Withdrawing Ixekizumab in Patients with Psoriatic Arthritis who Achieved Minimal Disease Activity: Results from a Randomized, Double-Blind Withdrawal Study

Laura C. Coates¹, Sreekumar G. Pillai², Hasan Tahir³, Ivo Valter¹, Vinod Chandran⁵, Hideto Kameda⁶, Masato Okada⁷, Lisa Kerr², Denise Alves², So Young Park², David H. Adams², Gaia Gallo², Matthew M. Hufford², Maja Hojnik², Philip J. Mease⁸, and Arthur Kavanaugh⁹ for the SPIRIT-P3 Study Group

ClinicalTrials.gov identifier: NCT02584855.

Supported by Eli Lilly and Company.

¹Laura C. Coates, MD: Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford and NIHR Oxford Biomedical Research Centre, Oxford University Hospitals NHS Foundation Trust, Oxford, UK; ²Sreekumar G. Pillai, PhD, Lisa Kerr, MSPH, Denise Alves, BPharm, So Young Park, PhD, David H. Adams, PhD, Gaia Gallo, MD, Matthew M. Hufford, PhD, Maja Hojnik, MD: Eli Lilly and Company, Indianapolis, Indiana; ³Hasan Tahir, MD: Division of Medicine, University College London, London, UK; ⁴Ivo Valter, MD: Center for Clinical and Basic Research, Tallinn, Estonia; ⁵Vinod Chandran, MD: University of Toronto, Toronto, Canada, Krembil Research Institute, University Health Network, Toronto, Canada, and Memorial University, This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi:10.1002/ART.41716

This article is protected by copyright. All rights reserved
Disclosures: Laura C. Coates has received consulting fees and/or speaking fees and/or honoraria from AbbVie, Amgen, Biogen, Boehringer Ingelheim, Celgene, Gilead, Janssen, Eli Lilly and Company, Medac, Pfizer, and UCB (less than $10,000 each) and Novartis (more than $10,000). Sreekumar G. Pillai is an employee of Eli Lilly and Company and owns stock options in Eli Lilly and Company. Hasan Tahir has received speaker fees and contributed to advisory boards for Novartis, AbbVie, Eli Lilly and Company, and Gilead (less than $10,000 each). Ivo Valter has no disclosures to report. Vinod Chandran has received consulting fees and/or speaking fees and/or honoraria from AbbVie, Amgen, Bristol-Myers Squibb, Celgene, Eli Lilly and Company, Janssen, Novartis, Pfizer, and UCB (less than $10,000 each) and has a spouse who is an employee of Eli Lilly and Company. Hideto Kameda has received consulting fees and/or speaking fees and/or honoraria from AbbVie, Astellas, Bristol-Myers Squibb, Chugai, Eisai, Gilead, Janssen, Novartis, Pfizer, and UCB (less than $10,000 each) and Asahi-Kasei, Eli Lilly and Company, and Mitsubishi-Tanabe (more than $10,000 each), and research support from AbbVie, Asahi-Kasei, Astellas, Chugai, Eisai, Mitsubishi-Tanabe, and Novartis. Masato Okada has received consulting fees and/or speaking fees and/or honoraria from Eli Lilly and Company (less than $10,000). Lisa Kerr, Denise Alves, So Young Park, David H. Adams, Gaia Gallo, Matthew M. Hufford, and Maja Hojnik are employees of Eli Lilly and Company and own stock or stock options in Eli Lilly and Company. Philip J. Mease has received consulting fees and/or speaking fees and/or honoraria from Amgen, Bristol-Myers Squibb, Boehringer Ingelheim, Celgene, Galapagos, Genentech, Gilead, GlaxoSmithKline, Sun, and UCB (less than $10,000 each) and AbbVie, Janssen, Eli Lilly and Company, Novartis, and Pfizer (more than $10,000 each). Arthur Kavanaugh has received consulting fees and/or speaking fees and/or honoraria from Eli Lilly and Company, Novartis, Pfizer, Amgen, and AbbVie (less than $10,000 each). See Appendix A for members of the SPIRIT-P3 Study Group.
Abstract

Objective. To evaluate the effect of withdrawing ixekizumab in patients with psoriatic arthritis (PsA) who had achieved minimal disease activity (MDA) after open-label ixekizumab treatment.

