Ixekizumab, an Interleukin-17A Antagonist in the Treatment of Ankylosing Spondylitis/Radiographic Axial Spondyloarthritis: 16 Week Results of a Phase 3 Randomized, Double-Blind, Active-and Placebo-Controlled Trial in Biologic Disease Modifying Anti-Rheumatic Drug-naïve patients (COAST-V)

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, and Hilde Carlier on behalf of the COAST-V study group

Department of Rheumatology, Leiden University Medical Centre, Leiden, the Netherlands (Désirée van der Heijde MD); Institute of Medicine, Chung Shan Medical University, Department of Internal Medicine, Chung Shan Medical University Hospital, Graduate Institute of Integrated Medicine, China Medical University, Taichung, Taiwan (James Chen-Chung Wei MD); Department of Rheumatology, Hopital Cochin, Paris, France (Maxime Dougados MD); Seattle Rheumatology Associates, Seattle, WA, USA (Philip Mease MD); Division of Arthritis & Rheumatic Diseases, Oregon Health & Science University, Portland, OR, USA (Atul Deodhar MD); Department of Medicine, University of Alberta, Edmonton, Alberta, Canada (Walter Maksymowych F.R.C.P. (C)); Department of Rheumatology, Ghent University Hospital, Ghent, Belgium (Filip Van den Bosch MD, PhD); Department of Rheumatology, Charite University Hospital, Berlin, Germany (Joachim Sieper MD, PhD); Department of Orthopaedic Biomaterial Science, Osaka University Graduate School of Medicine, Suita, Osaka, Japan (Tetsuya Tomita MD); Amsterdam Rheumatology and Clinical Immunology Center, Amsterdam, the Netherlands (Robert Landewé, MD, PhD); Eli Lilly and Company, Indianapolis, IN, USA (Fangyi Zhao PhD); Eli Lilly and Company, Indianapolis, IN, USA (Eswar Krishnan, MD); Eli Lilly and

Company, Indianapolis, IN, USA (David H. Adams, PhD); Eli Lilly and Company, Indianapolis, IN, USA (Beth Pangallo, PhD); Eli Lilly and Company, Indianapolis, IN, USA (Hilde Carlier MD).

Correspondence to:

Dr. Désirée van der Heijde

Department of Rheumatology

Leiden University Medical Centre

P.O. Box 9600

2300 RC Leiden, The Netherlands

Phone: +31715263423

Email: mail@dvanderheijde.nl

Abstract

Background: Biologic disease modifying anti-rheumatic drugs (bDMARDs) are recommended for radiographic axial spondyloarthritis (r-axSpA), otherwise known as ankylosing spondylitis, when conventional therapies fail. We report efficacy and safety results of a Phase 3 study of ixekizumab, a high-affinity monoclonal antibody that selectively targets IL-17A, in bDMARD-naïve patients with r-axSpA.

Methods: In this randomized, double-blind, Phase 3 study, adult patients with inadequate response/intolerance to NSAIDs, an established diagnosis of r-axSpA, and with radiographic sacroiliitis centrally defined by modified New York criteria and ≥1 spondyloarthritis feature according to Assessment of Spondyloarthritis International Society (ASAS) criteria were recruited from 84 sites (12 countries) in Europe, Asia, and North America. Patients were randomized 1:1:1:1 using a computer-generated random sequence to 80 mg subcutaneous ixekizumab every two (Q2W) or four (Q4W) weeks, 40 mg adalimumab Q2W (active reference arm), or placebo. The primary endpoint was the proportion of patients achieving an ASAS40 response at Week 16.

Findings: Between June 20, 2016 and August 22, 2017, 341 patients were randomized to placebo (N=87), adalimumab (N=90), ixekizumab Q2W (N=83), or ixekizumab Q4W (N=81). At Week 16, significantly more patients achieved ASAS40 with ixekizumab Q2W (n=43, 51·8%, p<0·0001), ixekizumab Q4W (n=39, 48·1%, p<0·0001), and adalimumab (n=32, 35·6%; p=0·0053) versus placebo (n=16, 18·4%). One serious infection occurred in each of the ixekizumab Q2W (1·2%), ixekizumab Q4W (1·2%), and adalimumab (1·1%) arms; none were reported with placebo. One (1·1%) *Candida* infection occurred in the adalimumab arm and one

(1·2%) patient receiving ixekizumab Q2W was adjudicated as having probable Crohn's disease. No opportunistic infections, malignancies, or deaths occurred.

Interpretation: Each dosing regimen of ixekizumab was superior to placebo for improving r-axSpA signs and symptoms in bDMARD-naïve patients; the safety profile was consistent with previous studies of ixekizumab. The adalimumab control arm performed as expected.

Funding: Eli Lilly and Company

Research in context

Evidence before this study

Pubmed was searched using the terms “ankylosing spondylitis”, “axial spondyloarthritis”, and “disease-modifying anti-rheumatic drugs”, including articles through May 30, 2018. Axial spondyloarthritis (axSpA) is a chronic immune-mediated disease characterized by inflammation of the spine and sacroiliac joint (SIJ), peripheral joint involvement, extra articular manifestations, and a strong genetic association with human leukocyte antigen (HLA)-B27. Radiographic axSpA (r-axSpA) was previously classified as ankylosing spondylitis (AS) in 1984 and updated to r-axSpA as part of the ASAS criteria. Both criteria sets require the same radiographically confirmed structural damage to the sacroiliac joint as well as at least one accompanying clinical element. Recommendations for the management of r-axSpA generally include exercise and physiotherapy in combination with non-steroidal anti-inflammatory drugs, sometimes accompanied by conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) to treat peripheral arthritis symptoms. Biologic DMARDs (bDMARDs) such as tumor necrosis factor inhibitors (TNFi) or anti-Interleukin (IL)-17 therapies are recommended for patients with persistent disease activity despite conventional therapy. In comparison to other chronic inflammatory conditions, the number of treatment options, other than those targeting TNF, are limited. Ixekizumab, a high-affinity monoclonal antibody that selectively targets IL-17A, is approved for the treatment of patients with moderate-to-severe psoriasis as well as patients with active psoriatic arthritis. However, prior to this study, the efficacy and safety of ixekizumab in patients with r-axSpA have not been evaluated.

Added value of this study

The primary and all major secondary endpoints of the COAST-V Phase 3 clinical study in r-axSpA 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. These findings indicate that ixekizumab, administered every two weeks or every four weeks, was superior to placebo for the treatment of active r-axSpA in patients who had not previously received treatment with bDMARDs. This study is the first to evaluate the efficacy and safety of ixekizumab for r-axSpA in bDMARD-naïve patients and is the first to include both a placebo control arm and active reference arm (adalimumab), thereby providing additional context to observed efficacy for ixekizumab. COAST-V is also the first Phase 3 clinical study in r-axSpA to include ASAS40, a stringent clinical measure indicating a high degree of clinical improvement, as a primary endpoint, where most other trials used ASAS20.

Implications of all the available evidence

The results of the COAST-V study provide additional evidence supporting the role of IL-17A in the pathogenesis of r-axSpA. Ixekizumab was efficacious in the treatment of r-axSpA with significant improvements in disease activity, health-related quality of life, function, and bone marrow edema of the spine and sacroiliac joint in bDMARD-naïve patients. Response with ixekizumab was numerically at least similar to response rates observed in the adalimumab arm. Overall, the findings of COAST-V indicate that ixekizumab could be a new treatment option for patients with r-axSpA.

Introduction

Axial spondyloarthritis (axSpA) is a chronic inflammatory disease that affects up to 1·4% of the adult population worldwide [1,2]. Although not all clinical features are present in all patients with axSpA, the disease is generally characterized by inflammation of the spine and sacroiliac joints (SIJ), progressive spinal ankylosis due to new bone formation, peripheral arthritis and enthesitis, as well as extra articular manifestations including anterior uveitis, psoriasis, and inflammatory bowel disease (IBD). The term axSpA covers patients with non-radiographic as well as radiographic axSpA (r-axSpA), which is also termed ankylosing spondylitis (AS) [3]. R-axSpA is characterized by radiographically defined structural damage of the SIJ. Its early onset in young adults, the chronic axial and extra-axial inflammation, and progressive irreversible structural damage may lead to significant morbidity and functional deterioration. Compared to the general population, patients with AS have increased rates of work disability, unemployment, and mortality, as well as a reduced quality of life [4,5].

Current treatment recommendations for the management of AS recommend non-pharmacological management along with nonsteroidal anti-inflammatory drugs (NSAIDs) as the first line of treatment. However, NSAID treatment is not always well tolerated and may be insufficient to control symptoms. Conventional synthetic disease modifying anti-rheumatic drugs (csDMARDs) are typically not effective for the treatment of axial symptoms, although they may have a limited role for the treatment of peripheral symptoms that coexist with axial disease. Treatment with tumor necrosis factor inhibitors (TNFi) is recommended for patients who have persistent disease activity despite conventional treatment [6,7]. However, a substantial proportion of patients fail to achieve adequate disease control or may be intolerant to TNFi [8,9].

Growing evidence indicates that cytokine signaling through the IL-17 pathway is a key contributor to the pathogenesis of axSpA, which has been further supported by recent clinical findings showing that anti-interleukin (IL)-17A therapy is an efficacious alternative to TNFi for AS [10-16]. However, in comparison to other chronic inflammatory conditions, treatment options other than those targeting TNF remain limited.

Ixekizumab is a high-affinity monoclonal antibody that selectively targets IL-17A and is approved for the treatment of active psoriatic arthritis and of moderate-to-severe plaque psoriasis [17-19]. Herein, we present the 16-Week results of COAST-V, a placebo- and active-controlled Phase 3 study investigating the efficacy and safety of ixekizumab in biologic DMARD (bDMARD)-naïve patients with r-axSpA.

Methods

Study design

COAST-V is a Phase 3, multicenter, randomized, double-blind, active- and placebo-controlled, clinical trial with a one-year duration, followed by an optional two-year extension study. Patient enrollment and data collection occurred at 84 sites in 12 countries including the Czech Republic, Germany, Hungary, the Netherlands, Poland, the Russian Federation, Canada, Japan, the Republic of Korea, Mexico, Taiwan, and the United States of America. The study was approved by the ethical review board at each participating site prior to the start of the study.

Participants

Eligible subjects were 18 years or older with an established diagnosis of r-axSpA and fulfilling Assessment of SpondyloArthritis international Society (ASAS) criteria (sacroiliitis on radiograph by mNY criteria and ≥1 spondyloarthritis feature). Reading of the SIJ radiograph was done centrally by two readers, with adjudication if necessary. All patients fulfilling ASAS criteria also fulfilled mNY criteria for AS. Inclusion criteria also required an inadequate response to ≥2 NSAIDs or a history of intolerance to NSAIDs, a history of back pain ≥3 months (with an age at onset <45 years), a baseline score ≥4 on the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), and a baseline score ≥4 on the total back pain numeric rating scale (NRS) at screening and baseline.

Exclusion criteria included total ankylosis of the spine (local reading), current or prior 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 patients or that could confound interpretation of study results. Prior or current treatment with bDMARDs was excluded, but

patients could continue to take stable doses of NSAIDs, protocol defined csDMARDs, oral glucocorticoids, and opioids. Complete inclusion and exclusion criteria are available in the appendix.

COAST-V was conducted in accordance with the ethical principles of the Declaration of Helsinki. All patients provided written informed consent before undergoing study-related procedures.

Randomization and masking

Randomization was determined by a computer-generated random sequence with stratification by country and screening C-Reactive Protein (CRP, ≤ or > 5 mg/L). Patients were randomized at a 1:1:1:1 ratio to receive 80 mg ixekizumab every two weeks (Q2W) or every four weeks (Q4W), 40 mg adalimumab Q2W (active reference arm), or placebo Q2W. The adalimumab treatment arm served as an in-study active control for comparison with placebo in order to more reliably reflect the generally anticipated efficacy within the current AS population than historical TNFi data would. Thus, the adalimumab control arm provides additional context for the interpretation of the ixekizumab results in the study population.

Patients assigned to ixekizumab treatment regimens were randomized in a 1:1 ratio to receive a starting dose of either 80 mg ixekizumab or 160 mg ixekizumab (two 80-mg injections) at Week 0. To maintain blinding, all patients received three injections at week 0 and two injections Q2W during the remainder of the blinded treatment dosing period, as further described in the supplementary appendix.

At week 16, patients entered an ongoing extended treatment period (Weeks 16 to 52), during which patients in the ixekizumab treatment arms remained on their assigned treatment and

patients in the placebo or adalimumab groups were randomly (in a blinded fashion) reassigned to receive one of the two ixekizumab dosing regimens. All patients continued to receive blinded treatment through Week 52. Patients who completed the one-year COAST-V study could enroll into an optional two-year extension study. At the time of publication of this report, COAST-V is still ongoing. Additional details on randomization and masking are provided in the supplementary appendix.

Procedures

Treatments were administered subcutaneously with prefilled manual syringes. Study visits occurred during screening and at Week 0 (baseline), 1, 2, 4, 8, 12, and 16 (primary endpoint). Assessment of study outcomes were conducted at screening and during each study visit with the exception of MRI of spine and SIJ (collected at screening and Week 16) as well as the SF-36 and ASAS Health Index (each collected at screening and Weeks 0, 4, 8, and 16).

