXE Q4W (N=114) | IXE Q2W (N=98) |
| Week 16                           | Week 52                 | Week 16                     | Week 52         | Week 16       | Week 52         |
| ASAS40                            | 39/78 (50.0)            | 43/72 (59.7)                | 43/81 (53.1)    | 42/74 (56.8)  | 29/100 (29.0)   | 39/88 (44.3)    | 30/91 (33.0)    | 30/80 (37.5)    |
| ASAS20                            | 52/78 (66.7)            | 53/72 (73.6)                | 57/81 (70.4)    | 59/74 (79.7)  | 55/100 (55.0)   | 60/88 (68.2)    | 46/91 (50.5)    | 47/80 (58.8)    |
| ASDAS clinically important improve | 50/78 (64.1)            | 51/72 (70.8)                | 50/80 (62.5)    | 51/74 (68.9)  | 51/100 (51.0)   | 53/85 (62.4)    | 48/91 (52.7)    | 44/78 (56.4)    |
| ASDAS major improvement           | 24/78 (30.8)            | 30/72 (41.7)                | 19/80 (23.8)    | 29/74 (39.2)  | 18/100 (18.0)   | 27/85 (31.8)    | 21/91 (23.1)    | 26/78 (33.3)    |
| ASDAS <2.1 (low disease activity) | 35/78 (44.9)            | 43/72 (59.7)                | 35/80 (43.8)    | 43/74 (58.1)  | 20/100 (20.0)   | 27/85 (31.8)    | 16/91 (17.6)    | 24/78 (30.8)    |
| ASDAS <1.3 (inactive disease)     | 13/78 (16.7)            | 18/72 (25.0)                | 9/80 (11.3)     | 16/74 (21.6)  | 4/100 (4.0)     | 10/85 (11.8)    | 5/91 (5.5)      | 4/78 (5.1)      |
| BASDAI50                          | 34/78 (43.6)            | 40/67 (59.7)                | 36/81 (44.4)    | 37/71 (52.1)  | 25/100 (25.0)   | 31/88 (35.2)    | 23/91 (25.3)    | 27/80 (33.8)    |
| Mean change from baseline (SD)    |                         |                             |                 |               |                 |                 |                 |                 |
| ASDAS                             | -1.5 (1.1)              | -1.8 (1.0)                  | -1.4 (0.9)      | -1.7 (1.0)    | -1.2 (1.0)      | -1.4 (1.1)      | -1.2 (1.1)      | -1.5 (1.2)      |
| BASDAI                            | -3.1 (2.4)              | -3.6 (2.3)                  | -2.7 (2.0)      | -3.3 (2.3)    | -2.3 (2.0)      | -2.9 (2.3)      | -2.1 (2.4)      | -2.8 (2.3)      |
| BASFI                             | -2.5 (2.3)              | -3.0 (2.2)                  | -2.5 (2.2)      | -3.1 (2.4)    | -1.8 (2.0)      | -2.6 (2.5)      | -2.1 (2.3)      | -2.5 (2.3)      |
| SF-36 PCS                         | 8.0 (8.2)               | 9.4 (9.0)                   | 8.0 (7.0)       | 9.0 (7.3)     | 6.8 (7.4)       | 8.0 (8.7)       | 6.3 (7.7)       | 8.2 (7.8)       |
| ASAS Health Index                 | -2.3 (3.3)              | -3.0 (3.2)                  | -2.9 (3.2)      | -3.7 (3.5)    | -2.2 (3.1)      | -3.0 (3.8)      | -1.9 (4.0)      | -2.9 (3.7)      |
| SPARCC MRI spine score            | -8.9 (16.2)             | -8.8 (17.3)                 | -8.7 (16.5)     | -8.5 (15.9)   | -3.2 (8.3)      | NA              | -5.1 (11.9)     | NA              |
| SPARCC MRI sacroiliac joint score  | -3.4 (7.6)              | -3.3 (8.7)                  | -4.1 (7.3)      | -4.2 (7.5)    | NA              | NA              | NA              | NA              |
| CRP, mg/L | -7.0 (17.0) | -9.4 (11.1) | -8.2 (15.5) | -10.2 (15.1) | -12.7 (31.7) | -10.6 (33.6) | -11.1 (19.6) | -10.4 (18.2) |

