



Baseline Characteristics and Treatment Response to Ixekizumab Categorised by Sex in Radiographic and Non-radiographic Axial Spondylarthritis Through 52 Weeks: Data from Three Phase III Randomised Controlled Trials

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ABSTRACT

Objectives: Assess baseline characteristics and treatment response to ixekizumab (IXE) categorised by sex in patients with radiographic axial spondyloarthritis (r-axSpA) and non-radiographic axSpA (nr-axSpA) up to 52 weeks.

Methods: Data were analysed from three randomised controlled trials of IXE through 52 weeks. Patients fulfilled ASAS classification criteria for r-axSpA or nr-axSpA and were randomised to receive 80 mg subcutaneous

administration of IXE every 2 weeks (Q2W) or 4 weeks (Q4W), or placebo (16 weeks COAST-V/W; 52 weeks COAST-X). Baseline characteristics and treatment outcomes were assessed. Patients were categorised by sex; methods included non-responder imputation for categorical variables, and modified baseline observation carried forward for continuous efficacy variables.

Results: At presentation, female patients had higher disease burden as reflected by significantly higher spinal pain at night, fatigue scores and pain/swelling in joints other than the neck, back or hip. ASAS40 response rate with the approved label dose, IXEQ4W, was achieved in 39% of male patients with r-axSpA by week 16, and 44% by week 52. For female patients, 16.7%

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and 33.3% achieved ASAS40 at week 16 and 52, respectively. In nr-axSpA, 46% of male patients achieved ASAS40 at week 16 and 30% at week 52. In total, 23.9% of female patients achieved ASAS40 at week 16, and 30.4% at week 52.

Conclusions: This analysis demonstrates that for the axSpA disease spectrum, female patients present with higher disease burden. Following treatment with IXE, there is a higher proportion of male responders up to 16 weeks, while female patients show less robust responses for the first 16 weeks but larger responses from weeks 16 through 52.

Trial Registration Numbers: NCT02696785, NCT02696798 and NCT02757352.

Keywords: Axial spondyloarthritis; Ixekizumab; Non-radiographic; Radiographic; Sex differences

Key Summary Points

Why carry out this study?

IXE has demonstrated superior efficacy to placebo in the treatment of patients with r-axSpA (COAST-V and COAST-W) and nr-axSpA (COAST-X).

This analysis confirms previous observations that the clinical presentations and responses to therapy may differ in male and female patients.

In this analysis, we demonstrate that for r-axSpA and nr-axSpA, female patients present with higher disease burden as reflected by higher scores in fatigue, spinal pain at night and pain/swelling in joints other than the neck, back or hip.

What was learned from this study?

Our findings indicate that for r-axSpA and nr-axSpA, male and female patients respond to therapy with IXE; however, female patients experience the maximum response later in their treatment course.

Future studies looking into this topic may provide further insights to the current data.

INTRODUCTION

Axial spondyloarthritis (axSpA) is a chronic inflammatory disease of the axial skeleton and sacroiliac joints and comprises two subtypes differentiated by the presence or absence of radiographic sacroiliitis, termed radiographic (r-axSpA, also referred to as ankylosing spondylitis [AS]) and non-radiographic (nr-axSpA).

A recent systematic review highlighted variability in assessment criteria that contributes to difficulty in determining the global incidence and prevalence rates of axSpA [1]. The incidence and prevalence of axSpA in the USA is estimated to be 1.4% [2]. Many studies in AS have included low numbers of female patients, and the analyses often do not account for the potential significance of sex differences in presentation and response to therapy [3]. Historically, AS was considered a male-predominant disease, with initial studies reporting male-to-female ratio of 10:1 [4]; however, this ratio has been revised and is now estimated to be 3:1 [5]. In patients with nr-axSpA, an equal male to female distribution has repeatedly been reported [6].

There are variations in clinical presentation between the sexes. Male patients with AS are more likely to develop radiographic spinal damage, which facilitates early diagnosis, whereas female patients develop more cervical spine and peripheral joint pain and have less frequent radiographic spinal damage [7]; however in patients with nr-axSpA, female patients show higher disease activity scores compared to male patients [8, 9]. A meta-analysis including 42 studies found that age of onset does not differ between male and female patients with spondyloarthritis (SpA) [10]; however, a mean delay in diagnosis showed sex-related differences, 8.8 years (7.4–10.1) for female patients and 6.5 (5.6–7.4) for male patients [10]. This may be in part the result of sex differences in the clinical presentation of patients, and suggests how female patients are frequently more likely to be underdiagnosed [3, 11]. Female patients with axSpA typically report higher Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) scores compared to male patients, specifically greater fatigue, total back pain and a

longer duration of morning stiffness [12, 13]. Female patients also report worse quality of life and more activity impairment [14].

It has been shown for r-axSpA that male patients are more likely to be prescribed biological disease-modifying antirheumatic drugs (bDMARDs) compared to female patients who are more likely to be prescribed sulfasalazine, NSAIDs, muscle relaxants (not the standard of care), anticonvulsants, opioids and glucocorticoids [15]. Sex differences in clinical presentation may also affect a clinician's perception of disease severity and activity, and thus influence disease management [16]. Cytokine signalling through the interleukin-17 (IL-17) pathway is a key contributor to the pathogenesis of axSpA, and IL-17A inhibitors are an efficacious alternative to tumour necrosis factor inhibitor (TNFi) for patients with axSpA [17, 18]. IL-17 signature studies have shown upregulated IL-17 gene expression in male patients compared to female patients [19]. Ixekizumab (IXE) is a high-affinity IL-17A monoclonal antibody and has demonstrated efficacy for patients with both r-axSpA and nr-axSpA [20, 21]. COAST-V was the first phase III clinical study assessing treatment with IXE in patients with r-axSpA and achieved ASAS40 as a primary endpoint [20]. This manuscript explores differences in male and female patients with r-axSpA and nr-axSpA who were included in three separate clinical trials of IXE. The first two trials included patients with r-axSpA who were either bDMARD-naïve (COAST-V) or TNFi-experienced (COAST-W). The third trial included patients with nr-axSpA who were bDMARD-naïve (COAST-X).