Outcomes

The primary objective was to compare ixekizumab (each dosing regimen) versus placebo at Week 16 as measured by the proportion of patients achieving an ASAS40 response. The major secondary objectives were to compare ixekizumab (each dosing regimen) versus placebo at Week 16 as measured by the proportion of patients achieving ASAS20, ≥50% improvement in the BASDAI score from baseline (BASDAI50), and Ankylosing Spondylitis Disease Activity Score (ASDAS) inactive disease (defined as ASDAS <1·3) as well as the change from baseline in ASDAS, Bath Ankylosing Spondylitis Functional Index (BASFI), Magnetic Resonance Imaging of the spine Spondyloarthritis Research Consortium of Canada (MRI SPARCC spine) score, SF-36 PCS, and the ASAS Health Index. Additional pre-specified secondary outcomes

reported are the change from baseline in CRP (mg/L) and change from baseline in MRI SPARCC SIJ score. Furthermore, a post-hoc assessment of the proportion of patients achieving an ASDAS <2·1 at Week 16 is provided.

The ASAS40 and ASAS20 are composite measures derived from four patient domains including the patient global (patient global assessment of disease activity), spinal pain (spinal pain NRS), function (BASFI), and Inflammation (mean of BASDAI questions five [intensity of morning stiffness] and six [duration of morning stiffness]). ASAS40 response is defined as a ≥40% improvement and an absolute improvement from baseline of ≥2-units (range 0-10) in ≥3 of 4 domains (Patient Global, Spinal Pain, Function, and Inflammation) without any worsening in the remaining domain. ASAS20 response is defined as a ≥20% improvement and an absolute improvement from baseline of ≥1 unit (range 0 to 10) in ≥3 of 4 domains, and no worsening of ≥20% and ≥1 unit (range 0-10) in the remaining domain [20-22]. ASAS40 and ASAS20 were determined at each post-baseline visit through week 16 (ASAS domains were assessed at screening, baseline, and at each patient visit). Additional details on study outcomes are provided in the supplementary appendix.

Sagittal MRI of the entire spine in all patients was done using T1-weighted and short-tau-inversion-recovery (STIR) sequences with three consecutive sagittal slices. MRI of the SIJ in all patients was done using six consecutive semicoronal slices. All MRIs were centrally read for bone marrow edema according to the SPARCC method by two independent readers that were blinded to treatment allocation and chronology of the images, with adjudication if necessary.

Safety outcomes included assessments of adverse events (AEs), vital signs, laboratory tests, and physical exams. AEs were classified according to the Medical Dictionary for Regulatory

Activities. A treatment-emergent adverse event (TEAE) during the blinded treatment dosing period was defined as an AE that first occurred or worsened after baseline and on or before the Week 16 visit. AEs of special interest included cytopenias, elevations in liver function tests, infections, injection site reactions, allergic reactions or hypersensitivities, cerebro-cardiovascular events, malignancies, IBD, and depression. Data on terms relating to cerebro-cardiovascular events and on suspected IBD were adjudicated by external Clinical Events Committees. Details on adjudication criteria are provided in the supplementary appendix.

Statistical Analysis

With 320 patients (80 patients per treatment group), this study was estimated to have approximately 96% power to test the superiority of ixekizumab Q2W to placebo for the ASAS 40 at Week 16 at a 5% type I error rate with the assumption of ASAS 40 response rate of 44% for ixekizumab Q2W and 16% for placebo. These assumptions were based on historical clinical studies of bDMARDs approved for AS.

Efficacy and health outcomes during the blinded treatment dosing period were analyzed for all randomized patients according to the treatment to which they were assigned (intention-to-treat population). The primary outcome (ASAS40) was also analyzed for the per-protocol set, defined as all randomized patients who were compliant with therapy, who did not have a subset of important protocol deviations that could impact the primary efficacy endpoint, and whose investigator site did not have significant good clinical practice issues that required a report to regulatory agencies prior to Week 16. Categorical efficacy outcomes and health outcomes variables were analyzed using logistic regression with nonresponder imputation for missing data. With the exception of MRI spine and SIJ, continuous efficacy and health outcomes variables

were analyzed using a mixed-effects model of repeated measures. SPARCC MRI spine and SIJ scores were analyzed using analysis of covariance based on observed case. Analyses of the ixekizumab Q2W and Q4W treatment groups were performed without regard to the Week 0 starting dose of 80 mg or 160 mg. In COAST-V, adalimumab represents an active reference arm for comparison to placebo. The study was not designed to test equivalence or non-inferiority of active treatment arms to each other. Statistical analyses were completed using SAS Version 9·2 or higher.

A graphical multiple testing strategy was used for primary and major secondary objectives for the ixekizumab Q2W and ixekizumab Q4W treatment arms to control overall family-wise type I error rate at a 2-sided α level of 0·05 (Supplementary Figures 1-3). Additional details regarding statistical analyses and the multiple testing strategy are available in the supplementary appendix.

Safety was assessed in a blinded fashion for all randomized patients receiving at least one dose of study drug.

COAST-V is registered on Clinicaltrials.gov (ID: NCT02696785)

Role of the funding source

An academic advisory committee was involved in the study design and data interpretation, together with authors from Eli Lilly and Company (Indianapolis IN, USA). Authors had full access to all the data in the study and had final responsibility for the decision to submit for publication. Lilly contributed to study design, data collection, data analysis, data interpretation, manuscript preparation, and publication decisions.

Results

Of 781 patients who were assessed for eligibility, 293 (37·5%) discontinued due to a lack of definite sacroilitis on SIJ radiograph by central reading. Other reasons for screen failure included lack of sufficient disease activity (defined as BASDAI ≥4 and total back pain NRS ≥4) (n=43 [5·5%]) and evidence or suspicion of active or latent tuberculosis (n=27 [3·5%]). In all, 341 patients were randomly assigned between June 20, 2016 and August 22, 2017 to placebo (87 patients), 40 mg adalimumab (90 patients, active reference arm), 80 mg ixekizumab Q2W (83 patients), or 80 mg ixekizumab Q4W (81 patients). Completion rates for the 16-week blinded treatment dosing period were 86 (98·9%) for placebo, 88 (97·8%) for adalimumab, 79 (95·2%) for ixekizumab Q2W, and 78 (96·3%) for ixekizumab Q4W. Nine patients discontinued prior to Week 16; reasons for discontinuation were AEs, lack of efficacy, or subject decision (Figure 1).

Baseline demographics and disease characteristics were similar among treatment arms (Table 1 and Supplementary Table 1). Mean age was 41·7 (SD 11·7), 81·2% of patients were male, and 62·6% were white race. Duration of symptoms since onset of r-axSpA was 16·0 (SD 10·3) years and duration of disease since diagnosis of r-axSpA was 7·7 (SD 8·4) years. At baseline, mean BASDAI score was 6·7 (SD 1·4) and 64·4% of patients had CRP levels >5 mg/L.

A graphical multiple testing strategy was used for analysis of the primary and major secondary objectives. Clinical improvements were rapid and were statistically significant versus placebo for the primary and all major secondary endpoints at Week 16. The primary efficacy endpoint, ASAS40 response at Week 16, was achieved by statistically significantly more patients receiving ixekizumab Q2W (n=43 [51·8%], p<0·0001), ixekizumab Q4W (n=39 [48·1%], p<0·0001) compared to patients receiving placebo (n=16 [18·4%]) (Figure 2 and Table 2). The proportion of

patients achieving ASAS20 response at Week 16 (major secondary endpoint) was statistically significantly greater with ixekizumab Q2W (n=57 [68·7%], p=0·0002), ixekizumab Q4W (n=52 [64·2%], p=0·0015) versus placebo (n=35 [40·2%]) (Figure 3 and Table 2). The adalimumab arm also showed statistically significant improvements versus placebo for ASAS40 (n=32 [35·6%], p=0·0053) and ASAS20 (n=53 [58·9%], p=0·0075) response at Week 16. Statistically significant improvements versus placebo were observed for all other major secondary endpoints at Week 16 for all active treatment arms including mean change from baseline in ASDAS, the proportion of patients with at least a 50% improvement from baseline in BASDAI score, mean change from baseline in BASFI, the proportion of patients with ASDAS <1·3 (inactive disease), mean change from baseline in bone marrow edema of the spine (MRI spine SPARCC score), mean change from baseline in SF-36 PCS score, and mean change from baseline in the ASAS health index (Table 2).

The Week 0 starting dose of 160 mg versus 80 mg did not lead to an incremental improvement of the results observed at Week 16. For patients in the ixekizumab Q2W treatment group, ASAS40 response at Week 16 was achieved by 25/45 (55·6%) patients receiving an 80 mg starting dose and 18/38 (47·4%) patients receiving a 160 mg starting dose. Similarly, for patients in the ixekizumab Q4W treatment group, 21/42 (50·0%) patients receiving an 80 mg starting dose and 18/39 (46·2%) patients receiving the 160 mg starting dose achieved ASAS40 response at Week 16. ASAS40 response at Week 16 was also analyzed for the per-protocol set. The per-protocol set excluded nine (10·8%) patients randomized to ixekizumab Q2W, five (6·2%) patients randomized to ixekizumab Q4W, 14 (15·6%) patients randomized to adalimumab, and eight (9·2%) patients randomized to placebo (Supplementary Table 2). ASAS40 response at Week 16 in the per-protocol set was also statistically significantly greater with ixekizumab Q2W (n=40

[54·1%], p<0·0001), ixekizumab Q4W (n=38 [50·0%], p<0·0001), and adalimumab (n=29 [38·2%], p=0·0031) compared to placebo (n=14 [17·7%]) (Table 2).

Statistically significant improvements versus placebo were also observed for all active treatment arms at Week 16 for the prespecified endpoints of mean change from baseline in MRI SIJ SPARCC score (indicating reduction in bone marrow edema of the SIJ) and mean change from baseline serum levels of C-reactive protein. A post-hoc analysis was also performed for the proportion of patients achieving ASDAS <2·1 (inactive or low disease activity). A statistically significantly greater proportion of patients achieved ASDAS <2·1 at Week 16 for all active treatment arms compared to placebo.

Adverse events during the blinded treatment dosing period of COAST-V are summarized in Table 3. The frequency of TEAEs were similar for each ixekizumab dosing regimen; most were mild or moderate in severity. The most common TEAEs (occurring in ≥5% of patients receiving ixekizumab) were nasopharyngitis and upper respiratory tract infection. Discontinuations due to AEs occurred in three (3·6%) patients receiving ixekizumab Q2W and one (1·1%) patient receiving adalimumab; no patients receiving ixekizumab Q4W discontinued due to AEs. Serious adverse events (SAEs) occurred for 1·2% of patients (one patient) in each ixekizumab treatment arm and 3·3% of patients (three patients) receiving adalimumab. No deaths occurred in any treatment group during the study.

Treatment-emergent infections occurred at similar frequencies across all active treatment arms. Three serious infections occurred during the blinded treatment dosing period; one each occurring in the ixekizumab Q2W (gastroenteritis), ixekizumab Q4W (urinary tract infection), and adalimumab (appendicitis). None of these serious infections resulted in study discontinuation.

There were no cases of opportunistic infection nor reactivation of latent tuberculosis in any treatment arm; one case of skin C*andida* infection occurred in the adalimumab group.

Injection site reactions were reported in four (4·7%) patients in the placebo arm, 11 (13·3%) patients in the ixekizumab Q2W arm, three (3·7%) patients in the ixekizumab Q4W arm, and seven (7·8%) patients in the adalimumab arm. One (1·2%) severe injection site reaction was reported in the ixekizumab Q2W arm; all other injection site reactions were mild or moderate in severity. Two patients in the ixekizumab Q2W arm (including the patient with a severe reaction) and one patient in the adalimumab arm discontinued treatment due to injection site reactions.

No malignancies were reported in any treatment group. Treatment-emergent allergic or hypersensitivity reactions were more frequent in the active treatment arms (n=3 [3·6%] for ixekizumab Q2W, n=3 [3·7%] for ixekizumab Q4W, n=4 [4·4%] for adalimumab) than placebo (n=1 [1·2%]); all were non-anaphylactic events. Depression was reported in one patient receiving adalimumab. No placebo or ixekizumab-treated patients had grade three or grade four neutropenia; one (1·1%) grade 3 neutropenia occurred in the adalimumab arm.

One patient in the ixekizumab Q2W treatment arm with a prior history of NSAID induced colitis (endoscopically confirmed) and gastroenteritis, and using NSAIDs as a concomitant therapy in the study, had a TEAE reported as Crohn's disease. This event was an SAE and occurred after study drug was discontinued due to gastrointestinal symptoms (after a total of four doses). This patient was adjudicated by the Clinical Events Committee as having "probable" Crohn's disease. Treatment-emergent anterior uveitis was reported in one patient (with a prior history of anterior uveitis) in the ixekizumab Q4W arm. Treatment-emergent psoriasis did not occur in any ixekizumab treated patients; one TEAE of psoriasis was reported in the adalimumab arm.

Treatment-emergent anti-drug antibodies (TE-ADA) in the ixekizumab treatment arms were detected in two (2·4%) ixekizumab Q2W patients and two (2·5%) ixekizumab Q4W patients. All TE-ADA positive patients had low titer (titer <1:160) and none were identified as having neutralizing anti-drug antibodies. For each ixekizumab treatment arm, there was no association between TE-ADA status and ASAS40 response, injection-site reactions, or potential allergic/hypersensitivity events.

Discussion

Ixekizumab significantly reduced the signs and symptoms of r-axSpA, as compared with placebo. An ASAS40 response at Week 16, the primary endpoint, was achieved in approximately 50% of patients in each ixekizumab group. Significant improvements over placebo were also observed for each ixekizumab regimen for all major secondary endpoints at week 16, including clinical disease activity, function, and quality of life. In addition to the above patient reported outcomes, a statistically significant treatment effect was seen on inflammation, as assessed by CRP and MRI.