ASAS, Assessment of SpondyloArthritis international Society; ASDAS, Ankylosing Spondylitis Disease Activity Score; BASFI, Bath Ankylosing Spondylitis Functional Index; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; bDMARD, biological disease-modifying antirheumatic drug; CRP, C-reactive protein; ITT, intent-to-treat; IXE Q4W, ixekizumab 80 mg every 4 weeks; IXE Q2W, ixekizumab 80 mg every 2 weeks; MBOCF, modified baseline observation carried forward; MRI, magnetic resonance imaging; NA, not applicable; NRI, non-responder imputation; SD, standard deviation; SF-36 PCS, Medical Outcomes Study 36-item Short-Form Health Survey Physical Component Score; SPARCC, Spondyloarthritis Research Consortium of Canada; TNFi, tumour necrosis factor inhibitor.
**Table S4** Week 52 efficacy endpoints for patients treated continuously treated with ixekizumab: COAST-V and COAST-W (ITT Population: mNRI, MI)

|                      | COAST-V (bDMARD-naïve) | COAST-W (TNFi-experienced) |
|----------------------|-------------------------|----------------------------|
|                      | IXE Q4W (N=81)          | IXE Q4W (N=114)            |
| Patients achieving response, n (%) |
| mNRI*               | 45 (55.6)               | 43 (37.7)                 |
| ASAS40              | 43 (51.8)               | 31 (31.6)                 |
| ASAS20              | 56 (69.1)               | 65 (57.0)                 |
| ASDAS Clinically important improvement | 62 (74.7) | 60 (52.6) |
| ASDAS major improvement | 53 (65.4) | 65 (57.0) |
| ASDAS <2.1 (low disease activity) | 54 (65.1) | 60 (52.6) |
| ASDAS <1.3 (inactive disease) | 18 (22.2) | 10 (8.8) |
| BASDAI50            | 45 (55.6)               | 35 (30.7)                 |
| Mean change from baseline (SD) |
| MI                  |                         |                           |
| ASDAS               | -1.7 (0.1)              | -1.4 (0.1)                |
| BASDAI              | -3.4 (0.3)              | -2.6 (0.2)                |
| BASFI               | -2.9 (0.3)              | -2.3 (0.2)                |
| SF-36 PCS           | 9.0 (1.1)               | 8.0 (0.9)                 |
| ASAS Health Index   | -2.8 (0.4)              | -2.8 (0.4)                |
| CRP, mg/L           | -9.1 (1.4)              | -13.4 (3.2)               |

*Missing data for patients who discontinued because of lack of efficacy or adverse events were treated as non-response. Missing data because of any other reason were first imputed using multiple imputation for continuous component variables. Categorical variables were then derived based on the imputed data set.

ASAS: Assessment of SpondyloArthritis international Society; ASDAS, Ankylosing Spondylitis Disease Activity Score; BASFI, Bath Ankylosing Spondylitis Functional Index; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; bDMARD, biological disease-modifying anti-rheumatic drug.
antirheumatic drug; CRP, C-reactive protein; ITT, intent-to-treat; IXE Q4W, ixekizumab 80 mg every 4 weeks; IXE Q2W, ixekizumab 80 mg every 2 weeks; MI, multiple imputation; mNRI, modified non-responder imputation; NA, not applicable; SD, standard deviation; SF-36 PCS, Medical Outcomes Study 36-item Short-Form Health Survey Physical Component Score; TNFi, tumour necrosis factor inhibitor.
### Table S5 Baseline and Week 16 and 52 concomitant NSAID use and ASAS-NSAID scores: COAST-V and COAST-W
(ETP population: observed data)

|                     | COAST-V (bDMARD-naïve) | COAST-W (TNFi-experienced) |
|---------------------|-------------------------|-----------------------------|
|                     | PBO/IXE (N=86)          | ADA/IXE (N=86)              |
|                     | IXE (N=78)              | IXE Q4W (N=79)              |
|                     | IXE Q4W/IXE Q4W (N=93)  | IXE Q4W/IXE Q4W (N=98)      |
|                     | IXE Q2W/IXE Q2W (N=90)  |                             |

| Concomitant NSAID use, n (%) |                     |                     |                     |                     |                     |                     |
|-----------------------------|---------------------|---------------------|---------------------|---------------------|---------------------|---------------------|
| Baseline                    | 78/86 (90.7)        | 80/86 (93.0)        | 71/78 (91.0)        | 76/79 (96.2)        | 75/93 (80.6)        | 75/98 (76.5)        |
| Week 16                     | 79/86 (91.9)        | 80/86 (93.0)        | 70/78 (89.7)        | 76/79 (96.2)        | 74/93 (79.6)        | 74/98 (75.5)        |
| Week 52                     | 72/83 (86.7)        | 72/82 (87.8)        | 59/73 (80.8)        | 66/74 (89.2)        | 62/81 (76.5)        | 71/89 (79.8)        |