Methods. SPIRIT-P3 was a multicenter, randomized, double-blind withdrawal study that enrolled biologic-naive adult patients with PsA to open-label ixekizumab (160 mg at week 0, 80 mg every two weeks [IXE Q2W]) for 36 weeks. Patients sustaining MDA for >3 consecutive months were randomized (between weeks 36-64) 1:1 to blinded IXE Q2W withdrawal (placebo) or continued IXE Q2W treatment up to week 104. The primary efficacy endpoint was time to relapse (loss of MDA) for randomized patients. Patients who relapsed were retreated with IXE Q2W until week 104.

Results. A total of 394 patients were enrolled and received open-label IXE Q2W. Of those, 158 (40%) patients achieved sustained MDA and were randomized to IXE Q2W withdrawal (placebo; N=79) or continued IXE Q2W treatment (N=79). Patients relapsed more rapidly with treatment withdrawal (median 22.3 weeks [95% CI 16.1-28.3]) vs continued IXE Q2W treatment (median not estimable, p<0.0001); 67 (85%) patients vs 30 (38%) patients relapsed, respectively. Median time to re-achieving MDA on retreatment was 4.1 weeks (95% CI 4.1-4.3); 64 (96%) of 67 patients who relapsed with treatment withdrawal re-achieved MDA on retreatment. Safety was consistent with the known safety profile for ixekizumab.

Conclusion. Continued ixekizumab therapy is superior to ixekizumab withdrawal in maintaining low disease activity in biologic-naive patients with PsA. Retreatment with ixekizumab following relapse may restore disease control in case of treatment interruption.

INTRODUCTION

Psoriatic arthritis (PsA) is a chronic, heterogeneous, inflammatory disease that may lead to serious disability if not appropriately treated.1–3 There are a number of disease-modifying antirheumatic drugs (DMARDs) available to patients with PsA, including conventional synthetic DMARDS (csDMARDs) and biologic agents (bDMARDs).4,5 These treatments can help patients achieve low disease activity or
remission across the manifestations of PsA; however, it is unclear whether patients in long-term low disease activity or remission need to continue treatment to maintain this outcome. Dose tapering or treatment discontinuation may potentially be cost effective and could limit potential side effects associated with PsA treatments. Data on treatment withdrawal in PsA are limited and inconsistent, with a few small observational, non-controlled studies available. These studies used various outcomes to evaluate the effect of bDMARD treatment withdrawal or to compare csDMARD and bDMARD withdrawal, or analyzed patients from a PsA registry, indicating that further assessment in a large, controlled withdrawal trial is warranted.

Ixekizumab, a high-affinity monoclonal antibody that selectively targets IL-17A, has been demonstrated to improve the signs and symptoms of active PsA in two phase 3 trials with long-term extensions (SPIRIT-P1 and SPIRIT-P2). The present study SPIRIT-P3 is the first large, multicenter, randomized, double-blind, placebo-controlled withdrawal study in patients with PsA. The study evaluated the efficacy and safety of withdrawing versus continuing ixekizumab in patients who had achieved stable minimal disease activity (MDA) on ixekizumab therapy and the impact of re-treatment after relapse.

PATIENTS AND METHODS

Trial design. SPIRIT-P3 was a phase 3, multicenter study with an initial open-label treatment period, followed by a randomized double-blind withdrawal period (Figure 1). The study was conducted at 86 sites in 12 countries (for a list of investigators, see Supplementary Appendix A). During the initial 36-week open-label treatment period, all patients received a starting dose of 160 mg ixekizumab at week 0, followed by 80 mg ixekizumab every two weeks (IXE Q2W) to week 36. Between week 36 and week 64, patients who achieved sustained MDA for ≥4 visits over three consecutive months were eligible for 1:1 blinded randomization to IXE Q2W (continued treatment) or IXE Q2W withdrawal (placebo) up to week 104. Patients who relapsed following ixekizumab withdrawal by no longer meeting MDA criteria received IXE Q2W in a blinded manner until week 104. Patients who did not meet randomization criteria by week 64 continued on open-label IXE Q2W uninterrupted up to week 104. Patients were discontinued from the study if they failed to achieve ≥20% improvement in tender
joint count (TJC) and swollen joint count (SJC) at week 24 or at any subsequent visit through week 104, except from the point of randomization until the visit after relapse for patients in the randomized withdrawal period. All patients signed informed consent before any study assessments, examinations, or procedures were performed. The study was approved by ethical or institutional review boards at each participating study site. The study was conducted in accordance with the consensus ethics principles of the Declaration of Helsinki, Council for International Organizations of Medical Sciences, and the International Conference on Harmonisation guideline for Good Clinical Practice, and in accordance with applicable laws and regulations. The trial was registered with ClinicalTrials.gov (NCT02584855) and the European Union Clinical Trials Register (2015-002433-22).