METHODS

Study Design

COAST-V (NCT02696785), COAST-W (NCT02696798) and COAST-X (NCT02757352) were phase III, multicentre, randomised, double-blind, active-controlled (COAST-V only) and placebo (PBO)-controlled, 52-week trials, followed by an optional 2-year extension. Baseline clinical characteristics and treatment

response of patients with r-axSpA were integrated from COAST-V and COAST-W and categorised by sex. Baseline clinical characteristics and treatment response of patients with nr-axSpA from COAST-X were analysed separately and categorised by sex.

The COAST-V, COAST-W and COAST-X trials were conducted in accordance with the standards of the Declaration of Helsinki and Good Clinical Practice Guidelines (CPMP/ICH/135/95). The master ethics committee was Schulman Associates IRB, Cincinnati, OH, USA. Full listings of investigators and sites are available in previously published manuscript supplements [20, 22]. All patients gave written informed consent before trial start.

Patients and Treatment Protocol

Patient eligibility criteria have been described previously [20, 21]. Patients in COAST-V/W were aged 18 years or older, with an established diagnosis of r-axSpA, and meeting Assessment of SpondyloArthritis International Society (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-naïve patients. In COAST-V, there was an additional active-reference arm in which patients were treated with 40 mg adalimumab every 2 weeks (Q2W). For COAST-X, eligible patients were aged 18 years or older, with a physician-established axSpA diagnosis, fulfilling ASAS criteria and had a treatment history for axSpA for at least 12 weeks. Patients meeting the radiologic criterion of the modified New York criteria (according to central reading by two readers and an adjudicator in case of a discrepancy) were excluded. Patients were randomised to receive 80 mg subcutaneous administration of IXE Q2W, every 4 weeks (Q4W) or PBO. COAST-X was a 52-week, double-blind, PBO-controlled trial; however, patients could switch to open-label IXEQ2W after week 16 and at the discretion of the primary investigator [21]; patients who switched to open-label treatment were analysed as non-responders.

Assessments

In this post hoc analysis, patients were categorised by sex. The primary objective was to compare the efficacy of IXE (all dosing regimens) versus PBO at weeks 16 and 52 (COAST-X), and the response up to week 52 in COAST-V and COAST-W, as measured by the proportion of patients achieving an ASAS40 response. The major secondary objectives were to compare IXE (all dosing regimens) versus PBO at weeks 16 and 52 (COAST-X) as measured by the proportion of patients achieving at least 50% improvement in the BASDAI score from baseline, and Ankylosing Spondylitis Disease Activity Score (ASDAS) inactive disease (defined as ASDAS < 1.3), as well as the change from baseline in ASDAS Low Disease Activity (LDA) (defined as ASDAS LDA < 2.1), Bath Ankylosing Spondylitis Functional Index (BASFI), magnetic resonance imaging of the spine SPARCC score, Medical Outcomes Study 36-Item Short Form Health Survey (SF-36) physical component summary, and the ASAS Health Index. Full inclusion/exclusion criteria, treatment protocols, safety outcomes and adverse events have been published for the three trials previously.

Statistical Analysis

Descriptive baseline clinical characteristics were categorised by sex to demonstrate the difference between male and female patients. In COAST-X, patients who switched to open label after week 16 were analysed as non-responders. To examine the statistical significance of the difference in baseline, Fisher's exact test or CMH test was conducted for categorical data, and analysis of covariance (ANCOVA) or analysis of variance (ANOVA) was conducted for continuous data.

Differences in response between IXE treatment groups versus PBO were assessed at week 16 (and at week 52 for COAST-X) for post-baseline efficacy assessments. Categorical assessments used the CMH test stratified by study for each sex subgroup for the integrated study (COAST-V and COAST-W), and Fisher's exact test for COAST-X. Continuous

assessments used the LSM change from baseline and *p* value vs PBO from ANCOVA models with covariates specific to the respective studies. Missing values were imputed using last observation carried forward.

RESULTS

Baseline Characteristics by Sex

There were statistically significant differences between male and female patients at age of disease onset, with female patients of older age, for patients with r-axSpA (mean \pm SD; female patients: 30.1 ± 10.1 years, male patients: 26.5 ± 8.7 years, $p = 0.002$) and nr-axSpA (female patients: 32 ± 10.7 years, male patients: 27.9 ± 7.7 years, $p = 0.002$). Female patients also had longer symptom duration (r-axSpA: 17.8 ± 12.2 years vs 16.7 ± 10.5 years; nr-axSpA: 12.3 ± 11.3 years vs 9.5 ± 9.2 years) than male patients. High disease activity, as measured by mean total BASDAI score, was reported for both female patients (r-axSpA: 7.4 ± 1.5 ; nr-axSpA: 7.4 ± 1.4) and male patients (r-axSpA: 7.1 ± 1.4 ; nr-axSpA: 6.9 ± 1.4). This difference was statistically significant in patients with nr-axSpA ($p = 0.013$). Female patients with nr-axSpA scored higher than male patients on all six BASDAI questions, and female patients with r-axSpA scored higher on five of the six BASDAI questions (Table 1). Female patients also reported higher scores on spinal pain at night than male patients (r-axSpA: 7.8 ± 1.7 vs 7.4 ± 1.5 ; nr-axSpA: 7.6 ± 1.8 vs 7.0 ± 1.8); this was significant for both r-axSpA and nr-axSpA (COAST-V/W: $p = 0.033$; COAST-X: $p = 0.027$). C-reactive protein levels were significantly higher in male patients versus female patients in patients with r-axSpA (female patients: 11.2 ± 12.8 vs male patients: 17.4 ± 25.5 , $p = 0.030$) but similar in patients with nr-axSpA (female patients: 12.3 ± 18.5 vs male patients: 12.1 ± 17.4 , $p = 0.931$).