Despite the greater exposure with the 80 mg Q2W regimen, descriptive analyses did not show a meaningful incremental increase in observed efficacy, as compared to the Q4W regimen. Similarly, descriptive analyses of the starting dose of ixekizumab at Week 0 did not indicate an incremental positive effect of the 160 mg relative to the 80 mg starting dose on Week 16 response rates for either ixekizumab regimen in bDMARD-naïve patients. However, additional data in different populations such as TNF-experienced patients is needed to further assess potential differences in efficacy between both regimens.

The safety profile of ixekizumab in COAST-V is consistent with published results of ixekizumab clinical studies in patients with moderate-to-severe psoriasis and in patients with active psoriatic arthritis [17-19]. Infections were more frequent in each active arm compared to placebo, but were mostly mild-to-moderate in severity and were consistent among the active treatment arms. One SAE adjudicated as “probable” Crohns in a patient with a colitis history, was reported in the Q2W arm. There was no signal for an increased risk of Grade 3 or Grade 4 neutropenia, *Candida* infection, or IBD with ixekizumab relative to placebo during the double-blind placebo controlled period. There were no suicides or suicidality-related adverse events in ixekizumab-treated

patients and no malignancies or deaths. The frequency of treatment-emergent anti-drug antibodies in the ixekizumab treatment arms were low and anti-ixekizumab antibodies were not associated with immune reactions or reduced efficacy.

TNFi agents and one anti-IL-17A therapy are the only approved biologic agents for AS. A key strength of the COAST-V study is the inclusion of adalimumab as an in-study active control arm to provide additional context for the interpretation of the ixekizumab results. The adalimumab control arm performed as expected with significant improvements versus placebo in all outcomes and with treatment effects generally being consistent with those reported in the adalimumab ATLAS study. Although larger head-to-head trials would be required to formally assess the efficacy and safety of ixekizumab relative to TNF-inhibitors, the ASAS40 response rate achieved with either ixekizumab regimen at week 16 was, numerically, at least similar to the response rate observed in the adalimumab arm in the present study as well as the response rate reported in the adalimumab ATLAS study. Thus, the present study supports that ixekizumab is effective in bDMARD naïve patients with r-axSpA.

Additional key strengths of the COAST-V study are the use of ASAS40 as the primary endpoint, reflecting major improvement and representing a more stringent endpoint than the commonly used ASAS20, inclusion of spinal and SIJ MRI as secondary endpoints, and enrollment of a geographically diverse population of subjects. Furthermore, COAST-V provides a focused evaluation of the efficacy of ixekizumab in bDMARD-naïve patients. Separate studies are ongoing to evaluate the efficacy and safety of ixekizumab, with specific focus on bDMARD-experienced patients with r-axSpA (COAST-W) and on bDMARD naïve patients with nonradiographic axSpA (COAST-X). The current dataset is limited to a short treatment period. Longer term data, which is being collected through one year of treatment in the present study as

	Placebo N=87[a]	Adalimumab Q2W N=90	Ixekizumab Q2W N=83	Ixekizumab Q4W N=81
Inflammatory back pain	86 (100·0%)	89 (98·9%)	82 (98·8%)	81 (100·0%)
Arthritis	29 (33·7%)	26 (28·9%)	24 (28·9%)	29 (35·8%)
Anterior uveitis	14 (16·3%)	19 (21·1%)	21 (25·3%)	17 (21·0%)
Psoriasis	8 (9·3%)	6 (6·7%)	3 (3·6%)	4 (4·9%)
Crohn's disease or ulcerative colitis	2 (2·3%)	1 (1·1%)	2 (2·4%)	1 (1·2%)
Dactylitis	2 (2·3%)	2 (2·2%)	3 (3·6%)	1 (1·2%)
Enthesitis	26 (30·2%)	22 (24·4%)	19 (22·9%)	24 (29·6%)
Good prior response to NSAIDs	61 (70·9%)	57 (63·3%)	61 (73·5%)	58 (71·6%)
Family history of spondyloarthritis	25 (29·1%)	23 (25·6%)	20 (24·1%)	22 (27·2%)
Positive for HLA-B27	76 (89·4%)	82 (91·1%)	75 (90·4%)	75 (92·6%)
CRP >5 mg/L at screening	57 (66·3%)	58 (64·4%)	54 (65·1%)	56 (69·1%)

Values are presented as n (%) of patients with either a current or history of each condition.
[a]The placebo population excludes one patient who was a screen failure and was accidentally randomized to placebo. This patient discontinued prior to receiving study drug.
Abbreviations: CRP = C-reactive protein; HLA-B27 = human leukocyte antigen B27; NSAID = non-steroidal anti-inflammatory drug; Q2W = every two weeks; Q4W = every four weeks

Supplementary Table 1. Spondyloarthritis features at baseline

well as during an optional two-year extension study, will further inform on the long-term efficacy and safety of ixekizumab.

In conclusion, each dosing regimen of ixekizumab resulted in rapid and significant improvement compared to placebo in key clinical domains of r-axSpA. The safety profile of ixekizumab in the present study is consistent with published results of ixekizumab clinical studies in patients with moderate-to-severe psoriasis or in patients with active psoriatic arthritis. The results of COAST-V confirm that IL-17A plays a role in the pathogenesis of r-axSpA, and validate the inhibition of IL-17A as a potential therapeutic approach in patients suffering from this disease.

Contributors

DvdH, DHA, and BP contributed to the design of the study and interpretation of the study results. C-CW contributed to conception of the work, acquisition of data, and interpretation of the study results. MD contributed to conception of the work, analysis of study results, and interpretation of the study results. PM and HC contributed to conception of the work, design of the study, and interpretation of study results. AD and FVdB, contributed to conception of the work and interpretation of the study results. WPM contributed to conception of the work, design of the study, acquisition of study results, and interpretation of the study results. JS contributed to conception of the work, design of the study, analysis of study results, and interpretation of study results. TT and EK contributed to interpretation of the study results. RL contributed to acquisition of study results, analysis of study results, and interpretation of the study results. FZ contributed to conception of the work, design of the study, acquisition of study results, analysis of study results, and interpretation of study results. All authors contributed to critical revisions and approved the final version of the manuscript.

Declaration of interests

DvdH has received consulting fees from AbbVie, Amgen, Astellas, AstraZeneca, BMS, Boehringer Ingelheim, Celgene, Daiichi, Eli Lilly and Company, Galapagos, Gilead, Glaxo-Smith-Kline, Janssen, Merck, Novartis, Pfizer, Regeneron, Roche, Sanofi, Takeda, and UCB and is director of Imaging Rheumatology bv. C-CW has served as a consultant for Pfizer, Celgene, Chugai, UCB Pharma, and TSH Taiwan; has received research grants from BMS, Janssen, Pfizer, Sanofi-Aventis, and Novartis; and has served on a speakers bureau for Abbott, BMS, Chugai, Eisai, Janssen, and Pfizer. MD has received research grants and consulting fees from Eli

Lilly and Company, Pfizer, AbbVie, and UCB pharma. PM has served as a consultant, speaker, and received research grants from AbbVie, Amgen, Bristol Myers Squibb, Celgene, Janssen, Novartis, Pfizer, and UCB pharma; has served as a consultant and received research grants from Eli Lilly and Company and Sun Pharma; and has served as a speaker for Genentech. AD has served on advisory boards and received research grants from AbbVie, Eli Lilly and Company, Janssen, Novartis, Pfizer, and UCB pharma. WM has received consulting fees, honoraria, research grants, and educational grants from AbbVie and Pfizer; has received consulting fees, honoraria, and educational grants from Novartis; has received consulting fees and honoraria from Eli Lilly and Company and UCB; and has received honoraria and educational grants from Janssen. FVdB received research grant support, consultancy honoraria, or speaker fees from AbbVie, Bristol-Myers Squibb, Celgene, Eli Lilly and Company, Janssen, Merck, Novartis, Pfizer, Sanofi, and UCB pharma. JS has served as a consultant and speaker for AbbVie, Janssen, Novartis, Merck, and Pfizer; has served as a consultant for Eli Lilly and Company; and has served as a speaker for UCB pharma. TT has received consulting fees and served on the speakers bureau for AbbVie, Astellas, Bristol-Myers-Squibb, Eisai, Eli Lilly and Company, Janssen, Mitsubishi Tanabe, Novartis, Takeda, and Pfizer. RL has served as a consultant or on advisory boards for AbbVie, Ablynx, Amgen, Astra-Zeneca, Bristol-Myers-Squibb, Celgene, Eli Lilly and Company, Janssen, Gilead, Galapagos, Glaxo-Smith-Kline, Novartis, Novo-Nordisk, Merck, Pfizer, Roche, Schering, TiGenix, and UCB Pharma; has received research grants from AbbVie, Amgen, Centocor, Novartis, Pfizer, Roche, Schering, and UCB Pharma; has served as a paid speaker for AbbVie, Amgen, Bristol-Myers Squibb, Janssen, Merck, Pfizer, Roche, Schering, and UCB Pharma; and is the director of Rheumatology Consultancy BV, a registered company

under Dutch Law. FZ, EK, DHA, and HC own stock and are employees of Eli Lilly and Company. BP owns stock in Eli Lilly and Company.

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Figure Legends

Figure 1: Patient disposition through Week 16 of COAST-V. *One patient was a screen failure who was accidentally randomized to placebo and discontinued prior to receiving study drug. Therefore, the patient was not counted as completing Week 16 study treatment nor discontinuing study treatment.

Figure 2: Proportion of patients achieving ASAS40 response through Week 16. Adalimumab represents an active reference arm; the study was not powered to test equivalence or noninferiority of active treatment arms to each other, including ixekizumab versus adalimumab. ASAS40 response is defined as a ≥40% improvement and an absolute improvement from baseline of ≥2-units (range 0-10) in ≥3 of 4 domains (Patient Global, Spinal Pain, Function, and Inflammation) without any worsening in the remaining domain. †p<0·0001, ‡p=0·0053. ASAS = Assessment of SpondyloArthritis international Society criteria.

Figure 3: Proportion of patients achieving ASAS20 response through Week 16. Adalimumab represents an active reference arm; the study was not powered to test equivalence or noninferiority of active treatment arms to each other, including ixekizumab versus adalimumab. ASAS20 response is defined as a ≥20% improvement and an absolute improvement from baseline of ≥1 unit (range 0 to 10) in ≥3 of 4 domains (Patient Global, Spinal Pain, Function, and Inflammation), and no worsening of ≥20% and ≥1 unit (range 0-10) in the remaining domain. †p=0·0002, ‡p=0·0015, *p=0·0075. ASAS = Assessment of SpondyloArthritis international Society criteria.

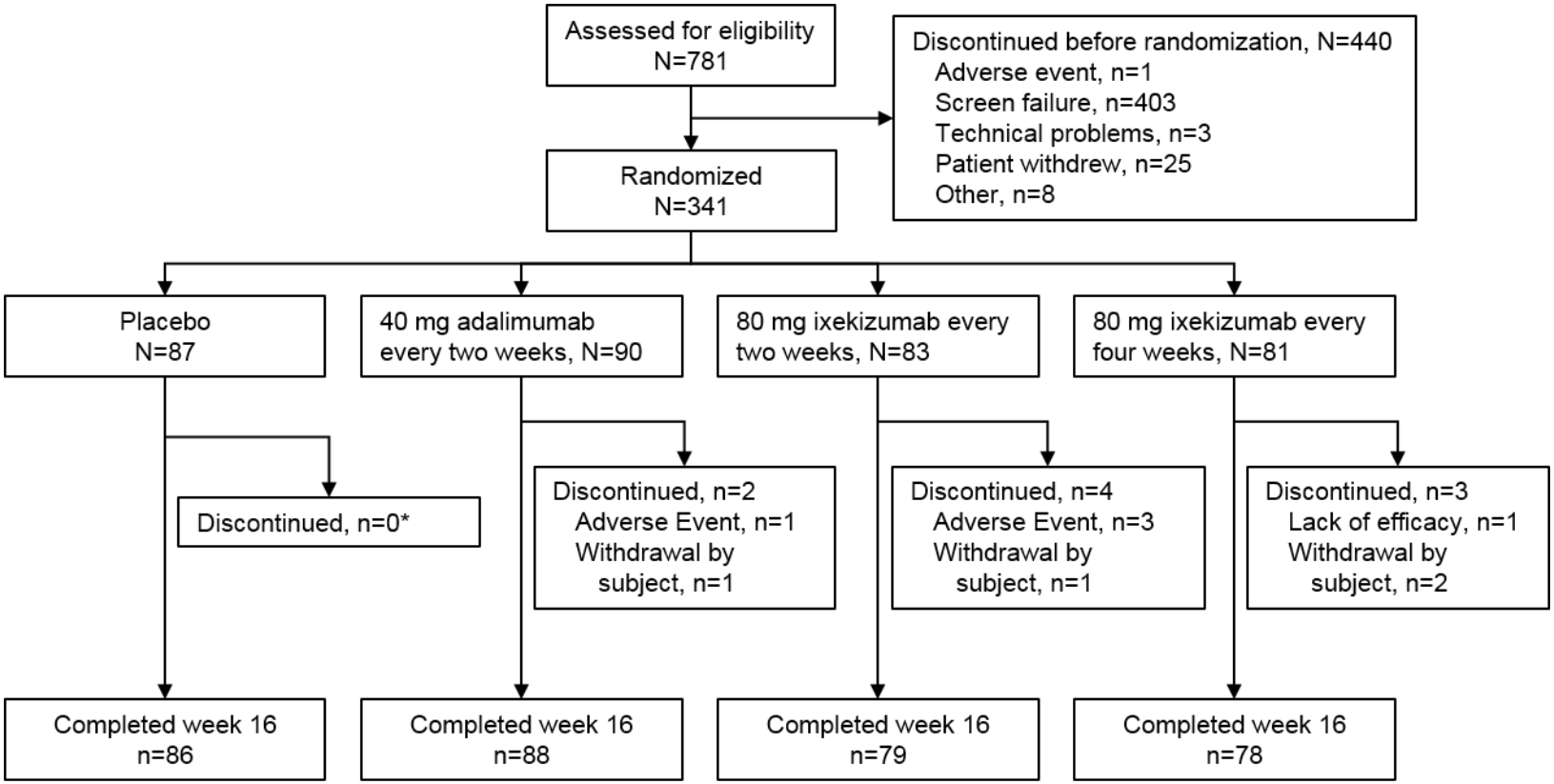
Assessed for eligibility
N=781
Discontinued before randomization, N=440
Adverse event, n=1
Screen failure, n=403
Technical problems, n=3
Patient withdrew, n=25
Other, n=8
Randomized
N=341
Placebo
N=87
40 mg adalimumab
every two weeks, N=90
80 mg ixekizumab every
two weeks, N=83
80 mg ixekizumab every
four weeks, N=81
Discontinued, n=0*
Discontinued, n=2
Adverse Event, n=1
Withdrawal by
subject, n=1
Discontinued, n=4
Adverse Event, n=3
Withdrawal by
subject, n=1
Discontinued, n=3
Lack of efficacy, n=1
Withdrawal by
subject, n=2
Completed week 16
n=86
Completed week 16
n=88
Completed week 16
n=79
Completed week 16
n=78