**Trial participants.** SPIRIT-P3 enrolled adults ≥18-years-old with a confirmed diagnosis of active PsA for ≥6 months and who met the Classification Criteria for Psoriatic Arthritis (CASPAR). Active PsA was defined as the presence of ≥3/68 tender and ≥3/66 swollen joints at screening and baseline. Patients were required to have documented inadequate response or intolerance to ≥1 csDMARD and active psoriatic skin lesions or a documented history of plaque psoriasis. Patients with current use of >1 csDMARDs; current or prior use of bDMARD or small-molecule agents for treatment of psoriasis or PsA; active Crohn’s disease or ulcerative colitis; or active uveitis were excluded.

During the initial open-label treatment period, alteration of csDMARD dosage and/or introduction of a new csDMARD were permitted. During the randomized withdrawal period, patients who were randomized were not permitted to alter csDMARD dosage and/or introduce a new csDMARD until the point of relapse. Patients who were not randomized could continue alteration of csDMARD dosage and/or introduction of a new csDMARD throughout the randomized withdrawal period.

**Randomization and blinding.** During the randomized withdrawal period, randomized treatment was assigned to eligible patients using an interactive web-response system. Treatment was assigned in a 1:1 ratio (stratified by geographic region and csDMARD use at the time of randomization) to blinded IXE Q2W (one 80-mg subcutaneous injection every two weeks) or matching placebo from week 36 to
week 104 in patients who qualified for randomized withdrawal criteria. Treatment assignment and dose adjustments remained blinded to patients, study site personnel, and investigators throughout the randomized withdrawal period from week 36 to week 104.

**Procedures.** Following open-label treatment with IXE Q2W, MDA was used to establish eligibility for entry into the randomized withdrawal period. Patients were assessed for MDA at each post-baseline visit starting at week 2. Patients were considered to have achieved MDA by fulfillment of ≥5 of 7 of the following disease activity measures: TJC ≤1, SJC ≤1, Psoriasis Area and Severity Index (PASI) total score ≤1 or body surface area (BSA) ≤3%, patient pain visual analogue scale (VAS) score ≤15, patient global disease activity VAS score ≤20, Health Assessment Questionnaire-Disability Index (HAQ-DI) score ≤0.5, and tender entheseal points ≤1. Patients who achieved sustained MDA for ≥4 visits over three consecutive months qualified for randomization to IXE Q2W or IXE Q2W withdrawal (placebo). The first opportunity for randomization at week 36 was based on three months of sustained MDA from week 24. Patients were considered to have relapsed if they lost MDA (meeting <5 of 7 of the criteria listed above) at any point in the randomized withdrawal period up to week 104.

**Efficacy and safety assessments.** The primary efficacy endpoint was time to relapse (loss of MDA) during the randomized withdrawal period. Secondary efficacy endpoints included the cumulative relapse rate and time to loss of response for each individual MDA component. Median time to regain MDA and sustained MDA was evaluated for patients who relapsed and were retreated with IXE Q2W during the randomized withdrawal period. Post hoc efficacy analyses were performed for patients who relapsed during the randomized withdrawal period and were conducted to assess the number of MDA components lost at the time of relapse, and to evaluate relapse rates in patients who achieved very low disease activity (VLDA; [VLDA+, 7/7 disease activity measures met]) and patients who achieved MDA but not VLDA (MDA+, VLDA-). Safety assessments included treatment-emergent adverse events, serious adverse events, and adverse events of special interest.

