Ixekizumab, an interleukin-17A antagonist in the treatment of ankylosing spondylitis or radiographic axial spondyloarthritis in patients previously untreated with biological disease-modifying anti-rheumatic drugs (COAST-V): 16 week results of a phase 3 randomised, double-blind, active-controlled and placebo-controlled trial

Désirée van der Heijde, James Cheng-Chung Wei, Maxime Dougados, Philip Mease, Atul Deodhar, Walter P Maksymowych, Filip Van den Bosch, Joachim Sieper, Tetsuya Tomita, Robert Landewé, Fangyi Zhao, Eswar Krishnan, David H. Adams, Beth Pangallo, Hilde Carlier on behalf of the COAST-V study group*

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RobotReviewer report

Risk of bias table

trial	design	n	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment
Van Der Heijde D, 2018	RCT	???	+	+	+	+

Characteristics of studies

Van Der Heijde D, 2018

Population	1. Inclusion criteria also required an inadequate response to at least two NSAIDs or a history of intolerance to NSAIDs, a history of back pain for at least 3 months (with an age at onset <45 years), a baseline score of at least 4 on the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), and a baseline score of at least 4 on the total back pain numeric rating scale at screening and baseline. 2. Eligible subjects were aged 18 years or older with an established diagnosis of radiographic axial spondyloarthritis and fulfilling Assessment of SpondyloArthritis international Society (ASAS) criteria (sacroiliitis on radiograph by modified New York criteria and at least one spondyloarthritis feature). 3. Exclusion criteria included total ankylosis of the spine (local reading), current or previous history of lymphoproliferative or malignant disease within 5 years of baseline , or other medical conditions, treatments, or procedures that could pose an unacceptable risk to pa tients or that could confound interpretation of study re sults.
Interventio n	1. matching placebo Q2W. Patients assigned to ixekizumab treatment regimens were randomly assigned in a 1:1 ratio to receive a starting dose of either 80 mg ixekizumab or 160 mg ixekizumab (two 80 mg injections) for the first dose at week 0. 2. At week 16, patients entered an ongoing extended treatment period (weeks 16 to 52), during which time patients in the ixekizumab treatment groups remained on their assigned treatment and patients in the placebo or adalimumab groups were randomly reassigned to receive one of the two ixekizumab dosing regimens, while maintaining masking of treatment allocation.

	3. This study is the first to assess the efficacy and safety of ixekizumab for radiographic axial spondyloarthritis in patients previously untreated with bDMARDs and is the first to include both a placebo control group and an active reference group (adalimumab), thereby providing additional context to observed efficacy for ixekizumab.
Outcomes	1. The major secondary objectives were to compare ixekizumab (all dosing regimens) versus placebo at week 16 as measured by the proportion of patients achieving ASAS20, at least a 50% improvement in the BASDAI score from baseline, and Ankylosing Spondylitis Disease Activity Score (ASDAS) inactive disease (defined as ASDAS 2. Added value of this study The primary and all major secondary endpoints of the COAST-V phase 3 clinical study in radiographic axial spondyloarthritis were achieved at week 16, with a safety profile consistent with studies of ixekizumab in patients with moderate-to-severe psoriasis and active psoriatic arthritis. 3. Inclusion criteria also required an inadequate response to at least two NSAIDs or a history of intolerance to NSAIDs, a history of back pain for at least 3 months (with an age at onset <45 years), a baseline score of at least 4 on the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), and a baseline score of at least 4 on the total back pain numeric rating scale at screening and baseline.

Bias	Judgement	Support for judgement
Random sequence generation	low	1. Randomisation and masking Patients were allocated to treatment by a computergenerated random sequence with stratification by country and results of a C-reactive protein (CRP) screen (,â§5 mg/L or > 5 mg/L). 2. At week 16, patients entered an ongoing extended treatment period (weeks 16 to 52), during which time patients in the ixekizumab treatment groups remained on their assigned treatment and patients in the placebo or adalimumab groups were randomly reassigned to receive one of the two ixekizumab dosing regimens, while maintaining masking of treatment allocation. 3. matching placebo Q2W. Patients assigned to ixekizumab treatment regimens were randomly assigned in a 1:1 ratio to receive a starting dose of either 80 mg ixekizumab or 160 mg ixekizumab (two 80 mg injections) for the first dose at week 0.
Allocation concealment	low	1. matching placebo Q2W. Patients assigned to ixekizumab treatment regimens were randomly assigned in a 1:1 ratio to receive a starting dose of either 80 mg ixekizumab or 160 mg ixekizumab (two 80 mg injections) for the first dose at week 0. 2. All MRIs were centrally read for bone marrow oedema according to the Spondyloarthritis Research Consortium of Canada (SPARCC) method by two independent readers that were masked to treatment allocation and chronology of the images, with adjudication if necessary. 3. Randomisation and masking Patients were allocated to treatment by a computergenerated random sequence with stratification by country and results of a C-reactive protein (CRP) screen (,â§5 mg/L or > 5 mg/L).
Blinding of participants and personnel	low	1. To maintain blinding, all patients received three injections at week 0 and two injections Q2W during the remainder of the blinded treatment dosing period (appendix). 2. All MRIs were centrally read for bone marrow oedema according to the Spondyloarthritis Research Consortium of Canada (SPARCC) method by two independent readers that were masked to treatment

		allocation and chronology of the images, with adjudication if necessary. 3. matching placebo Q2W. Patients assigned to ixekizumab treatment regimens were randomly assigned in a 1:1 ratio to receive a starting dose of either 80 mg ixekizumab or 160 mg ixekizumab (two 80 mg injections) for the first dose at week 0.
Blinding of outcome assessment	low	1. All MRIs were centrally read for bone marrow oedema according to the Spondyloarthritis Research Consortium of Canada (SPARCC) method by two independent readers that were masked to treatment allocation and chronology of the images, with adjudication if necessary. 2. The primary outcome (ASAS40) was also analysed for the per-protocol set, defined as all patients randomly assigned to treatment who were compliant with therapy, who did not have a subset of important protocol deviations that could affect the primary efficacy endpoint, and whose investigator site did not have substantial good clinical practice issues that required a report to regulatory agencies before week 16. 3. Blood samples for analysis of serum drug concentrations were time-matched to samples for anti-drug antibody testing and were obtained at baseline and each postbaseline visit during the masked treatment dosing period.

References

1. Van Der Heijde D et al. Articles Ixekizumab, an interleukin-17A antagonist in the treatment of ankylosing spondylitis or radiographic axial spondyloarthritis in patients previously untreated with biological disease- modifying anti-rheumatic drugs (COAST-V): 16 week results of a phase 3 randomised, double-blind, active-controlled and placebo-controlled trial Lancet 2018. 382(9906); 1705-13 PMID: 24035250