Figure 1

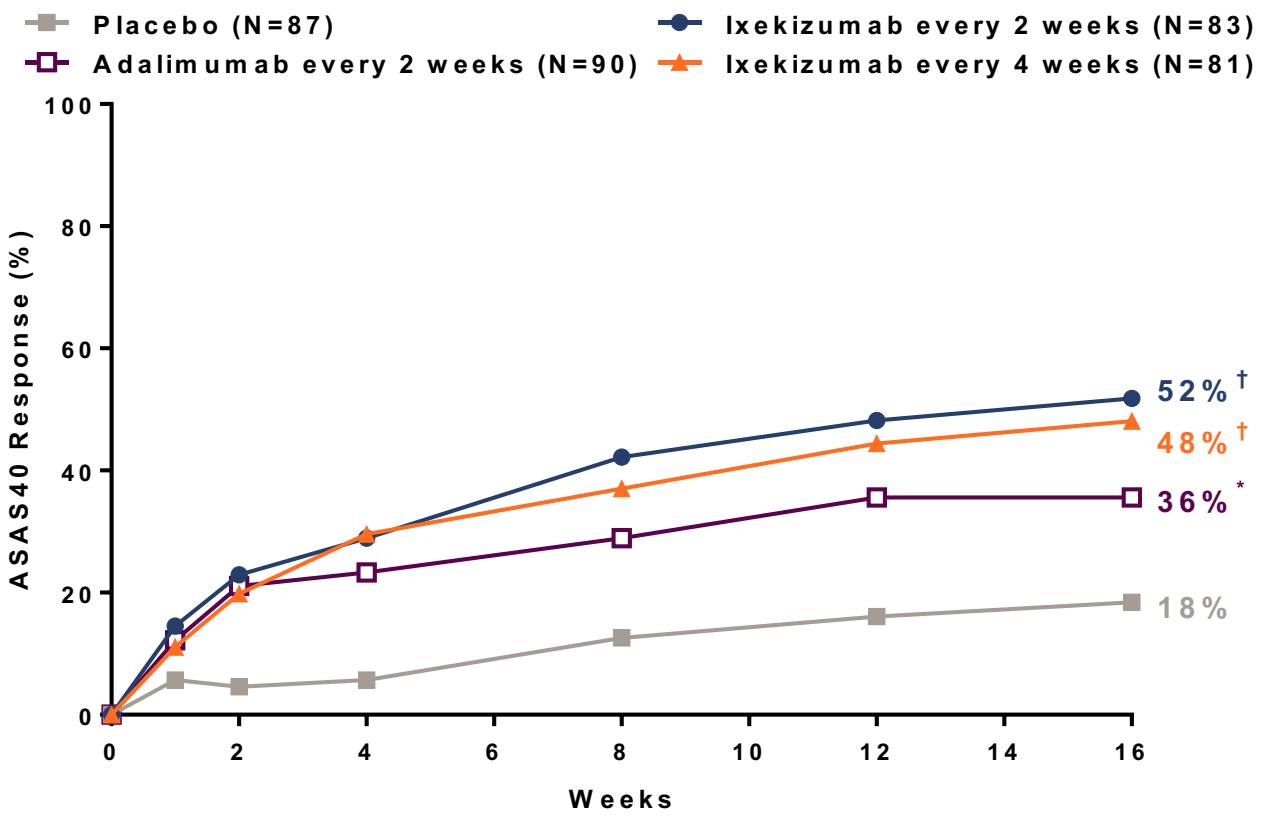
Placebo (N=87)
Ixekizumab every 2 weeks (N=83)
Adalimumab every 2 weeks (N=90)
Ixekizumab every 4 weeks (N=81)
ASAS40 Response (%)
100
80
60
40
20
0
0
2
4
6
8
10
12
14
16
Weeks
52% †
48% †
36% *
18%

Figure 2

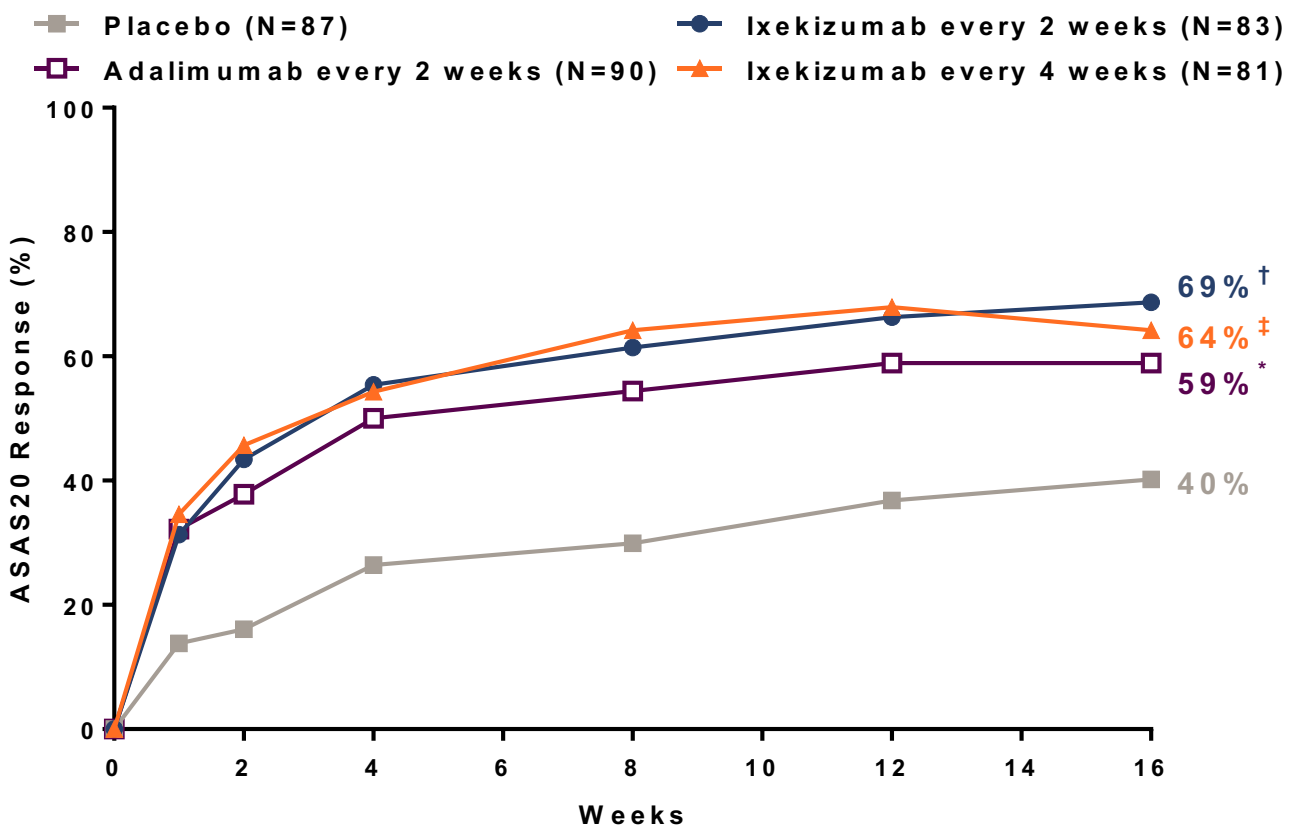
Placebo (N=87)
Ixekizumab every 2 weeks (N=83)
Adalimumab every 2 weeks (N=90)
Ixekizumab every 4 weeks (N=81)
ASAS20 Response (%)
100
80
60
40
20
0
0
2
4
6
8
10
12
14
16
Weeks
69% †
64% ‡
59% *
40%

Figure 3

	Placebo N=87[a]	Adalimumab Q2W N=90	Ixekizumab Q2W N=83	Ixekizumab Q4W N=81
Age (years)	42·7 (12·0)	41·8 (11·4)	41·3 (11·2)	41·0 (12·1)
Sex, n (%)				
Male	71 (82·6%)	73 (81·1%)	64 (77·1%)	68 (84·0%)
Female	15 (17·4%)	17 (18·9%)	19 (22·9%)	13 (16·0%)
Race, n (%)				
White	52 (60·5%)	57 (63·3%)	52 (62·7%)	52 (64·2%)
Asian	28 (32·6%)	29 (32·2%)	25 (30·1%)	25 (30·9%)
Other	6 (7·0%)	4 (4·4%)	6 (7·2%)	4 (4·9%)
Weight (kg)	79·9 (17·1)	78·2 (17·2)	76·6 (13·8)	77·6 (14·7)
<70 kg	25 (29·1)	29 (32·2)	29 (34·9)	24 (29·6)
≥70 kg	61 (70·9)	61 (67·8)	54 (65·1)	57 (70·4)
Age of onset of AxSpA (years)	26·4 (8·4)	26·5 (8·6)	25·8 (8·2)	25·4 (7·7)
Duration of symptoms since AxSpA onset (years)	16·6 (10·1)	15·6 (9·3)	15·8 (10·6)	15·8 (11·2)
Duration of disease since AxSpA diagnosis (years)	6·8 (7·6)	7·5 (7·5)	8·2 (9·0)	8·3 (9·6)
NSAID use at baseline, n (%)	78 (90·7%)	83 (92·2%)	79 (95·2%)	72 (88·9%)
csDMARDs use at baseline, n (%)	31 (36·0%)	32 (35·6%)	29 (34·8%)	33 (40·7%)
Sulfasalazine, n (%)	23 (26·7%)	25 (27·8%)	25 (30·1%)	24 (29·6%)
Methotrexate, n (%)	8 (9·3%)	8 (8·9%)	4 (4·8%)	9 (11·1%)
Patient global assessment of disease activity NRS	7·1 (1·7)	7·1 (1·7)	7·1 (1·6)	6·9 (1·5)
CRP (mg/L)	16·0 (21·0)	12·5 (17·6)	13·4 (15·3)	12·2 (13·3)
CRP >5 mg/L, n (%)	60 (69·8)	52 (57·8)	55 (66·3)	52 (64·2)
ASDAS	3·9 (0·7)	3·7 (0·8)	3·8 (0·8)	3·7 (0·7)
BASDAI	6·8 (1·2)	6·7 (1·5)	6·7 (1·6)	6·8 (1·3)
BASFI	6·4 (1·9)	6·1 (2·1)	6·3 (2·1)	6·1 (1·8)
ASAS Health Index	8·1 (3·5)	8·2 (3·7)	8·4 (3·6)	7·5 (3·3)
SF-36 PCS	32·0 (8·3)	33·5 (8·3)	34·1 (7·6)	34·0 (7·5)
MRI SPARCC spine	15·8 (21·2)	20·0 (28·4)	16·6 (23·8)	14·5 (20·6)
MRI SPARCC sacroiliac joint	5·0 (9·6)	4·7 (11·2)	6·4 (10·9)	4·5 (9·1)

Unless otherwise indicated, values are presented as mean (SD). Data are presented for patients with non-missing values

[a]The placebo population excludes one patient who was a screen failure and was accidentally randomized to placebo. This patient discontinued prior to receiving study drug.