**Statistical analysis.** Sample size was determined by assuming that out of approximately 400 patients who entered the initial open-label treatment period, 34% (136 patients) would meet sustained MDA.
criteria and qualify for entry into the randomized withdrawal period (68 per treatment group); it was further assumed that approximately 60% and 20% of patients in the IXE Q2W withdrawal or IXE Q2W groups, respectively, would relapse (no longer meet MDA). According to these assumptions, 39 patients were needed to meet relapse criteria in the combined treatment groups to achieve 95% power to test the superiority of IXE Q2W to IXE Q2W withdrawal (placebo) for time to relapse at a two-sided 0.05 \( \alpha \) significance level.

The open-label population was defined as all patients who received at least 1 dose of open-label IXE Q2W during the open-label treatment period. The randomized withdrawal intent-to-treat (ITT) population included all randomized patients (those who achieved sustained MDA and three patients who did not achieve sustained MDA who were inadvertently randomized). Patients in the randomized withdrawal ITT population were analyzed according to the treatment to which they were assigned (IXE Q2W withdrawal [placebo] or continued IXE Q2W treatment). The relapse population was defined as all randomized patients who relapsed (no longer met MDA) after randomization and received at least one dose of IXE Q2W after relapse.

The primary efficacy endpoint was time to relapse (loss of MDA) during the randomized withdrawal period for the randomized withdrawal ITT population. Kaplan-Meier product limit method was used to estimate survival curves for time to variables. Treatment comparisons were performed using a log-rank test, adjusting for geographic region and csDMARD use at the time of randomization. P-values <0.05 were considered statistically significant. Time to relapse in weeks = (date of relapse – date of first injection of randomized dose of study treatment in the randomized double-blind withdrawal period +1)/7. Patients completing the withdrawal period without meeting relapse criteria were censored at the date of completion (the date of the last scheduled visit in the withdrawal period). Patients without a date of completion or discontinuation were censored at the latest non-missing date from the following dates: date of last injection of study treatment in the withdrawal period and date of last attended visit in the withdrawal period.

Cumulative proportion of relapse was analyzed using a logistic regression model with treatment, geographic region, and csDMARD use at the time of randomization as factors. Since the first
opportunity for randomization at week 36 was based on three months of sustained MDA from week 
24 in a 104-week study, the cumulative proportion of relapse was analyzed up to the first 40 weeks of 
the randomized withdrawal period.

Safety data are presented for the randomized withdrawal ITT population and for the all IXE combined 
safety population, comprised of all patients who received at least one dose of ixekizumab during the 
study.

RESULTS

Patient disposition and baseline characteristics. Between November 18, 2015 and October 30, 
2018, 511 patients were screened, of whom 100 (20%) failed screening (see Supplementary Figure 
S1). 394 patients were enrolled into the study and treated with open-label IXE Q2W. 291 (74%) 
patients completed the open-label treatment period by week 36; 103 (26%) discontinued the study. 
The main reason for discontinuation was lack of efficacy. A total of 158 (40%) of 394 patients 
achieved sustained MDA and qualified for double-blind randomization (79 to IXE Q2W withdrawal 
[placebo] and 79 to continued IXE Q2W treatment). A total of 133 (34%) of 394 patients did not 
achieve sustained MDA. These patients were not randomized and continued on open-label IXE Q2W 
(Supplementary Figure S1).

Patients enrolled in the study (open-label population) had symptoms of PsA for an average of 8 years, 
a mean age of 47 years, and 54% were female. The majority of patients used concomitant csDMARDs 
(most commonly methotrexate) and had high disease activity at baseline, with a mean TJC score of 
21, mean SJC score of 10, and 70% and 84% had enthesitis by Leeds Enthesitis Index (LEI) and 
Spondyloarthritis Research Consortium of Canada (SPARCC) index, respectively (Table 1). Patients 
in the randomized withdrawal ITT population were more frequently male and had numerically lower 
disease activity compared to the open label population. Within the randomized withdrawal ITT 
population, baseline demographics and disease characteristics were generally well balanced between 
IXE Q2W withdrawal and continued IXE Q2W treatment groups (Table 1).
**Clinical end points.** Patients relapsed (lost MDA) more rapidly with treatment withdrawal compared to continued IXE Q2W treatment ($p<0.0001$) (Figure 2). The median time to relapse for the IXE Q2W withdrawal group was 22.3 weeks (95% CI 16.1 to 28.3), while the median time to relapse for the IXE Q2W continued treatment group was not estimable, as less than 50% of patients had relapsed by the end of the study period. The cumulative relapse rate in the first 40 weeks of the randomized withdrawal period was significantly higher for the treatment withdrawal group (73%; 58 of 79 patients) compared to the group who continued IXE Q2W treatment (34%; 27 of 79 patients) ($p<0.0001$). The cumulative relapse rate from week 24 to week 104 was significantly higher for the treatment withdrawal group (85%; 67 of 79 patients) compared to the group who continued IXE Q2W treatment (38%; 30 of 79 patients) ($p<0.0001$).