A higher proportion of male patients than female patients had a history of anterior uveitis for r-axSpA (23.8% vs 17.9%), and conversely, more female patients than male patients had a

history of anterior uveitis for nr-axSpA (15.2% vs 7.1%).

The proportion of patients who were human leukocyte antigen B27 positive was higher for male patients compared with female patients for r-axSpA (86.9% vs 79.5%) and nr-axSpA (76.3% vs 70.7%), but the differences were not significant.

Treatment Response by Sex

ASAS40

For IXEQ4W (approved label dose) male patients with r-axSpA, 39% ($n = 62/159$) achieved ASAS40 at week 16; this was sustained at week 52 (44%). Male patients with nr-axSpA achieved an ASAS40 response of 46% at week 16, which was significant over PBO (IXEQ4W: $n = 23/50$, 46%; PBO: $n = 8/44$, 18.2%, $p = 0.005$); at week 52, male ASAS40 response was 30%. Female patients with r-axSpA achieved an ASAS40 response of 16.7% ($n = 6/36$) at week 16, which was statistically different from PBO ($p = 0.041$); this response rose to 33.3% at week 52. Female patients with nr-axSpA achieved an ASAS40 response of 23.9% at week 16, which was not significant over PBO (IXEQ4W: $n = 11/46$, 23.9%; PBO: $12/61$, 19.7%, $p = 0.640$); however, female patients showed a significant response compared to PBO at week 52 (IXEQ4W: $n = 14/46$, 30.4%; PBO: $5/61$, 8.2%, $p = 0.004$) (Fig. 1).

ASDAS-LDA (< 2.1)

For IXEQ4W (approved label dose), the proportion of male patients with r-axSpA who achieved ASDAS-LDA (< 2.1) response was significantly greater compared to PBO at week 16 (male patients: $n = 49/159$, 30.8%; PBO: $n = 15/159$, 9.4%, $p < 0.001$). This response was not significant for PBO in female patients (IXEQ4W: $n = 6/36$, 16.7%; PBO: $n = 1/32$, 3.1%, $p = 0.110$). A higher response rate was observed for male patients with nr-axSpA versus PBO at week 16 (IXEQ4W: $n = 19/49$, 38.8%; PBO: $n = 5/44$, 11.4%, $p = 0.004$), which was sustained at week 52 (IXEQ4W: $16/49$, 32.7%; PBO: $4/44$, 9.1%, $p = 0.010$). There was no significant response compared to PBO for female patients

with nr-axSpA at week 16 (IXEQ4W: $n = 7/45$, 15.6%; PBO: $8/61$, 13.1%, $p = 0.782$), but by week 52 there was a significant response versus PBO (IXEQ4W: $n = 12/45$, 26.7%; PBO: $n = 5/61$, 8.2%, $p = 0.015$) (Fig. 2).

BASDAI

The overall BASDAI response rate in patients with r-axSpA saw a greater change from baseline response in male patients versus PBO at week 16 ([LSM \pm SE] IXEQ4W male patients [$n = 159/195$]: -2.65 ± 0.16 ; PBO: -1.35 ± 0.16 , $p < 0.001$) than female patients (IXEQ4W female patients [$n = 36/195$]: -1.86 ± 0.34 ; PBO: -0.66 ± 0.36 , $p = 0.015$) (Table 2). For BASDAI Q6 (duration of morning stiffness), female patients displayed greater change from baseline response (IXEQ4W: -2.17 ± 0.4 ; PBO: -0.90 ± 0.43 , $p = 0.030$). Significant responses were also seen in male patients compared to PBO at week 16 in spinal pain at night (IXEQ4W: -3.24 ± 0.19 ; PBO: -1.50 ± 0.19 , $p < 0.001$), BASFI (IXEQ4W: -2.21 ± 0.16 ; PBO: -1.08 ± 0.16 , $p < 0.001$) and SF-36 Physical Component Score (IXEQ4W: 7.15 ± 0.55 ; PBO: 3.06 ± 0.55 , $p < 0.001$). Significant responses varied in these measures when observed in female patients at week 16 (Table 2).