ASAS = Assessment of SpondyloArthritis international Society criteria; ASDAS = Ankylosing Spondylitis Disease Activity Score; AxSpA = axial spondyloarthritis; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; BASFI = Bath Ankylosing Spondylitis Functional Index; CRP = c-reactive protein; csDMARD = conventional synthetic disease modifying anti-rheumatic drug; MRI = magnetic resonance imaging; NRS = numeric rating scale; NSAID = Non-steroidal anti-inflammatory drug; Q2W = every two weeks; Q4W = every four weeks; SF-36 PCS = Medical Outcomes Study 36-item Short-Form Health Survey Physical Component Score; SPARCC = Spondyloarthritis Research Consortium of Canada

Table 1. Baseline demographics and disease characteristics according to assigned treatment

Intention-to-treat population										
	Placebo N=87	Adalimumab Q2W N=90			Ixekizumab Q2W N=83			Ixekizumab Q4W N=81		
	Response	Response	p value	Difference vs placebo (95% CI)	Response	p value	Difference vs placebo (95% CI)	Response	p value	Difference vs placebo (95% CI)
Patients achieving response, n (%)										
ASAS40	16 (18·4%)	32 (35·6%)	0·0053	17·2% (4·4% to 30·0%)	43 (51·8%)	<0·0001	33·4 (19·9% to 46·9%)	39 (48·1%)	<0·0001	29·8% (16·2% to 43·3%)
ASAS20	35 (40·2%)	53 (58·9%)	0·0075	18·7% (4·2% to 33·1%)	57 (68·7%)	0·0002	28·4 (14·1% to 42·8%)	52 (64·2%)	0·0015	24·0% (9·3% to 38·6%)
BASDAI50	15 (17·2%)	29 (32·2%)	0·0119	15·0% (2·5% to 27·5%)	36 (43·4%)	0·0002	26·1% (12·8% to 39·4%)	34 (42·0%)	0·0003	24·7% (11·4% to 38·1%)
ASDAS <1·3 (inactive disease)	2 (2·3%)	14 (15·6%)	0·0087	13·3% (5·1% to 21·4%)	9 (10·8%)	0·0405	8·5% (1·2% to 15·9%)	13 (16·0%)	0·0074	13·8% (5·2% to 22·3%)
ASDAS <2·1 (inactive-to-low disease activity)	11 (12·6%)	34 (37·8%)	0·0002	25·1% (12·9% to 37·3%)	35 (42·2%)	<0·0001	29·5% (16·8% to 42·2%)	35 (43·2%)	<0·0001	30·6% (17·7% to 43·4%)
Least squares mean change from baseline (SE)										
ASDAS	-0·46 (0·10)	-1·30 (0·10)	<0·0001	-0·84 (-1·11 to -0·57)	-1·37 (0·10)	<0·0001	-0·91 (-1·18 to -0·63)	-1·43 (0·10)	<0·0001	-0·97 (-1·25 to -0·70)
CRP (mg/L)	1·4 (1·9)	-7·2 (1·9)	0·0014	-8·6 (-13·9 to -3·4)	-6·6 (2·0)	0·0036	-8·0 (-13·4 to -2·6)	-5·2 (2·0)	0·0161	-6·6 (-12·0 to -1·2)
BASFI	-1·16 (0·22)	-2·14 (0·21)	0·0012	-0·97 (-1·56 to -0·39)	-2·43 (0·22)	<0·0001	-1·27 (-1·86 to -0·67)	-2·39 (0·22)	<0·0001	-1·22 (-1·83 to -0·62)
MRI SPARCC spine score	-1·51 (1·15)	-11·57 (1·11)	<0·0001	-10·07 (-13·2 to -6·9)	-9·58 (1·17)	<0·0001	-8·08 (-11·2 to -4·9)	-11·02 (1·16)	<0·0001	-9·51 (-12·6 to -6·4)
MRI SPARCC sacroiliac joint score	0·9 (0·6)	-4·2 (0·6)	<0·0001	-5·1 (-6·7 to -3·5)	-4·3 (0·6)	<0·0001	-5·2 (-6·8 to -3·6)	-4·0 (0·6)	<0·0001	-4·9 (-6·5 to -3·3)
SF-36 PCS	3·64 (0·75)	6·90 (0·73)	0·0020	3·26 (1·20 to 5·31)	7·97 (0·77)	<0·0001	4·33 (2·23 to 6·42)	7·70 (0·78)	0·0002	4·05 (1·94 to 6·16)
ASAS Health Index	-1·25 (0·30)	-2·30 (0·29)	0·0122	-1·05 (-1·87 to -0·23)	-2·74 (0·31)	0·0005	-1·49 (-2·32 to -0·66)	-2·36 (0·31)	0·0100	-1·11 (-1·95 to -0·27)
Per-protocol set										
	Placebo N=79	Adalimumab Q2W N=76			Ixekizumab Q2W N=74			Ixekizumab Q4W N=76		
	Response	Response	p value	Difference vs placebo (95% CI)	Response	p value	Difference vs placebo (95% CI)	Response	p value	Difference vs placebo (95% CI)
Patients achieving response, n (%)										
ASAS40	14 (17·7%)	29 (38·2%)	0·0031	20·4%	40 (54·1%)	<0·0001	36·3%	38 (50·0%)	<0·0001	32·3%

	(6·6% to 34·2%)	(22·2% to 50·5%)	(18·2% to 46·3%)

p-values are for comparisons with placebo
Score ranges for continuous outcome measures: BASFI, 0-10; MRI SPARCC spine score, 0-414; MRI SPARCC sacroiliac joint score, 0-72; SF-36 PCS, 0-100; ASAS Health Index, 0-17
Adalimumab represents an active reference arm; the study was not powered to test equivalence or noninferiority of active treatment arms to each other, including ixekizumab versus adalimumab.
ASAS = Assessment of SpondyloArthritis international Society criteria; ASDAS = Ankylosing Spondylitis Disease Activity Score; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; BASFI = Bath Ankylosing Spondylitis Functional Index; CI = confidence interval; DMARD = disease modifying anti-rheumatic drug; MRI = magnetic resonance imaging; Q2W = every two weeks; Q4W = every four weeks; SE = standard error; SF-36 PCS = Medical Outcomes Study 36-item Short-Form Health Survey Physical Component Score; SPARCC = Spondyloarthritis Research Consortium of Canada

Table 2. Efficacy endpoints at Week 16 of the COAST-V study.

	Placebo N=86	Adalimumab Q2W N=90	Ixekizumab Q2W N=83	Ixekizumab Q4W N=81
	n (%)	n (%)	n (%)	n (%)
Treatment-emergent adverse events	34 (39·5%)	44 (48·9%)	36 (43·4%)	34 (42·0%)
Mild	22 (25·6%)	28 (31·1%)	28 (33·7%)	22 (27·2%)
Moderate	11 (12·8%)	14 (15·6%)	6 (7·2%)	12 (14·8%)
Severe	1 (1·2%)	2 (2·2%)	2 (2·4%)	0
Discontinuation due to adverse event	0	1 (1·1%)	3 (3·6%)	0
Serious adverse event	0	3 (3·3%)	1 (1·2%)	1 (1·2%)
Death	0	0	0	0
Common adverse events[a]				
Nasopharyngitis	6 (7·0%)	6 (6·7%)	5 (6·0%)	6 (7·4%)
Upper respiratory tract infection	4 (4·7%)	2 (2·2%)	4 (4·8%)	7 (8·6%)
Adverse events of special interest				
Neutropenia				
Grade 1	2 (2·3%)	18 (20·2%)	8 (9·8%)	6 (7·5%)
Grade 2	1 (1·2%)	3 (3·4%)	3 (3·7%)	2 (2·5%)
Grade 3	0	1 (1·1%)	0	0
Grade 4	0	0	0	0
Hepatic	1 (1·2%)	2 (2·2%)	1 (1·2%)	1 (1·2%)
Infections	13 (15·1%)	19 (21·1%)	17 (20·5%)	16 (19·8%)
Serious infections	0	1 (1·1%)	1 (1·2%)	1 (1·2%)
Candida infections	0	1 (1·1%)	0	0
Reactivated tuberculosis	0	0	0	0
Injection site reactions	4 (4·7%)	7 (7·8%)	11 (13·3%)	3 (3·7%)
Allergic reactions and hypersensitivities	1 (1·2%)	4 (4·4%)	3 (3·6%)	3 (3·7%)
Potential anaphylaxis	0	0	0	0
Cerebrocardiovascular events	0	0	0	1 (1·2%)
Malignancies	0	0	0	0
Inflammatory bowel disease	0	0	1 (1·2%)	0
Depression	0	1 (1·1%)	0	0

[a]Common TEAEs are defined as those that occurred at a frequency ≥5% for patients receiving ixekizumab (both dosing regimen populations combined).
Adalimumab represents an active reference arm; the study was not powered to test equivalence or noninferiority of active treatment arms to each other, including ixekizumab versus adalimumab.
Q2W = every two weeks; Q4W = every four weeks

Table 3. Adverse events during the 16-Week blinded treatment dosing period of COAST-V

Supplementary appendix

List of COAST-V investigators

Group de recherche en maladies osseuses, Quebec, Quebec, Canada
Louis Bessette

University of Alberta Hospital, Edmonton, Alberta, Canada
Walter Maksymowych

Centre de Recherche Musculo-Squelettique, Trois-Rivieres, Quebec, Canada
Frederic Morin

St. Clare's Mercy Hospital, St. John's, Newfoundland, Canada
Proton Rahman

Arthrohelp s.r.o., Pardubice, Czech Republic
Zdenek Dvorak

Revmatologicky ustav, Praha, Czech Republic
Radka Moravcova

Interni a revmatologicka ambulance, Inrea s.r.o., Ostrava, Czech Republic
Martina Malcova

Rheumazentrum Prof. Neeck, Bad Doberan, Mecklenburg-Vorpommern, Germany
Gunther Neeck

Charité Universitätsmedizin Berlin, Berlin, Germany
Denis Poddubnyy

Universitätsklinikum Köln, Nordrhein-Westfalen, Germany
Andrea Rubbert-Roth

Dr. Rethy Pal Korhaz es Rendelointezet, Bekescsaba, Bekes, Hungary
Tibor Balazs

Revita Reumatologiai Kft., Budapest, Hungary
Regina Cseuz

Vital Medical Center, Veszprem, Hungary
Edit Drescher

Orszagos Reumatologiai es Fizioterapias Intezet, Budapest, Hungary
Gyula Poor

Osaka University Hospital, Suita-shi, Osaka, Japan
Tetsuya Tomita

Kochi Medical School Hospital, Nankoku, Kochi, Japan
Yoshinori Taniguchi

St. Lukes International Hospital, Chuo-Ku, Tokyo, Japan
Mitsumasa Kishimoto

Juntendo University Hospital, Bunkyo-ku, Tokyo, Japan
Kurisu Tada

Kagawa University Hospital, Kita-gun, Kagawa, Japan
Hiroaki Dobashi

Osaka City University Hospital, Osaka, Japan
Kentaro Inui

Sasebo Chuo Hospital, Sasebo, Nagasaki, Japan
Yukitaka Ueki

Kuwana City Medical Center, Kuwana, Mie, Japan
Yoshifuji Matsumoto

Red Cross Okayama Hospital, Okayama, Japan
Yoshinobu Koyama

Tenri Yorozu Sodansho Hospital, Tenri, Nara, Japan
Kazuhiro Hatta

Hokkaido University Hospital, Sapporo, Hokkaido, Japan
Tatsuya Atsumi

Osaka City General Hospital, Osaka, Japan
Hitoshi Goto

The Hospital of Hyogo College of Medicine, Nishinomiya, Hyogo, Japan
Kiyoshi Matsui

Yamagata University Hospital, Yamagata, Japan
Yuya Takakubo

Kyung Hee University Hospital, Seoul, South Korea
Seung-Jae Hong
Yeon-Ah Lee

Seoul St. Mary's Hospital, Seoul, South Korea
Ji Hyeon Ju

Chungnam National University Hospital, Daejeon, South Korea
Seong Wook Kang

Hanyang University Medical Center, Seoul, South Korea
Tae-Hwan Kim

Asan Medical Center, Songpa-gu, Seoul, South Korea
Chang Keun Lee

Seoul National University Hospital, Seoul, South Korea
Eun Bong Lee

Konkuk University Hospital, Seoul, South Korea
Sang Heon Lee

Gangnam Severance Hospital, Seoul, South Korea
Min-Chan Park

Seoul Municipal Boramae Hospital, Seoul, South Korea
Kichul Shin

Kyunghee University Hospital at Gangdong, Seoul, South Korea
Sang-Hoon Lee

Medical Care and Research, S.A. de C.V., Merida, Yucatan, Mexico
Aaron Alejandro Barrera Rodriguez

Ctro Inv en Artritis y Osteoporosis SC, Mexicali, Baja California, Mexico
Fidencio Cons-Molina

Clinica en Investigación en Reumatologia y Obesidad S.C., Guadalajara, Jalisco, Mexico
Sergio Duran Barragan

Hospital Universitario de Monterrey, Monterrey, Nuevo Leon, Mexico
Cassandra Skinner

Investigación y Biomedicina de Chihuahua, SC, Chihuahua, Mexico
Cesar Pacheco Tena

Unidad de Investigacion en Enfermedades Cronico Degenerative, Guadalajara, Jalisco, Mexico
Cesar Ramos Remus

Centro de Alta Especialidad Reumatologia Inv del Potosi SC, San Luis Potosi, Mexico
Juan Cruz Rizo Rodriguez

Academisch Medisch Centrum, Amsterdam, the Netherlands
Marleen van de Sande

Antonius Ziekenhuis, Sneek, the Netherlands
Ed Griep

Reade, center for Rehabilitation and Rheumatology, Amsterdam, the Netherlands
Mike Nurmohamed

Reumatika Centrum Reumatologii, Warszawa, Poland
Malgorzata Szymanska

Lubelskie Centrum Diagnostyczne, Swidnik, Poland
Tomasz Blicharski

Centrum Medyczne AMED, Warszawa, Poland
Anna Dudek

NZOZ ZDROWIE Osteo-Medic, Bialystok, Poland
Artur Racewicz

Szpital Uniwersytecki nr 2 im. Dr J. Biziela, Bydgoszcz, Poland
Rafal Wojciechowski

Clinical Rheumatology Hospital #25, St. Petersburg, Russia
Galina Matsievskaya

City Clinical Hospital N1, Moscow, Russia
Evgeniya Shmidt

V.A. Nasonova Research Institute of Rheumatology, Moscow, Russia
Marina Stanislav