Time to relapse in the individual components of MDA was also significantly shorter for patients in the treatment withdrawal group compared to the continued IXE Q2W treatment group, for patients who met the MDA component at randomization and lost response during the randomized withdrawal period (Figure 3). A total of 72% of patients lost TJC $\leq 1$ in a median of 22.3 weeks in the treatment withdrawal group vs 48% in a median of 64.3 weeks in the continued IXE Q2W treatment group ($p=0.0022$); 45% of patients lost SJC $\leq 1$ in a median of 28.7 weeks in the treatment withdrawal group vs 15% in the continued IXE Q2W treatment group, median not estimable ($p<0.0001$); 44% of patients lost PASI total score $\leq 1$ in a median of 36.0 weeks in the treatment withdrawal group vs 12% in the continued IXE Q2W treatment group, median not estimable ($p<0.0001$) and 24% of patients lost BSA $\leq 3\%$ in the treatment withdrawal group vs 4% in the continued IXE Q2W treatment group, medians not estimable ($p=0.0001$); 90% of patients lost patient pain VAS score $\leq 15$ in a median of 16.1 weeks in the treatment withdrawal group vs 42% in the continued IXE Q2W treatment group, median not estimable ($p<0.0001$); and 76% of patients lost patient global disease activity VAS score $\leq 20$ in a median of 20.6 weeks in the treatment withdrawal group vs 26% in the continued IXE Q2W treatment group, median not estimable ($p<0.0001$) (see Supplement for Kaplan-Meier time to loss of all individual components).

In the treatment withdrawal group, the majority of patients lost TJC (72%), patient pain VAS (90%), and patient global disease activity VAS (76%) components. In the continued IXE Q2W treatment
group, fewer patients lost skin response (12% PASI, 4% BSA) compared to the withdrawal group (44% PASI, p<0.0001; 24% BSA, p=0.0001), and the components lost most commonly were TJC (48%) and patient pain VAS (42%). No significant differences were noted between treatment groups in the loss of HAQ-DI and enthesitis MDA criteria.

Median time to re-achieving MDA on retreatment following relapse was 4.1 weeks (95% CI 4.1 to 4.3) in the IXE withdrawal/IXE retreatment group and 4.7 weeks (95% CI 4.1 to 8.3) in the continued IXE/IXE retreatment group, where week 0 represented the start of retreatment (Figure 4a). Sixty-four of 67 (95.5%) patients in the IXE withdrawal/IXE retreatment group and 27 of 30 (90.0%) patients in the continued IXE/IXE retreatment group re-achieved MDA during the retreatment period.

Median time to re-achieving sustained MDA (≥4 visits over three consecutive months) on retreatment following relapse was 16.1 weeks (95% CI 16.1 to 17.1) in the IXE withdrawal/IXE retreatment group and 28.1 weeks (95% CI 16.1 to 40.1) in the continued IXE/IXE retreatment group, where week 0 represented the start of retreatment (Figure 4b). Fifty-one of 58 (87.9%) patients in the IXE withdrawal/IXE retreatment group and 18 of 29 (62.1%) patients in the continued IXE/IXE retreatment group re-achieved sustained MDA during the retreatment period.

In the post hoc analysis of the randomized withdrawal ITT population, patients with VLDA (7/7 disease activity measures met) were balanced between the two treatment groups at the time of randomization (see Supplementary Figure S2). Of the 37 patients in the treatment withdrawal group who achieved VLDA at randomization, 30 (81%) relapsed (lost MDA) during the randomized withdrawal period; seven patients maintained MDA. Of the 40 patients in the continued IXE Q2W group who achieved VLDA at randomization, ten (25%) relapsed (lost MDA) during the randomized withdrawal period; 30 patients maintained MDA.