In patients with nr-axSpA, male patients showed a greater change from baseline compared to PBO at week 16 for BASDAI Q2 (spinal pain) (male patients: -2.99 ± 0.33 ; PBO: -1.61 ± 0.37 , $p = 0.006$), Q6 (duration of morning stiffness) (male patients: -2.98 ± 0.37 ; PBO: -1.34 ± 0.41 , $p = 0.003$) and BASFI (male patients: -2.40 ± 0.32 ; PBO: -1.35 ± 0.35 , $p = 0.028$). These changes were sustained at week 52 for Q6 (duration of morning stiffness) (male patients: -3.05 ± -0.38 ; PBO: -1.58 ± 0.43 , $p = 0.010$) and BASFI (male patients: -2.64 ± 0.35 ; PBO: -1.50 ± 0.39 , $p = 0.029$) with the addition of a significant change in BASDAI Q5 (morning stiffness) (male patients: -3.09 ± -0.37 ; PBO: -1.89 ± 0.41 , $p = 0.030$). No significant changes from baseline were seen for female patients with nr-axSpA at week 16. At week 52, female patients showed a greater improvement versus PBO in four out of

Table 1 Demographics and baseline clinical characteristics of patients with r-axSpA (COAST-V and COAST-W) and nr-axSpA (COAST-X) categorised by sex

Characteristic	Patients with r-axSpA (<i>N</i> = 376)			Patients with nr-axSpA (<i>N</i> = 198)		
	Male (<i>n</i> = 298)	Female (<i>n</i> = 78)	<i>p</i> value	Male (<i>n</i> = 99)	Female (<i>n</i> = 99)	<i>p</i> value
Age (years), mean (SD)	42.8 (12.0)	47.6 (12.6)	0.003*	37.0 (13.0)	43.9 (12.7)	< 0.001*
BMI, kg/m ² , mean (SD)	27.3 (5.6)	27.6 (6.1)	0.807	27.2 (4.9)	27.8 (6.2)	0.428
Age at r-axSpA or nr-axSpA onset (years), mean (SD)	26.5 (8.7)	30.1 (10.1)	0.002*	27.9 (7.7)	32.0 (10.7)	0.002*
Duration of symptoms since axSpA onset (years), mean (SD)	16.7 (10.5)	17.8 (12.2)	0.420	9.5 (9.2)	12.3 (11.3)	0.057
DMARDs use, <i>n</i> (%) ^a	93 (31.2)	23 (29.5)	0.825	42 (42.4)	40 (40.4)	0.885
HLA-B27 positive, <i>n</i> (%)	259 (86.9)	62 (79.5)	0.114	74 (76.3)	70 (70.7)	0.420
Anterior uveitis, current or historical, <i>n</i> (%)	71 (23.8)	14 (17.9)	0.273	7 (7.1)	15 (15.2)	0.112
CRP, mg/L, mean (SD)	17.4 (25.5)	11.2 (12.8)	0.030*	12.1 (17.4)	12.3 (18.5)	0.931
ASDAS, mean (SD)	4.0 (0.8)	3.9 (0.7)	0.304	3.7 (0.8)	3.9 (0.8)	0.143
ASAS-HI, mean (SD)	8.9 (3.7)	9.8 (3.7)		8.8 (3.4)	9.5 (3.5)	
BASDAI score, mean (SD)	7.1 (1.4)	7.4 (1.5)	0.179	6.9 (1.4)	7.4 (1.4)	0.013*
Fatigue/tiredness (BASDAI Q1), mean (SD)	7.4 (1.6)	7.8 (1.5)	0.036*	7.0 (1.6)	7.9 (1.5)	< 0.001*
Spinal pain score (BASDAI Q2), mean (SD)	7.9 (1.5)	8.0 (1.5)	0.682	7.5 (1.4)	7.9 (1.5)	0.029*
Pain/swelling in joints other than neck, back, or hip (BASDAI Q3), mean (SD)	6.5 (2.1)	6.9 (2.2)	0.129	6.6 (2.3)	7.2 (1.9)	0.039*
Discomfort when tender to the touch/pressure (BASDAI Q4), mean (SD)	6.8 (1.8)	7.0 (1.9)	0.339	6.6 (1.9)	6.8 (1.8)	0.404
Morning stiffness (BASDAI Q5), mean (SD)	7.5 (1.6)	7.7 (1.8)	0.504	7.3 (1.7)	7.7 (1.9)	0.137
Duration of morning stiffness (BASDAI Q6), mean (SD)	6.5 (2.3)	6.5 (2.8)	0.944	6.3 (2.3)	6.6 (2.5)	0.392
Spinal pain at night NRS, mean (SD)	7.4 (1.5)	7.8 (1.7)	0.033*	7.0 (1.8)	7.6 (1.8)	0.027*
Spinal pain NRS, mean (SD)	7.5 (1.5)	7.8 (1.6)	0.291	7.2 (1.5)	7.5 (1.8)	0.186
Fatigue Severity NRS, mean (SD)	7.1 (1.7)	7.3 (2.0)	0.300	7.0 (1.6)	7.4 (1.7)	0.091
BASFI score, mean (SD)	6.8 (1.8)	7.0 (2.0)	0.466	6.2 (1.8)	6.7 (2.1)	0.108
SF-36 PCS score, mean (SD)	30.9 (8.3)	28.9 (8.2)	0.075	33.1 (7.7)	32.1 (7.2)	0.348

Table 1 continued

Characteristic	Patients with r-axSpA (N = 376)			Patients with nr-axSpA (N = 198)		
	Male (n = 298)	Female (n = 78)	p value	Male (n = 99)	Female (n = 99)	p value
SF36 MCS score, mean (SD)	47.2 (12.7)	44.4 (12.2)	0.087	48.5 (11.3)	46.4 (13.2)	0.231

p value is based on CMH test stratified by study for categorical data and ANCOVA for continuous data with sex and study as independent factors. *p value is obtained to assess the difference in male and female

ANCOVA analysis of covariance, ASDAS Ankylosing Spondylitis Disease Activity Score, BASDAI Bath Ankylosing Spondylitis Disease Activity Index, BASFI Bath Ankylosing Spondylitis Functional Index, BMI body mass index, CRP C-reactive protein, DMARD disease-modifying antirheumatic drug, HLA-B27 human leukocyte antigen B27, nr-axSpA non-radiographic axial spondyloarthritis, NRS numeric rating scale, Q question, r-axSpA radiographic axial spondyloarthritis, SD standard deviation, SF-36 MCS Medical Outcomes Study 36-Item Short Form Health Survey Mental Component Score, SF-36 PCS Medical Outcomes Study 36-Item Short Form Health Survey Physical Component Score