Ryazan Regional Clinincal Cardiology Dispensary, Ryazan, Russia
Sergey Yakushin

Clinical Hospital for Emergency Care, Yaroslavl, Russia
Olga Ershova

Saratov Regional Clinical Hospital, Saratov, Russia
Andrey Rebrov

Chi-Mei Medical Center, Tainan, Taiwan
Hung-An Chen

Chang Gung Memorial Hospital – Kaohsiung, Kaohsiung City, Taiwan
Ying-Chou Chen

National Taiwan University Hospital, Taipei City, Taiwan
Song-Chou Hsieh

China Medical University Hospital, Taichung, Taiwan
Joung-Liang Lan

Chung Shan Medical University Hospital, Taichung City, Taiwan
Cheng-Chung Wei

Physician Research Collaboration, LLC, Lincoln, NE, USA
Melvin Churchill

Articularis Healthcare Group, INC dba Columbia Arthritis Ctr, Columbia, SC, USA
Kathleen Flint

New England Research Associates, Trumbull, CT, USA
Geoffrey Gladstein

Desert Medical Advances, Palm Desert, CA, USA
Maria Greenwald

Klein and Associates MD, PA, Hagerstown, MD, USA
Mary Howell

Arthritis Consultants INC, Saint Louis, MO, USA
Akgun Ince

Sarasota Arthritis Center, Sarasota, FL, USA
Jeffrey Kaine

Center for Arthritis & Osteoporosis, Elizabethtown, KY, USA
Daksha Mehta

Arizona Arthritis Research, PLC, Phoenix, AZ, USA
Eric Peters

Marietta Rheumatology, Marietta, GA, USA
Roel Querubin

Univ of Texas Health Science Center – Houston, Houston, TX, USA
John Reveille

Clinical Research Center of CT/NY, Danbury, CT, USA
Richard Roseff

Glacier View Research Institute, Kalispell, MT, USA
Roger Diegel

Care Access Research - Huntington Beach, Huntington Beach, CA, USA
Christine Thai

Inclusion Criteria

Patients are eligible to be included in the study only if they meet all of the following criteria at screening or as specified:

[1] Have an established diagnosis of rad-axSpA with sacroiliitis defined radiographically according to the mNY criteria based on central reading: sacroiliitis grade ≥2 bilaterally or grades 3 to 4 unilaterally.
-and-
At least 1 SpA feature, according to ASAS criteria.
[2] Patients have a history of back pain ≥3 months with age at onset <45 years.
[3] Have active rad-axSpA defined as BASDAI ≥4 and total back pain ≥4 on an NRS at screening and baseline.
[4] Must have had an inadequate response, as determined by the investigator, to 2 or more NSAIDs at the therapeutic dose range for a total duration of at least 4 weeks OR have a history of intolerance to NSAIDs.
[5] Patients must have a history of prior therapy for axSpA of at least 12 weeks prior to screening. Examples of prior therapy may include but are not limited to physical therapy and NSAID treatment.
[6] If taking NSAIDs or cyclooxygenase-2 (COX-2) inhibitors, the dose must be stable for at least 2 weeks prior to baseline randomization.
[7] Are ambulatory male or female patients ≥18 years of age at time of screening.
[8] Must agree to use a reliable method of birth control. If a male patient, patient agrees to use a reliable method of birth control during the study and for at least 12 weeks following the last dose of investigational product, whichever is longer. Methods of birth control include, but are not limited to, condoms with spermicide and male sterilization.
-or-
If a female patient is a woman of childbearing potential who tests negative for pregnancy and agrees to use a reliable method of birth control or remain abstinent during the study and for at least 12 weeks following the last dose of investigational product, whichever is longer. Methods of contraception include, but are not limited to oral contraceptives, contraceptive patch, injectable or implantable contraceptives, intrauterine device, vaginal ring, diaphragm with contraceptive gel, or condom with contraceptive foam.
-or-
If a female patient is a woman of nonchildbearing potential, she is not required to use any method of birth control. Nonchildbearing potential is defined as women who have had surgical sterilization (hysterectomy or bilateral oophorectomy or tubal ligation) or women who are ≥60 years of age or women ≥40 and <60 years of age who have had a cessation of menses for ≥12 months and a follicle stimulating hormone (FSH) test confirming nonchildbearing potential (≥40 mIU/mL or ≥40 IU/L).
[9] Have given written informed consent approved by Lilly, or its designee, and the Investigational Review Board (IRB)/Ethical Review Board (ERB) governing the site.

Exclusion Criteria

Patients will be excluded from study enrollment if they meet any of the following criteria at screening or as specified:
[10] Have total ankylosis of the spine, as assessed locally, based on lateral radiographs of the cervical and lumbar spine.
[11] Have any condition or contraindication as addressed in the local labeling for adalimumab that would preclude the patient from participating in this protocol.
[12] Have a history of other systemic inflammatory diseases (such as but not limited to: lupus, vasculitis or RA), or other chronic pain conditions (such as but not limited to fibromyalgia) that might confound the evaluations of benefit from ixekizumab therapy. Patients with psoriasis that have never received and do not require systemic

treatment for psoriasis, such as but not limited to oral agents or biologic therapies, can be included provided these patients fulfill the entry criteria.
[13] Have active Crohn's disease (CD) or active ulcerative colitis (UC). Patients may be enrolled if they have had a history of IBD, including CD and UC, but have had no exacerbation for ≥6 months prior to baseline randomization and, if currently on treatment, must be on stable treatment for ≥6 months prior to baseline randomization.
[14] Have evidence of active anterior uveitis (an acute episode) within the last 4 weeks prior to baseline randomization. These patients may be rescreened only one time ≥4 weeks after resolution of acute symptoms.
[15] Have current or a history of lymphoproliferative disease, or signs or symptoms of lymphoproliferative disease within 5 years prior to baseline randomization; or have active or history of malignant disease within 5 years prior to baseline randomization.
[16] Have a history of fluid overload, myocardial infarction (MI), uncompensated heart failure, or evidence of new-onset ischemic heart disease or in the opinion of the investigator other serious cardiac disease, within 12 weeks prior to baseline randomization.
[17] Presence of significant uncontrolled cerebrocardiovascular events (for example, unstable angina, unstable arterial hypertension, moderate-to-severe heart failure [New York Heart Association class III/IV], or cerebrovascular accident) at screening that, in the opinion of the investigator, pose an unacceptable risk to the patient if participating in the study or of interfering with the interpretation of data.
[18] Presence of any comorbid respiratory, hepatic, renal, gastrointestinal, endocrine, hematologic disorders, at screening that, in the opinion of the investigator, pose an unacceptable risk to the patient if participating in the study or of interfering with the interpretation of data.
[19] Presence of any neurologic or neuropsychiatric disorders, at screening that, in the opinion of the investigator, poses an unacceptable risk to the patient if participating in the study or of interfering with the interpretation of data.
[20] Presence of significant uncontrolled neuropsychiatric disorder; have recent history (within 30 days prior to screening visit [Visit 1] and any time between screening visit [Visit 1] and baseline randomization [Visit 2]) of a suicide attempt; or have a score of 3 on Item 12 (Thoughts of Death or Suicide) of the Quick Inventory of Depressive Symptomatology-self report (16 items) (QIDSSR16) at screening or baseline randomization or are clinically judged by the investigator to be at risk for suicide.
[21] Have presence or personal history or family history (first degree relative) of demyelinating disorder. First degree means child, parent, or sibling, provided a blood relationship exists.
[22] Patients who have in the past 12 weeks prior to baseline randomization: had a serious infection (for example, pneumonia, cellulitis), have been hospitalized for an infection, or have received intravenous (IV) antibiotics for an infection.
-or-
In the past 24 weeks prior to baseline randomization had a serious bone or joint infection.
-or-
Have ever had an infection of an artificial joint or an infection that occurs with increased incidence in an immunocompromised host (including, but not limited to, *Pneumocystis jirovecii* pneumonia, symptomatic histoplasmosis, or coccidioidomycosis).
[23] Have a known immunodeficiency or are immunocompromised to an extent such that participation in the study would pose an unacceptable risk to the patient.
[24] Have or had a herpes zoster or any other clinically apparent varicella-zoster virus infection within 12 weeks of baseline randomization.
[25] Have any other active or recent infection within 4 weeks of baseline randomization that in the opinion of the investigator, would pose an unacceptable risk to the patient if participating in the study. These patients may be rescreened one time ≥4 weeks after resolution of symptoms.
[26] Have known allergy to rubber or latex.
[27] Have a known allergy or hypersensitivity to any biologic therapy that would pose an unacceptable risk to the patient if participating in this study.
[28] Have had surgical treatment of a joint that is to be assessed in the study within 8 weeks prior to baseline randomization or will require surgical treatment of a joint that is to be assessed in the study during the first 16 weeks of the trial.
[29] Have had any major surgery within 8 weeks prior to baseline randomization, or will require major surgery during the study that in the opinion of the investigator and in consultation with Lilly or its designee would pose an unacceptable risk to the patient.

[30] Have received cDMARDs and/or other therapies such as but not limited to gold salts, cyclosporine, azathioprine, dapsone, 6-mercaptopurine, mycophenolate mofetil, or any other immunosuppressive agents within 4 weeks prior to baseline randomization. Exception: MTX (oral or parenteral up to 25 mg/week), sulfasalazine (up to 3 g/day), or hydroxychloroquine (up to 400 mg/day) may be allowed IF at stable dose for at least 4 weeks prior to baseline randomization.
-and-
If used, must not be in any combination with other cDMARDs. If MTX is used, local standard of care is to be followed for concomitant administration of folic or folinic acid with MTX.
[31] Use of oral corticosteroids >10 mg/day prednisone or its equivalent. If patients are taking prednisone or its equivalent and the dose is ≤10 mg/day, the dose must be stable for at least 4 weeks prior to baseline randomization.
[32] Have received any prior, or are currently receiving, treatment with biologic or other immunomodulatory agents, including investigational therapies (such as but not limited to Janus kinase [JAK] inhibitors, TNF inhibitors, IL-1, IL-6, IL-23 , IL-17 [including ixekizumab], IL-17R, T cell, or B cell targeted therapies).
[33] Are currently enrolled in, have participated, or discontinued from a clinical trial involving an investigational product or nonapproved use of a drug or device within the last 30 days prior to screening or a period of at least 5 half-lives of the last administration of the drug, whichever is longer. Investigational products that are biologic or other immunomodulatory agents are not permitted regardless of washout period (described in criterion above).
[34] Are currently enrolled in any other clinical trial involving an investigational product or any other type of medical research judged not to be scientifically or medically compatible with this study.
[35] Are currently receiving or have received treatment with denosumab within 6 months prior to baseline randomization.
[36] Have received any parenteral glucocorticoid administered by intra-articular, intramuscular, or IV injection within 6 weeks prior to baseline randomization, or for whom a parenteral injection of glucocorticosteroids is anticipated during the Blinded Treatment Dosing Period (Period 2) of the study.
[37] Use of any opiate analgesic at average daily doses >30 mg/day of morphine or its equivalent or use of variable doses of any opiate analgesic within 6 weeks prior to baseline randomization. Exception for patients with pain that may interfere with undergoing an MRI: patient may receive premedication of ≤30 mg of morphine or equivalent, on the day of the MRI, for significant pain as judged by the investigator.
[38] Had a live vaccination within 12 weeks prior to baseline randomization, or intend to have a live vaccination during the course of the study, or within 12 weeks of completing treatment in this study, or have participated in a vaccine clinical study within 12 weeks prior to baseline randomization. Investigators are to review the vaccination status of their patients and follow the local guidelines for adult vaccination with nonlive vaccines intended to prevent infectious disease prior to therapy. Killed/inactive or subunit vaccines are expected to be safe; however, their efficacy with concomitant ixekizumab treatment is unknown.
[39] Had a vaccination with Bacillus Calmette-Guérin (BCG) within 12 months prior to baseline randomization, or intend to have this vaccination with BCG during the course of the study, or within 12 months of completing treatment in this study.
[40] Have a body temperature ≥38°C (100·5°F) at baseline randomization. These patients may be rescreened one time ≥4 weeks after documented resolution of elevated temperature.
[41] Have evidence or suspicion of active or latent TB.
[42] Are positive for human immunodeficiency virus serology (HIV); that is, positive for human immunodeficiency virus antibody (HIVAb).
[43] Have evidence of or test positive for hepatitis B virus (HBV) by testing positive for HBV surface antigen (HBsAg+) or anti-hepatitis B core antibody positive (HBcAb+) and are HBV DNA positive. Patients who are HBcAb+ and HBV DNA negative may be enrolled in the study. Patients who meet these criteria at screening will be identified by the central laboratory and monitored during the study.
[44] Have evidence of or test positive for hepatitis C virus (HCV). A positive test for HCV is defined as positive for hepatitis C antibody (anti–HCV Ab) and positive via a confirmatory test for HCV (for example, HCV-polymerase chain reaction).
[45] Have electrocardiogram (ECG) abnormalities that are considered clinically significant and would pose an unacceptable risk to the patient if participating in the study.
[46] Patients having contraindications to MRI (for example, claustrophobia, pacemakers, aneurysm clips, intraocular metallic fragments). For claustrophobia, premedication with benzodiazepine is allowed (investigator should assess for potential interactions with other concomitant medication(s) such as opiates).
Laboratory tests may not be repeated unless there is a technical error or clinical reason to believe a result may need to be retested within the screening period. Laboratory tests can be repeated a maximum of 1 time, and results must

be received and reviewed prior to randomization. For eligibility, the most recent lab panel must not meet any of the following criteria:
[47] At screening, have a neutrophil count <1500 cells/µL (<1·50x10^3/µL or <1·50 GI/L).
[48] At screening, have a lymphocyte count <800 cells/µL (<0·80x10^3/µL or <0·80 GI/L).
[49] At screening, have a platelet count <100,000 cells/µL (<100x10^3/µL or <100 GI/L).
[50] At screening, have aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >2·5 times the upper limit of normal (>2·5xULN).
[51] At screening, have a total white blood cell (WBC) count <3000 cells/µL (<3·00x10^3/µL or <3·00 GI/L).
[52] At screening, have hemoglobin <8·5 g/dL (85·0 g/L) for male patients and <8·0 g/dL (80 g/L) for female patients.
[53] Have other clinical laboratory test results at screening that are outside the normal reference range for the population and are considered clinically significant, per investigator assessment.
[54] Have donated blood >450 mL within the last 4 weeks prior to screening, or intend to donate blood during the course of the study. Patients who have donated blood may be rescreened one time ≥4 weeks have passed since initial screening.
[55] Are women who are lactating or breastfeeding.
[56] Are investigator site personnel directly affiliated with this study and/or their immediate families. Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted.
[57] Are Lilly employees or its designee or are employees of third-party organizations involved in the study.
[58] Are unwilling or unable to comply with the use of a data collection device to directly record data from the patient.
[59] Have any other condition that precludes the patient from following and completing the protocol, in the opinion of the investigator.