In the same post hoc analysis, of the 40 patients in the treatment withdrawal group who achieved MDA but not VLDA at randomization, 36 (90%) relapsed (lost MDA) during the randomized withdrawal period; four patients maintained MDA (see Supplementary Figure S2). Of the 38 patients in the continued IXE Q2W group who achieved MDA but not VLDA at randomization, 19 (50%) patients relapsed (lost MDA) during the randomized withdrawal period; 19 patients maintained MDA.
Safety. Overall, safety data were consistent with previous IXE PsA studies with no unexpected safety signals (Table 2). Two deaths (0.5%) occurred during the open-label treatment period. One patient died due to an accidental drowning, which was not considered related to study drug. The other was considered by the investigator to be related to study drug with death resulting from pneumonia. One (0.3%) case of inflammatory bowel disease (adjudicated as Crohn’s disease) was reported during the open-label treatment period. The patient had a previous history of irritable bowel syndrome, and the event resulted in study discontinuation.

DISCUSSION

In the SPIRIT-P3 study of biologic-naive patients with active PsA who achieve sustained MDA with the open-label treatment of IXE Q2W, continued ixekizumab therapy was superior to withdrawal in maintaining MDA. Ixekizumab withdrawal resulted in significantly earlier relapse and a higher proportion of patients relapsing compared to continued treatment. Further, ixekizumab withdrawal, compared with continued treatment, was associated with more and earlier relapse in the majority of individual components of MDA. Importantly, retreatment with ixekizumab resulted in a rapid return to MDA for the vast majority of patients who relapsed upon ixekizumab withdrawal. Overall safety findings were consistent with previous ixekizumab PsA studies.20

The attainment of remission or, alternatively, a state of low disease activity is a treatment goal in chronic inflammatory diseases including PsA. MDA is a recommended and clinically relevant treat-to-target outcome in PsA,21 and is also increasingly being used as an endpoint in clinical trials due to its discriminatory capacity between different treatments.22 We defined sustained achievement of MDA as a strict criterion to randomize patients and loss of MDA as the relapse criteria. In SPIRIT-P3, 73% of the patients who achieved sustained MDA relapsed in the first 40 weeks when ixekizumab was withdrawn, while only 34% of the patients relapsed in the continuous treatment group. Relapse started as early as 4 weeks after ixekizumab withdrawal, which was the first time point of assessment after randomization. Treatment withdrawal impacted multiple components of PsA. TJC, patient global disease activity, and pain were the most frequently lost components with ixekizumab withdrawal; the latter two were consistent with a smaller randomized withdrawal study in PsA patients who relapsed.
following discontinuation of tumor necrosis factor (TNF) inhibitor therapy (ten of 12 total treated). These observations imply that patient-reported outcomes are important indicators to assess fluctuations in disease activity, along with objective measure of disease activity such as SJC or skin scores. Of note in the SPIRIT-P3 study, significantly more patients saw re-emergence of psoriasis with treatment withdrawal compared to those who continued ixekizumab treatment. When re-treated with IXE Q2W after relapse, 96% of patients in the withdrawal group regained MDA. Many patients regained MDA as early as 4 weeks, which was the first time point of assessment after re-treatment. Of the 30 patients assigned to the continued treatment group who lost MDA and continued to receive IXE Q2W, 27 (90%) patients regained MDA, and the median time to regain MDA was 4.7 weeks. The loss of MDA on continued ixekizumab treatment may partially be due to a nocebo effect, or reflective of temporal fluctuation in the sign and symptoms of the disease, which is supported by the rapid restoration of MDA even though the actual treatment was not changed. A small proportion of patients (12 [15%] out of 79) in the withdrawal group did not relapse during the randomized withdrawal period. These patients represent drug-free remission, and the characteristics of those patients who achieve long-term remission on drug withdrawal will be of much value in clinical practice; however, the number of these patients was small, and the duration of follow-up in this study up to 104 weeks may not be long enough to reliably determine true long-term drug-free remission status.