^aDMARDs included methotrexate, sulfasalazine and hydroxychloroquine

six BASDAI questions, BASDAI Q1 (fatigue/tiredness) (female patients: -2.33 ± 0.36 ; PBO: -1.36 ± 0.32 , $p = 0.044$), Q2 (spinal pain) (female patients: -2.26 ± 0.36 ; PBO: -1.18 ± 0.32 , $p = 0.026$), Q3 (pain/swelling in other joints) (female patients: -2.19 ± 0.39 ; PBO: -0.65 ± 0.34 , $p = 0.003$) and Q5 (morning stiffness) (female patients: -2.66 ± 0.39 ; PBO: -1.37 ± 0.34 , $p = 0.013$) (Table 3).

For treatment responses in IXEQ2W patients with r-axSpA and nr-axSpA, refer to Supplementary Tables 1 and 2.

DISCUSSION

Baseline Characteristics by Sex

Several studies considering sex (gender) differences have revealed that female patients with axSpA have a longer diagnostic delay compared to male patients [3, 6, 23], with the disease severity presenting differently between the two sexes. The reasons for these differences are not clear, but factors such as differences in immune, hormonal and genetic responses may play a role [3]. The results of this analysis suggest potentially important clinical differences between male and female patients with r-axSpA and nr-axSpA. Female patients with r-axSpA and nr-axSpA experienced longer duration of symptoms since axSpA onset than male patients, in

line with previous studies [23, 24], supporting observations that sex differences in clinical presentation of patients with axSpA can lead to delayed diagnosis in female patients [3, 11] and highlighting the need for more awareness of potential clinical differences in presentation between male and female patients.

Higher BASDAI scores at baseline in female patients compared with male patients have been found in other studies [9, 25]. In this analysis, female patients with r-axSpA scored numerically higher than male patients on five of the six symptoms assessed by BASDAI at baseline (fatigue/tiredness, spinal pain, pain/swelling in other joints, discomfort/tenderness to touch/pressure and morning stiffness). This trend was also visible in female patients with nr-axSpA, with added statistical significance, suggesting a somewhat higher disease burden in female patients within the axSpA spectrums in line with previous studies [3].

In this analysis, C-reactive protein levels were significantly higher in male patients compared to female patients with r-axSpA but similar in patients with nr-axSpA.

Treatment Response by Sex

This post hoc analysis suggests that male patients achieve a peak response earlier than female patients, but with continuation of