Randomization and Masking

Site personnel, patients, and the sponsor study team remained blinded to treatment through the blinded treatment dosing period. Randomization to treatment groups was determined by a computer-generated random sequence using an interactive web-response system (IWRS). Site personnel confirmed the correct treatments were assigned by entering a confirmation number found on the product packaging into the IWRS. Randomization was stratified by country and screening C-Reactive Protein (CRP, ≤ or > 5 mg/L) to achieve between group comparability. Investigational products were supplied in prefilled manual syringes with study-specific labels. The study had a double-dummy design, meaning that ixekizumab and the adalimumab active reference arm each had their own matching placebos. Ixekizumab and its matching placebo were visually indistinguishable from each other but visibly different from adalimumab and its matching placebo; adalimumab and its matching placebo were also visually indistinguishable.

To maintain blinding, all patients received three injections at Week 0. Patients randomized to ixekizumab with a 160-mg starting dose received two 80-mg injections of ixekizumab and one injection of adalimumab placebo. Patients randomized to ixekizumab with an 80-mg starting dose received one 80-mg ixekizumab injection and two placebo injections (one adalimumab placebo and one ixekizumab placebo). Patients randomized to adalimumab received two injections of ixekizumab placebo and one injection of 40 mg adalimumab. Patients randomized to placebo received two injections of ixekizumab placebo and one injection of adalimumab placebo. For the remainder of the blinded treatment dosing period, all patients received two injections Q2W. For patients randomized to ixekizumab Q2W, patients received one injection of 80 mg ixekizumab and one injection of adalimumab placebo Q2W (Weeks 2 to 14). For patients randomized to ixekizumab Q4W, patients received one 80 mg injection of ixekizumab and one injection of adalimumab placebo Q4W at Weeks 4, 8, and 12, and two injections of placebo (one ixekizumab placebo and one adalimumab placebo) at Weeks 2, 6, 10, and 14. Patients randomized to adalimumab received one 40-mg injection of adalimumab and one injection of ixekizumab placebo Q2W during Weeks 2 to 14. Patients randomized to placebo received two injections of placebo (one ixekizumab placebo and one adalimumab placebo) Q2W during Weeks 2 to 14.

Adjudication of Cerebrocardiovascular Events and Suspected Inflammatory Bowel Disease

Data on preferred terms associated with cerebrocardiovascular events and on suspected IBD were collected and adjudicated by an external Clinical Events Committee (CEC). The CEC of IBD was composed of external experts in IBD and used register EPIdemiologique des Maladies de l'Appereil Digestif (EPIMAD) criteria for adjudication of suspected IBD.[1] For adjudication of cerebrocardiovascular events, the CEC included a chairman, two cardiologists, and a neurologist. The purpose of the CEC was to adjudicate events in a blinded, consistent, and unbiased manner to ensure that events were evaluated uniformly by a single group.

Outcome Measures

The BASDAI is a patient-reported, 6-item questionnaire used to assess the severity of five major symptoms of rad-axSpA.[2] Questions assess the severity of 1) fatigue, 2) spinal pain, 3) peripheral arthritis, 4) enthesitis, 5) intensity of morning stiffness, and 6) duration of morning stiffness using a 0 to 10 NRS.[2,3] A BASDAI50 response is defined as a ≥50% improvement in score from baseline. BASDAI assessments occurred at screening, baseline, and Week 1, 2, 4, 8, 12, and 16 visits.

The ASDAS is a composite measure used to assess disease activity in ankylosing spondylitis composed of 5 domains: Total back pain (BASDAI item 2), Patient global (patient global assessment of disease activity), Peripheral pain and swelling (BASDAI item 3), Duration of morning stiffness (BASDAI item 6), and CRP (mg/L). Calculation of ASDAS score is determined as (0·121 * total back pain) + (0·110 * patient global) + (0·073 * peripheral pain and swelling) + (0·058 * duration of morning stiffness) + (0·579 * Ln [CRP + 1]). If CRP is <2 mg/L or below the limit of detection, then 2 mg/L was used in the calculation. ASDAS inactive disease is defined as ASDAS <1·3.[2,4,5] ASDAS inactive disease and change from baseline in ASDAS was determined at screening, baseline, and Week 1, 2, 4, 8, 12, and 16 visits.

The BASFI is a 10 item patient reported assessment of basic functional activities. Responses to each question are collected using a NRS ranging from 0-10, with higher scores indicating worse function. The final BASFI score is calculated as the mean of the responses on the 10 individual items.[2,6] BASFI was assessed at screening, baseline, and Week 1, 2, 4, 8, 12, and 16 visits.

Bone marrow edema of the spine and SIJ was assessed using the MRI SPARCC spine and SIJ scores. All 23 disco-vertebral units of the spine from C2-S1 were scored for MRI SPARCC spine. Each disco-vertebral unit was scored on a scale ranging from 0-18, resulting in a total score of up to 414; higher scores represent worse disease.[7] Bone marrow edema on MRI of the SIJ was assessed in all patients on six consecutive semicoronal slices. The presence or absence of BME was determined in four quadrants of each sacroiliac joint. Both the left and right SIJ were scored for BME on a scale ranging from 0 to 72, with higher scores representing worse disease.

The SF-36 is a 36 item patient-reported outcome measure to assess two overall domains of mental (mental component summary [MCS]) and physical (PCS) well-being. Summary scores range from 0-100, with higher scores indicating better levels of function or health. Individual items are answered on Likert scales. Version 2 of the SF-36 was used with a recall period of 1 week.[8] SF-36 was assessed at screening, baseline, Week 4, Week 8, and Week 16 visits.

The ASAS Health Index is a 17-item, patient-reported outcome measure to assess the impact of interventions for SpA, including axSpA. Each item consists of a question with a binary response of either "I agree" (scored as 1) or "I do not agree" (scored as 0), resulting in a total score ranging from 0 (good health) to 17 (poor health).[9] ASAS Health Index was assessed at screening, baseline, Week 4, Week 8, and Week 16 visits.

The patient global assessment of disease activity NRS and the spinal pain NRS were measured as components of ASAS20/40 response. CRP was also evaluated as a component of ASDAS response. These assessments were collected at screening, baseline, and Week 1, 2, 4, 8, 12, and 16 visits. The patient global assessment of disease activity is a single-item, patient-reported measure that asks "How active was your spondylitis on average during the last week?", recorded on an NRS scale ranging from 0 (not active) to 10 (very active). The spinal pain NRS is a two-item, patient reported measure that asks, on average during the last week: "How much pain of your spine due to ankylosing spondylitis do you have?" and "How much pain of your spine due to ankylosing spondylitis do you have at night?". Both questions are rated on an NRS ranging from 0 (no pain) to 10 (most severe pain); only the first question was used to assess ASAS20/40 response.[2]

Neutropenia grades were defined according to Common Terminology Criteria for Adverse Events; defined as grade 1 if ≥1·5 X 10^9/L to 2·0 X 10^9/L, grade 2 if ≥1·0 X 10^9/L to <1·5 X 10^9/L, grade 3 if ≥0·5 X 10^9/L to <1·0 X 10^9/L, and grade 4 if <0·5 X 10^9/L.

In addition to the primary and major secondary outcomes collected in COAST-V and reported here, the following outcomes were also assessed and will be published elsewhere:

- Proportion of patients who achieved ASAS5/6 and partial remission by ASAS criteria
- Change from baseline in the individual components of the ASAS criteria
- Proportion of patients who experienced clinically important improvement (change of ASDAS from baseline ≥1·1) or major improvement (change of ASDAS from baseline ≥2·0).
- Change from baseline in BASDAI
- Change from baseline in mobility
    - Bath Ankylosing Spondylitis Metrology Index (BASMI) (linear) and individual components
    - Chest expansion
    - Change from baseline in occiput to wall distance
- Change from baseline in SPARCC SIJ Structural Score (SSS)
- Change from baseline in MRI of the spine (Ankylosing Spondylitis Spinal Magnetic Resonance Imaging activity-Berlin Score [ASSpiMRI-Berlin])
- Change from baseline in Maastricht Ankylosing Spondylitis Enthesitis Score (MASES)
- Change from baseline in SPARCC Enthesitis Score
- Incidence and severity of peripheral arthritis by tender (TJC) and swollen joint count scores (SJC) of 46/44 joints.
- Change from baseline in the following health outcome measures:
    - Fatigue NRS score
    - Jenkins Sleep Evaluation Questionnaire (JSEQ)
    - Work Productivity Activity Impairment-Spondyloarthritis (WPAI-SpA) scores
    - SF-36 mental component scores (MCS)
    - Quick Inventory of Depressive Symptomatology-Self Report 16 items (QIDS-SR16) Score
- NSAID intake (ASAS-NSAID score and % of patients taking NSAIDs)
- Assessment of the relationship between exposure and efficacy, and exposure and immunogenicity
    - Serum trough concentrations of ixekizumab
    - Model parameters for the exposure-response relationship between ixekizumab serum trough concentrations and efficacy endpoints (such as ASAS20 and ASAS40) at week 16 and/or 52
    - Ixekizumab serum trough concentrations associated with anti-drug antibody titer subgroups

Statistical analyses

Categorical efficacy and health outcome variables were analyzed using logistic regression with treatment, geographic region, and baseline CRP status (≤ or > 5 mg/L) in the model with nonresponder imputation for missing data. SPARCC MRI spine and SIJ scores were analyzed using analysis of covariance based on observed case with treatment, geographic region, baseline CRP status (≤ or > 5 mg/L), and baseline value in the model. All other continuous efficacy and health outcome variables were analyzed using a mixed-effects model of repeated measures, which included treatment, geographic region, baseline CRP status (≤ or > 5 mg/L), baseline value, visit, baseline value-by-visit, and treatment-by-visit interaction in the model.

A multiple testing strategy for the primary and major secondary objectives was used to control the family-wise type I error rate at a 2-sided α level of 0·05. A graphical multiple testing procedure was used (Supplementary figure 1).[10] The graphical approach is a closed testing procedure and strongly controls the family-wise error rate.[11] The eight secondary outcomes were grouped into two tiers. Testing occurred as follows:

- Step 1: The primary outcome (ASAS40) is tested for ixekizumab 80 mg Q2W versus placebo at a two-sided α=0·05. If the null hypothesis is not rejected, no further testing is conducted as the α for that test is

considered 'spent' and cannot be passed to other endpoints. If the null hypothesis is rejected, then step 2 is performed.

- Step 2: The primary outcome (ASAS40) is tested for ixekizumab 80 mg Q4W versus placebo at a two-sided $\alpha=0{\cdot}05$. As in step 1, if the null hypothesis is not rejected, no further testing is conducted but if the null hypothesis is rejected, then step 3 is performed.
- Step 3: $\alpha=0{\cdot}025$ is distributed to the Tier 1 secondary outcomes for ixekizumab 80 mg Q2W and the remaining $\alpha=0{\cdot}025$ is distributed to Tier 1 secondary outcomes for ixekizumab 80 mg Q4W (Supplementary figure 2).

The major secondary endpoints for each dose is tested according to the procedure specified by the graphs. The testing process continues for the remaining outcomes by allocating the remaining α to the next set of outcomes as long as at least one hypothesis can be rejected. Each time a hypothesis is rejected, the graph is updated to reflect the reallocation of α, which is considered "recycled". This iterative process of updating the graph and reallocating α is repeated until all major secondary hypotheses have been tested or no remaining hypotheses can be rejected at their corresponding α level [11]. The weights along the edges for α allocation between ixekizumab 80 mg Q2W and ixekizumab 80 mg Q4W outcomes as well as within each of the tiers were prespecified (Supplementary figures 1-3).