SPIRIT-P3 is the first large, multicenter, randomized, double-blind withdrawal trial in PsA completed to date. A few previous non-controlled observational and open-label studies investigated the possibility of continued PsA remission/low disease activity following csDMARD and/or bDMARD withdrawal. These studies differed in the patient population, definition of remission/low disease activity and flare, and provided conflicting results. Two small studies (n=26 and n=17) showed that the vast majority of PsA patients quickly lost disease control upon csDMARD or bDMARD discontinuation, while two somewhat larger studies (n=47 and n=236) reported that up to 24% of patients may be able to maintain drug-free remission for up to 18 to 56 weeks. Finally, in an analysis of TNF inhibitor withdrawal in a cohort of 325 patients from the CORRONA registry, 45% of patients lost low disease activity in a median of 29 months, indicating that some PsA patients maintained clinical benefit upon TNF inhibitor discontinuation. Beside several other important
methodological differences, prior duration of TNF therapy in the CORRONA registry patients was for
the mean of 1.5 years, which is significantly longer than the maximum 36-week duration of open-
label ixekizumab treatment prior to withdrawal in our study. While the duration of prior low disease
activity was not reported in CORRONA, the duration of prior remission/low disease activity was
found to be a positive predictor for maintaining drug-free disease control in rheumatoid arthritis.\textsuperscript{23,24}
Similar to our findings in PsA, withdrawal of biologic (TNF inhibitor) treatment has generally been
shown to result in rapid flare in patients with axial spondyloarthritis, another subset of the
spondyloarthritis group of diseases.\textsuperscript{25–28} It remains to be evaluated what patient and disease
characteristics, including some potential biomarkers, may predict the outcome of treatment
discontinuation in patients with PsA.

The SPIRIT-P3 study has limitations that should be considered. The approved dosing regimen for
PsA in the United States and Europe is ixekizumab every four weeks (IXE Q4W), while the dose used
in this study was IXE Q2W. This study was started when the pivotal phase 3 studies in PsA (SPIRIT-
P1 and P2) were still ongoing, evaluating the safety and efficacy of ixekizumab at two dosing
regimens: 80 mg Q2W or Q4W. The efficacy and safety of ixekizumab at the two dosing regimens are
similar;\textsuperscript{12,15} thus, the results from this study are scientifically and clinically relevant. The study was
designed to assess complete treatment discontinuation and did not assess dose reduction. Approaches
in clinical practice may differ, where patients may taper or discontinue treatment after longer periods
of sustained remission/low disease activity than assessed in this study.

In conclusion, continued ixekizumab therapy was superior to withdrawal in maintaining MDA in
biologic-naive patients with PsA who achieved sustained MDA on ixekizumab Q2W. Among patients
who relapsed after ixekizumab withdrawal, the vast majority regained MDA after retreatment with
ixekizumab Q2W. These results indicate that continuous ixekizumab treatment is optimal for
maintaining good disease control in PsA; however, patients can regain disease control after
retreatment with ixekizumab in case of treatment interruption.
AUTHOR CONTRIBUTIONS

All authors contributed to data analyses and interpretation of study results and gave critical revisions and approved the final version of the manuscript.

Study conception and design. Coates, Kerr, Adams.

Acquisition of data. Pillai, Tahir, Valter, Alves, Adams.

Analysis and interpretation of data. Coates, Pillai, Tahir, Valter, Chandran, Kameda, Okada, Kerr, Alves, Park, Adams, Gallo, Hufford, Hojinik, Mease, Kavanaugh.

ROLE OF THE STUDY SPONSOR

Eli Lilly and Company (Indianapolis, IN, USA) funded this study. Eli Lilly and Company contributed to the study design, data collection, data analysis, data interpretation, preparation of the manuscript, and the decision to submit the paper for publication. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication. All authors critically revised the manuscript. Medical writing support was provided by Melody Pupols, PhD of Syneos Health (support for this assistance was funded by Eli Lilly and Company) and Emily K. Blue, PhD (an employee of Eli Lilly and Company). We also thank the investigators of SPIRIT-P3 (see Supplementary Appendix A) for their contributions and the patients who participated in SPIRIT-P3.
REFERENCES

1. Mease PJ, Armstrong AW. Managing patients with psoriatic disease: the diagnosis and pharmacologic treatment of psoriatic arthritis in patients with psoriasis. Drugs 2014;74:423–41.

2. Zachariae H, Zachariae R, Blomqvist K, Davidsson S, Molin L, Mørk C, et al. Quality of life and prevalence of arthritis reported by 5,795 members of the Nordic Psoriasis Associations. Data from the Nordic Quality of Life Study. Acta Derm Venereol 2002;82:108–13.