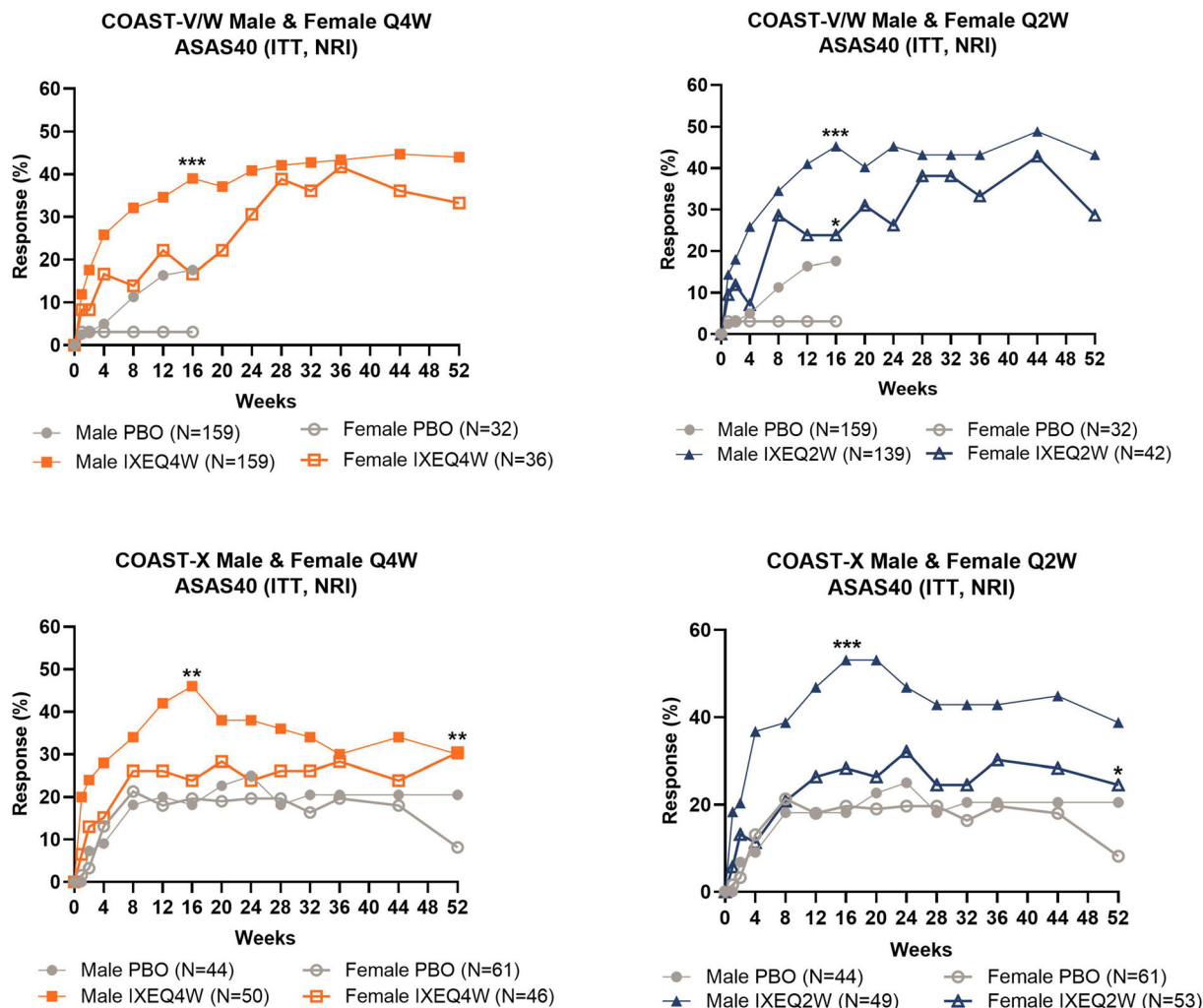


Fig. 1 COAST-V/W and COAST-X ASAS40 (ITT, NRI). Patients initially randomised to PBO in COAST-V/W switched to IXEQ2W or Q4W at week 16 by study design; PBO data are summarised up to week 16. Data displayed as mean. Significantly greater response rate versus PBO following IXE treatment denoted by * ($p \leq 0.05$), **

($p \leq 0.01$), *** ($p \leq 0.001$). ASAS40 Assessment in SpondyloArthritis International Society 40%, Q4W every 4 weeks, Q2W every 2 weeks, ITT intent-to-treat population, NRI non-responder imputation, PBO placebo, IXE ixekizumab

treatment, female patients continue to improve over time.

Research evaluating sex differences in pain largely focuses on understanding biological and psychosocial variables in pain [26, 27]. Biological explanations range from identified differences in gonadal hormones to neurochemistry, with psychological explanations ranging from typical gender roles to varying coping mechanisms between the sexes [28]. Sex-influenced access to healthcare, and associated diagnosis,

assessment and management have also been considered [29].

Current research suggests that disease activity (BASDAI) scores are significantly higher in women and that they have significantly lower response rates to treatment with TNFi [3, 12]. Data on sex differences in other biologics, such as IL-17 inhibitors, are limited [23]. As stated previously, a higher burden of disease was evident in this study for female patients at baseline with female patients having significantly higher