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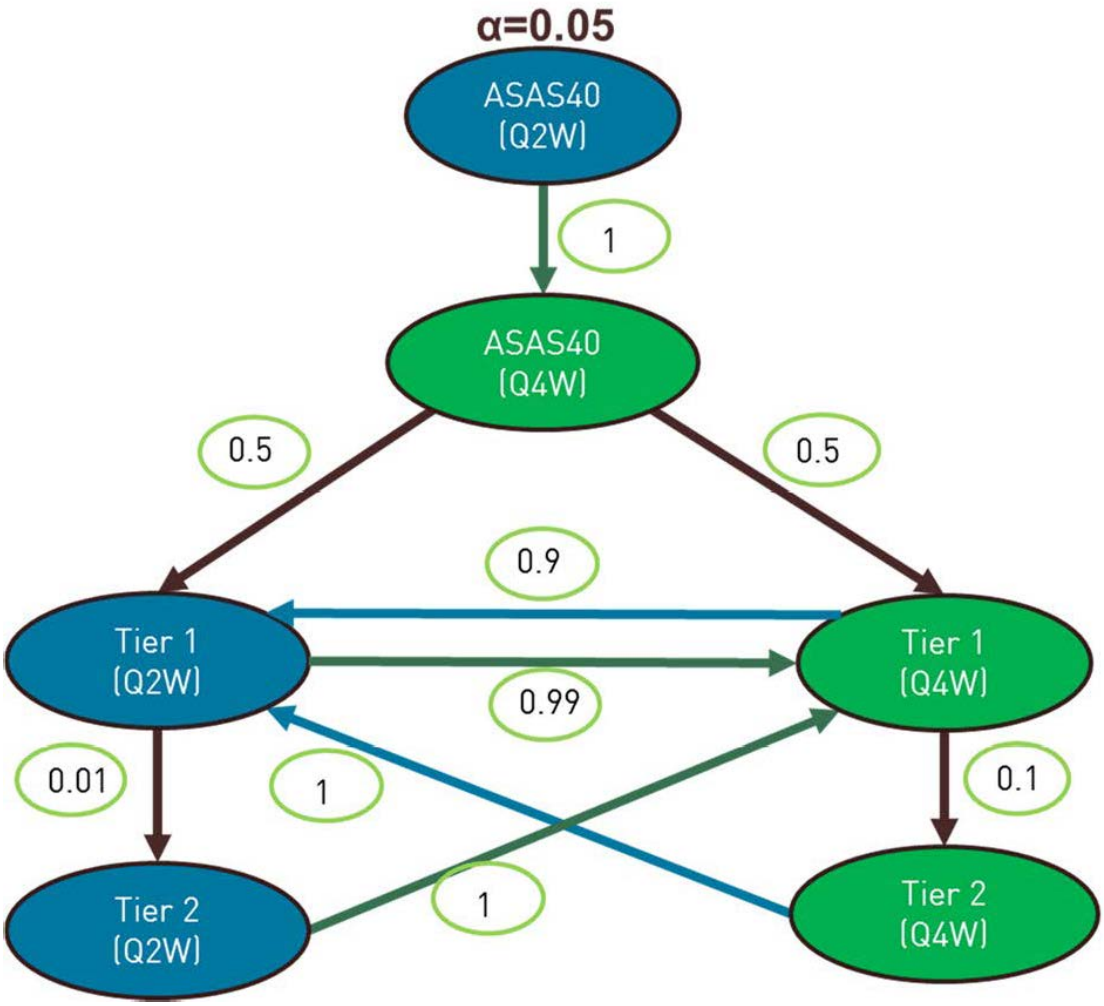
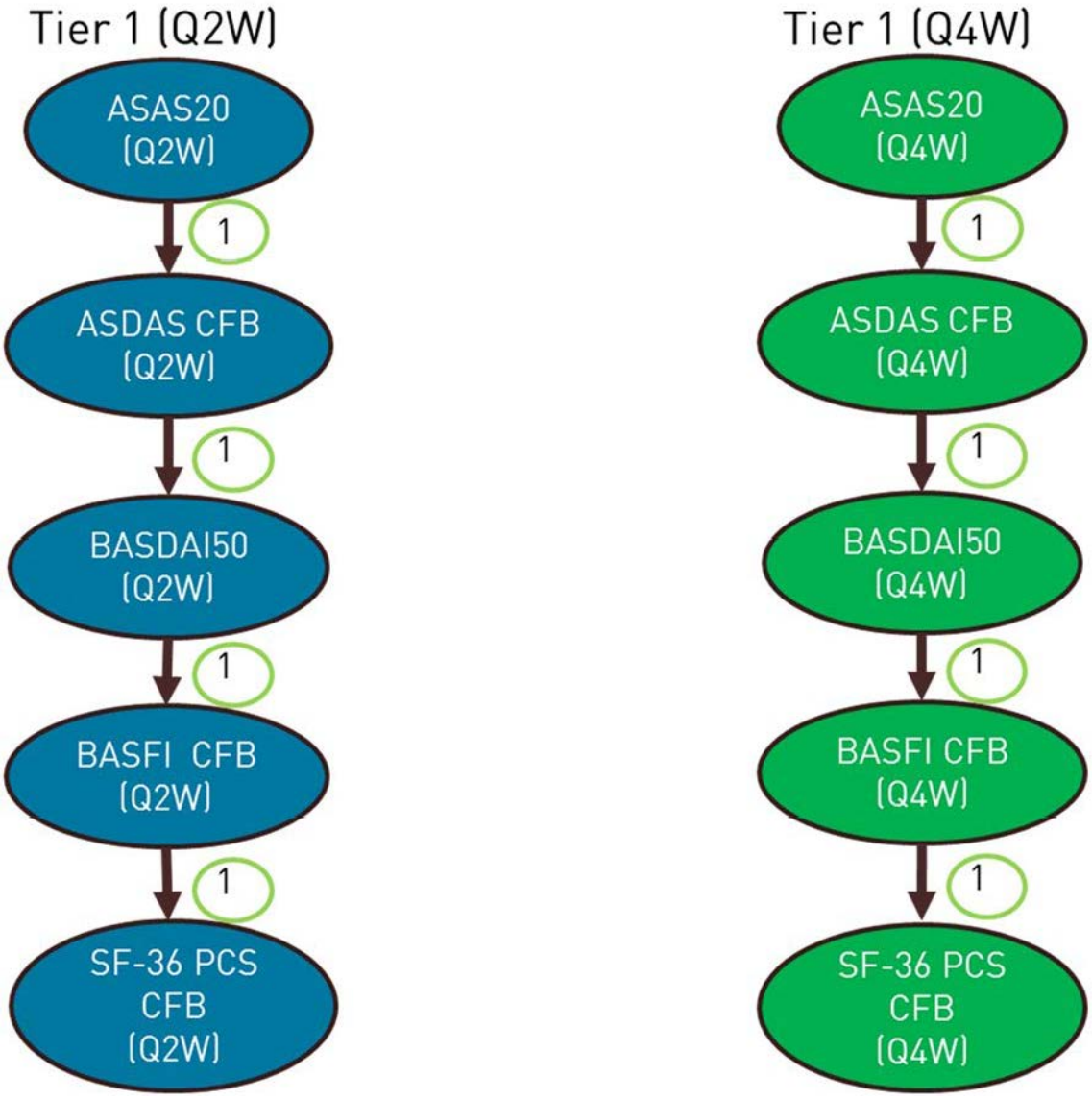
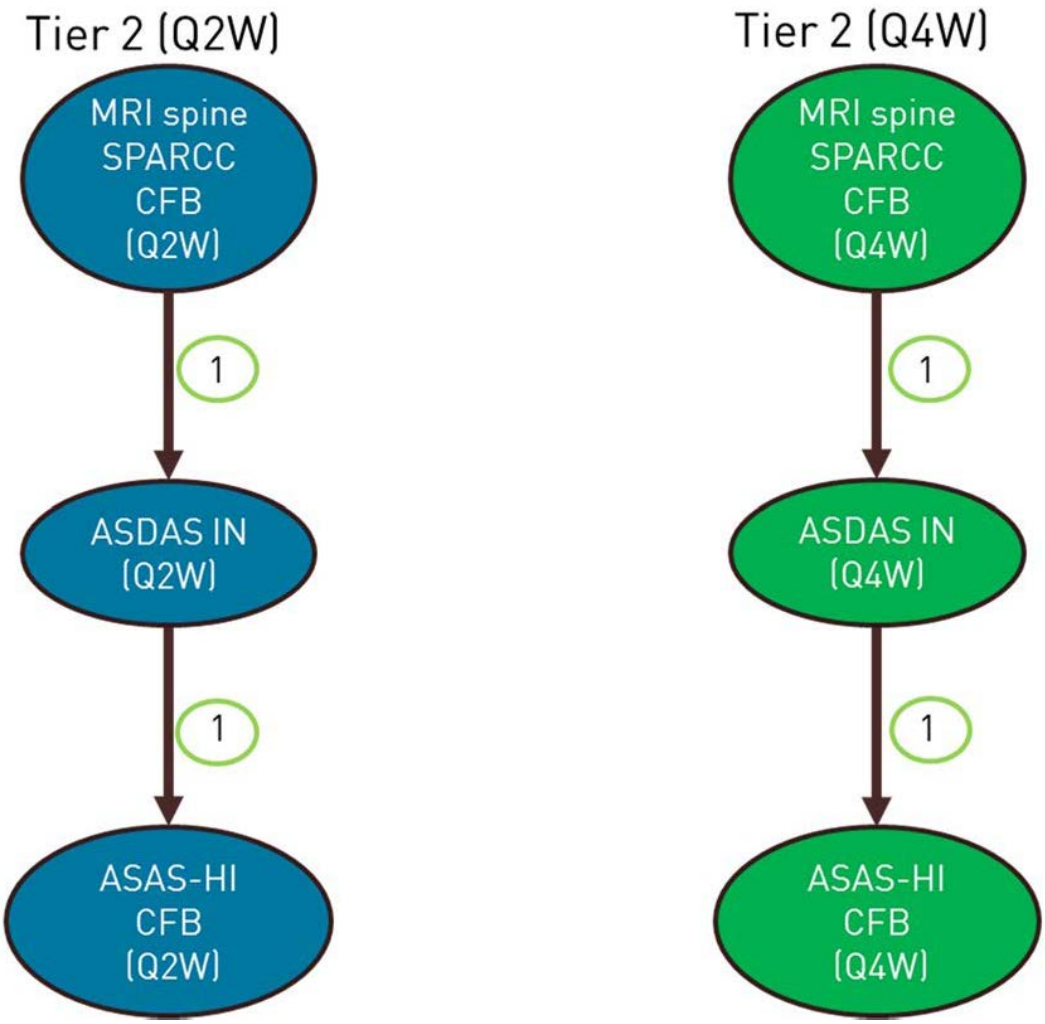


Supplementary figure 1. Illustration of graphical multiple testing procedure with initial α allocation and weights. Initial α allocation was 0·05, the weights for α allocation are shown along the arrows. Abbreviations: ASAS = Assessment of SpondyloArthritis international Society; Q2W = 80 mg ixekizumab every two weeks; Q4W = 80 mg ixekizumab every four weeks



Supplementary figure 2. Graphical multiple testing scheme used within the Tier 1 group of endpoints. The weights for α allocation are shown along the arrows. Abbreviations: ASAS = Assessment of SpondyloArthritis international Society; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; BASFI = Bath Ankylosing Spondylitis Functional Index; SF-36 PCS = Short Form 36 Physical Component Score; CFB = change from baseline; Q2W = 80 mg ixekizumab every two weeks; Q4W = 80 mg ixekizumab every four weeks



Supplementary Figure 3. Graphical multiple testing scheme used within the Tier 2 group of endpoints. The weights for α allocation are shown along the arrows. Abbreviations: ASAS-HI = Assessment of Spondyloarthritis International Society Health Index; ASDAS IN = ASDAS Ankylosing Spondylitis Disease Activity Score Inactive Disease; CFB = change from baseline; MRI Spine SPARCC = MRI of spine Spondyloarthritis Research Consortium of Canada Score; Q2W = 80 mg ixekizumab every two weeks; Q4W = 80 mg ixekizumab every four weeks

	Placebo N=87[a]	Adalimumab Q2W N=90	Ixekizumab Q2W N=83	Ixekizumab Q4W N=81
Inflammatory back pain	86 (100·0%)	89 (98·9%)	82 (98·8%)	81 (100·0%)
Arthritis	29 (33·7%)	26 (28·9%)	24 (28·9%)	29 (35·8%)
Anterior uveitis	14 (16·3%)	19 (21·1%)	21 (25·3%)	17 (21·0%)
Psoriasis	8 (9·3%)	6 (6·7%)	3 (3·6%)	4 (4·9%)
Crohn's disease or ulcerative colitis	2 (2·3%)	1 (1·1%)	2 (2·4%)	1 (1·2%)
Dactylitis	2 (2·3%)	2 (2·2%)	3 (3·6%)	1 (1·2%)
Enthesitis	26 (30·2%)	22 (24·4%)	19 (22·9%)	24 (29·6%)
Good prior response to NSAIDs	61 (70·9%)	57 (63·3%)	61 (73·5%)	58 (71·6%)
Family history of spondyloarthritis	25 (29·1%)	23 (25·6%)	20 (24·1%)	22 (27·2%)
Positive for HLA-B27	76 (89·4%)	82 (91·1%)	75 (90·4%)	75 (92·6%)
CRP >5 mg/L at screening	57 (66·3%)	58 (64·4%)	54 (65·1%)	56 (69·1%)

Values are presented as n (%) of patients with either a current or history of each condition.
[a]The placebo population excludes one patient who was a screen failure and was accidentally randomized to placebo. This patient discontinued prior to receiving study drug.
Abbreviations: CRP = C-reactive protein; HLA-B27 = human leukocyte antigen B27; NSAID = non-steroidal anti-inflammatory drug; Q2W = every two weeks; Q4W = every four weeks

Supplementary Table 1. Spondyloarthritis features at baseline