| ASAS-NSAID*, mean (SD)      |                     |                     |                     |                     |                     |                     |
|-----------------------------|---------------------|---------------------|---------------------|---------------------|---------------------|---------------------|
| Baseline                    | 83.3 (26.6)         | 81.8 (27.1)         | 75.6 (29.2)         | 84.9 (29.7)         | 82.2 (36.3)         | 80.4 (40.4)         |
| Change from baseline        | -0.9 (7.9)          | 0.5 (4.6)           | -2.1 (12.7)         | 0.3 (4.2)           | -0.7 (11.4)         | -1.5 (9.6)          |
| Week 16                     | -10.3 (27.5)        | -5.9 (20.9)         | -7.6 (25.4)         | -9.9 (27.9)         | -9.8 (34.4)         | -5.5 (19.6)         |
| Week 52                     | -2.3 (24.0)         |                     |                     |                     |                     |                     |

*Among patients who were receiving concomitant NSAIDs at baseline. COAST-V: N=78 (PBO/IXE), N=80 (ADA/IXE), N=71 (IXE Q4W/IXE Q4W), and N=76 (IXE Q2W/IXE Q2W); COAST-W: N=75 (PBO/IXE), N=75 (IXE Q4W/IXE Q4W), and N=64 (IXE Q2W/IXE Q2W).

ADA, adalimumab; ASAS, Assessment of SpondyloArthritis international Society; bDMARD, biological disease-modifying antirheumatic drug; ETP, extended treatment period; IXE Q4W, ixekizumab 80 mg every 4 weeks; IXE Q2W, ixekizumab 80 mg every 2 weeks; NSAID, nonsteroidal anti-inflammatory drug; PBO, placebo; SD, standard deviation; TNFi, tumour necrosis factor inhibitor.
Table S6 Summary of individual inflammatory bowel disease cases reported in COAST-V (bDMARD-naïve) or COAST-W (TNF-experienced) through Week 52

| Study   | Sex/Age* | AS symptom duration | Treatment group | Study period | Prior GI medical history | AE | Adjudication result | IXE exposure† | TNFi stop before baseline‡ |
|---------|----------|---------------------|----------------|--------------|--------------------------|----|---------------------|---------------|---------------------------|
| COAST-V | Male/47 years | 18 years | IXE Q2W | Week 0–16 | NSAID-induced colitis | CD | Probable | 74 days | NA |
| COAST-V | Female/26 years | 11 years | ADA/IXE Q2W | Week 16–52 | No relevant GI history | CD | Definitive | 150 days | 178 days§ (adalimumab) |
| COAST-V | Female/56 years | 37 years | IXE Q4W/IXE Q4W | Week 16–52 | UC since 2009 | IBD nos | Probable | 147 days | NA |
| COAST-V | Female/61 years | 28 years | PBO/IXE Q4W | Week 16–52 | Gastritis, peptic ulcer, appendectomy | CD | Probable | 64 days | NA |
| COAST-V | Female/54 years | 18 years | PBO/IXE Q4W | Week 16–52 | UC since 2015 | UC | Probable | 191 days | NA |
| COAST-W | Male/66 years | 25 years | PBO | Week 0–16 | UC since 1983 | UC | Probable | None | 181 days (golimumab) |
| COAST-W | Male/26 years | 6 years | IXE Q4W | Week 0–16 | Intermittent diarrhoea since 2011, anaemia (2012–2014) | IBD nos | Probable | 41 days | 205 days (certolizumab pegol) |
| COAST-W | Male/36 years | 14 years | IXE Q4W | Week 0–16 | Anal cyst and fistula (2010–NA), abdominal pain (2010–2016) | CD | Probable | 23 days | 68 days (infliximab) |
| COAST-W | Male/64 years | 45 years | IXE Q4W | Week 0–16 | UC since 2002 | UC | Probable | 1 day | 72 days (adalimumab) |

*Age at time of enrolment.
†Time of first IXE dose to time of event start in days.
‡TNFi stop before baseline: represent total days elapsed since last dose of TNFi to first dose of study drug.
§Time between last dose of ADA and first dose of IXE.
ADA, adalimumab; AE, adverse event; AS, ankylosing spondylitis; CD, Crohn's disease; GI, gastrointestinal; IBD nos, inflammatory bowel disease not otherwise specified; IXE, ixekizumab; IXE Q4W, ixekizumab 80 mg every 4 weeks; IXE Q2W, ixekizumab 80 mg every 2 weeks; NA, not applicable; PBO, placebo; TNFi, tumour necrosis factor inhibitor; UC, ulcerative colitis.