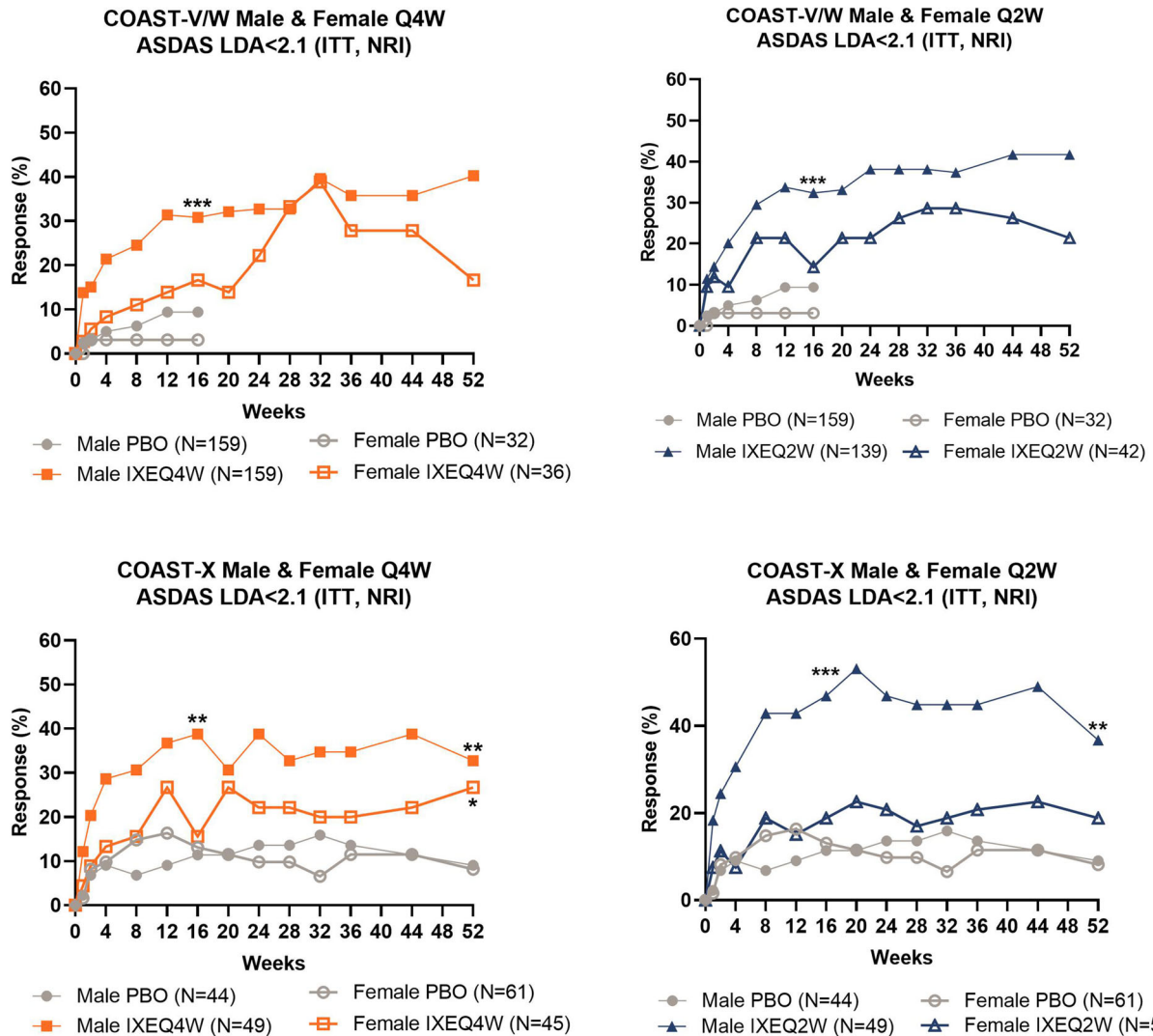


Fig. 2 ASDAS LDA < 2.1 response rate (%) across three treatment groups. Data displayed as mean. Significantly greater response rate versus PBO following IXE treatment denoted by * ($p \leq 0.05$), ** ($p \leq 0.01$), *** ($p \leq 0.001$).

ASDAS Ankylosing Spondylitis Disease Activity Score, LDA low disease activity, Q4W every 4 weeks, Q2W every 2 weeks, ITT intent-to-treat population, NRI non-responder imputation, PBO placebo, IXE ixekizumab

pain and fatigue scores. Male patients with r-axSpA showed greater response rates versus PBO across most of the treatment parameters measured. Female patients with r-axSpA and nr-axSpA displayed delayed attainment of peak responses to treatment with the approved label dose, with a higher percentage of male patients achieving ASAS40 and ASDAS < 2.1 at week 16 than female patients, despite similar retention rates.

A 2013 study by van der Horst-Bruinsma et al. [25] examining the impact of gender on clinical, functional and patient-reported treatment outcomes using data pooled from four AS clinical trials demonstrated similar early stage (week 12) findings to this analysis where, although both gender groups showed improvements, female patients showed significantly smaller changes. The higher age at disease onset seen in female patients in both r-axSpA and nr-

Table 2 Individual items change from baseline (mBOCF ANCOVA) at week 16 in patients with r-axSpA (COAST-V/W)

	Week 16					
	Patients with r-axSpA (COAST-V/W)					
	Male			Female		
	PBO (n = 158)	IXE80Q4W (n = 159)	p value	PBO (n = 32)	IXE80Q4W (n = 36)	p value
BASDAI score, LSM (SE)	− 1.35 (0.16)	− 2.65 (0.16)	< 0.001*	− 0.66 (0.36)	− 1.86 (0.34)	0.015*
Fatigue/tiredness (BASDAI Q1), LSM (SE)	− 1.30 (0.17)	− 2.39 (0.17)	< 0.001*	− 0.71 (0.38)	− 1.64 (0.36)	0.078
Spinal pain (BASDAI Q2), LSM (SE)	− 1.32 (0.18)	− 3.06 (0.18)	< 0.001*	− 0.75 (0.39)	− 2.06 (0.37)	0.014*
Pain/swelling in other joints (BASDAI Q3), LSM (SE)	− 1.52 (0.19)	− 2.30 (0.19)	0.004*	− 0.44 (0.43)	− 1.57 (0.40)	0.053
Tenderness to touch/pressure (BASDAI Q4), LSM (SE)	− 1.52 (0.18)	− 2.64 (0.18)	< 0.001*	− 0.53 (0.41)	− 1.57 (0.39)	0.064
Morning stiffness (BASDAI Q5), LSM (SE)	− 1.39 (0.18)	− 3.14 (0.18)	< 0.001*	− 0.77 (0.41)	− 2.44 (0.38)	0.003*
Morning stiffness duration (BASDAI Q6), LSM (SE)	− 0.87 (0.19)	− 2.68 (0.19)	< 0.001*	− 0.90 (0.43)	− 2.17 (0.40)	0.030*
Spinal pain at night NRS, LSM (SE)	− 1.50 (0.19)	− 3.24 (0.19)	< 0.001*	− 0.81 (0.42)	− 2.24 (0.39)	0.013*
BASFI, LSM (SE)	− 1.08 (0.16)	− 2.21 (0.16)	< 0.001*	− 0.60 (0.36)	− 1.16 (0.34)	0.258
SF-36 PCS, LSM (SE)	3.06 (0.55)	7.15 (0.55)	< 0.001*	0.95 (1.21)	4.95 (1.15)	0.017*

Significantly greater response rate versus PBO following IXE treatment denoted by * ($p \leq 0.05$)

BASDAI Bath Ankylosing Spondylitis Disease Activity Index, *LSM* least squared mean, *SE* standard error, *BASFI* Bath Ankylosing Spondylitis Functional Index, *SF-36* short form-36, *PCS* Physical Component Score, *PBO* placebo, *Q2W* every 2 weeks, *Q4W* every 4 weeks, *r-axSpA* radiographic axial spondyloarthritis, *mBOCF* modified baseline observation carried forward, *ANCOVA* analysis of covariance

axSpA in this analysis may have contributed to the higher disease burden observed at baseline. van der Horst-Bruinsma et al. [25] further suggested that this higher burden at baseline may lead to more resistant disease and a reduced response to treatment compared to male patients, particularly earlier on in treatment, as seen in this analysis. The differences in the proportion of the responses cannot be explained from this post hoc analysis. While a recent study revealed increased Th17 repertoire and elevated IL-17 levels in male patients compared to female patients [19], our study revealed

that female patients showed a significant response to IXE although the response was initially delayed. This analysis, in line with previous studies [25], highlights a greater disease severity and lessened treatment response in female patients. Future studies looking into this topic may provide further insights to the current data.

A limitation of this study was the lack of pre-specified criteria in COAST-X to allow patients to switch to open label at week 16 and be analysed as non-responders, which may have resulted in the ASAS40 response rate drop seen

Table 3 Individual items change from baseline (mBOCF ANCOVA) at week 16 and week 52 in patients with nr-axSpA (COAST-X)

	Week 16						Week 52					
	Patients with nr-axSpA (COAST-X)			Patients with nr-axSpA (COAST-X)			Patients with nr-axSpA (COAST-X)			Patients with nr-axSpA (COAST-X)		
	Male		Female	Male		Female	Male		Female	Male		Female
PBO (n = 42)	IXE80Q4W (n = 50)	p value	PBO (n = 61)	IXE80Q4W (n = 46)	p value	PBO (n = 42)	IXE80Q4W (n = 50)	p value	PBO (n = 61)	IXE80Q4W (n = 46)	p value	
BASDAI score, LSM (SE)	- 1.70 (0.33)	- 2.69 (0.30)	0.029*	- 1.34 (0.27)	- 1.64 (0.32)	0.465	- 1.83 (0.36)	- 2.82 (0.33)	0.040*	- 1.09 (0.30)	- 2.20 (0.34)	0.014*
Fatigue/tiredness (BASDAI Q1), LSM (SE)	- 1.98 (0.37)	- 2.32 (0.33)	0.499	- 1.51 (0.30)	- 2.03 (0.34)	0.261	- 1.98 (0.39)	- 2.51 (0.35)	0.307	- 1.36 (0.32)	- 2.33 (0.36)	0.044*
Spinal pain (BASDAI Q2), LSM (SE)	- 1.61 (0.37)	- 2.99 (0.33)	0.006*	- 1.36 (0.30)	- 1.89 (0.35)	0.252	- 2.01 (0.39)	- 2.99 (0.35)	0.061	- 1.18 (0.32)	- 2.26 (0.36)	0.026*
Pain/swelling in other joints (BASDAI Q3), LSM (SE)	- 1.72 (0.39)	- 2.54 (0.35)	0.120	- 1.18 (0.32)	- 1.40 (0.37)	0.653	- 1.69 (0.42)	- 2.68 (0.38)	0.080	- 0.65 (0.34)	- 2.19 (0.39)	0.003*
Tenderness to touch/pressure (BASDAI Q4), LSM (SE)	- 1.73 (0.38)	- 2.78 (0.34)	0.039*	- 1.12 (0.31)	- 0.99 (0.36)	0.779	- 1.86 (0.41)	- 3.00 (0.37)	0.039*	- 0.89 (0.34)	- 1.89 (0.39)	0.053
Morning stiffness (BASDAI Q5), LSM (SE)	- 1.91 (0.38)	- 2.97 (0.35)	0.041*	- 1.57 (0.32)	- 2.21 (0.36)	0.186	- 1.89 (0.41)	- 3.09 (0.37)	0.030*	- 1.37 (0.34)	- 2.66 (0.39)	0.013*
Morning stiffness duration (BASDAI Q6), LSM (SE)	- 1.34 (0.41)	- 2.98 (0.37)	0.003*	- 1.00 (0.34)	- 1.65 (0.39)	0.207	- 1.58 (0.43)	- 3.05 (0.38)	0.010*	- 1.03 (0.35)	- 2.13 (0.39)	0.039*
Spinal pain at night NRS, LSM (SE)	- 1.79 (0.40)	- 2.76 (0.37)	0.077	- 1.64 (0.33)	- 2.08 (0.38)	0.389	- 2.08 (0.42)	- 3.01 (0.38)	0.102	- 1.36 (0.35)	- 2.31 (0.40)	0.073
BASFI, LSM (SE)	- 1.35 (0.35)	- 2.40 (0.32)	0.028*	- 1.27 (0.29)	- 1.58 (0.33)	0.471	- 1.50 (0.39)	- 2.64 (0.35)	0.029*	- 1.15 (0.32)	- 2.01 (0.36)	0.076
SF-36 PCS, LSM (SE)	7.21 (1.22)	10.03 (1.11)	0.087	3.69 (1.00)	5.87 (1.15)	0.155	7.13 (1.33)	10.40 (1.20)	0.068	3.13 (1.09)	6.33 (1.25)	0.054

Significantly greater response rate versus PBO following IXE treatment denoted by * ($p \leq 0.05$)

BASDAI Bath Ankylosing Spondylitis Disease Activity Index, *LSM* least squared mean, *SE* standard error, *BASFI* Bath Ankylosing Spondylitis Functional Index, *SF-36* short form-36, *PCS* Physical Component Score, *PBO* placebo, *Q2W* every 2 weeks, *Q4W* every 4 weeks, *nr-axSpA* radiographic axial spondyloarthritis, *mBOCF* modified baseline observation carried forward, *ANCOVA* analysis of covariance

in male patients with nr-axSpA. Additionally, the disproportion in the number of male and female patients in the r-axSpA trials limits the validity when comparing responses between the two sexes.

CONCLUSION

This analysis demonstrates that, in general, female patients had higher disease burden than male patients for the axSpA disease spectrum. Our findings indicate that, while female patients show lower ASAS40 response rates than male patients at week 16, IXE is efficacious in treating male and female patients with AS and nr-axSpA. Nonetheless, female patients tend to experience achievement of response later in their treatment course.

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Data Availability. Lilly provides access to all individual participant data collected during the trial, after anonymization, with the exception of pharmacokinetic or genetic data. Data are available to request 6 months after the indication studied has been approved in the USA and EU and after primary publication acceptance, whichever is later. No expiration date of data requests is currently set once data 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 details on submitting a request, see the instructions provided at www.vivli.org.

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