3. Boehncke WH, Menter A. Burden of disease: psoriasis and psoriatic arthritis. Am J Clin Dermatol 2013;14:377–88.

4. Gossec L, Smolen JS, Ramiro S, de Wit M, Cutolo M, Dougados M, et al. European League Against Rheumatism (EULAR) recommendations for the management of psoriatic arthritis with pharmacological therapies: 2015 update. Ann Rheum Dis 2016;75:499–510.

5. Lee MP, Lii J, Jin Y, Desai RJ, Solomon DH, Merola JF, et al. Patterns of systemic treatment for psoriatic arthritis in the US: 2004–2015. Arthritis Care Res (Hoboken) 2018;70:791–6.

6. Araujo EG, Finzel S, Englbrecht M, Schreiber DA, Faustini F, Hueber A, et al. High incidence of disease recurrence after discontinuation of disease-modifying antirheumatic drug treatment in patients with psoriatic arthritis in remission. Ann Rheum Dis 2015;74:655–60.

7. Moverley A, Coates L, Marzo-Ortega H, Waxman R, Torgerson D, Cocks K, et al. A feasibility study for a randomised controlled trial of treatment withdrawal in psoriatic arthritis (REmoval of treatment for patients in REmission in psoriatic ArThritis (RETREAT (F))). Clin Rheumatol 2015;34:1407–12.

8. Chimenti MS, Esposito M, Giunta A, Graceffa D, Bobino G, Teoli M, et al. Remission of psoriatic arthritis after etanercept discontinuation: analysis of patients' clinical characteristics leading to disease relapse. Int J Immunopathol Pharmacol 2013;26:833–8.
Cantini F, Niccoli L, Nannini C, Cassarè E, Pasquetti P, Olivieri I, et al. Frequency and duration of clinical remission in patients with peripheral psoriatic arthritis requiring second-line drugs. Rheumatology (Oxford) 2008;47:872–6.

Huynh DH, Boyd TA, Etzel CJ, Cox V, Kremer J, Mease P, et al. Persistence of low disease activity after tumour necrosis factor inhibitor (TNFi) discontinuation in patients with psoriatic arthritis. RMD Open 2017;3:e000395.

Liu L, Lu J, Allan BW, Tang Y, Tetreault J, Chow C, et al. Generation and characterization of ixekizumab, a humanized monoclonal antibody that neutralizes interleukin-17A. J Inflamm Res 2016;9:39–50.

Mease PJ, van der Heijde D, Ritchlin CT, Okada M, Cuchacovich RS, Shuler CL, et al. Ixekizumab, an interleukin-17A specific monoclonal antibody, for the treatment of biologic-naive patients with active psoriatic arthritis: results from the 24-week randomised, double-blind, placebo-controlled and active (adalimumab)-controlled period of the phase III trial SPIRIT-P1. Ann Rheum Dis 2017;76:79–87.

van der Heijde D, Gladman DD, Kishimoto M, Okada M, Rathmann SS, Moriarty SR, et al. Efficacy and safety of ixekizumab in patients with active psoriatic arthritis: 52-week results from a phase III study (SPIRIT-P1). J Rheumatol 2018;45:367–77.

Chandran V, van der Heijde D, Fleischmann RM, Lespessailles E, Helliwell PS, Kameda H, et al. Ixekizumab treatment of biologic-naive patients with active psoriatic arthritis: 3-year results from a phase III clinical trial (SPIRIT-P1). Rheumatology (Oxford) 2020 (ahead of print). doi: 10.1093/rheumatology/kez684.

Nash P, Kirkham B, Okada M, Rahman P, Combe B, Burmester G, et al. Ixekizumab for the treatment of patients with active psoriatic arthritis and an inadequate response to tumour necrosis factor inhibitors: results from the 24-week randomised, double-blind, placebo-controlled period of the SPIRIT-P2 phase 3 trial. Lancet 2017;389:2317–27.
Genovese MC, Combe B, Kremer JM, Tsai T, Behrens F, Adams DH, et al. Safety and efficacy of ixekizumab in patients with PsA and previous inadequate response to TNF inhibitors: week 52 results from SPIRIT-P2. Rheumatology (Oxford) 2018;57:2001–11.

Orbai AM GA, Kerr L, Constantin A. Efficacy and safety of ixekizumab in patients with active psoriatic arthritis and previous inadequate response to TNF inhibitors: two-year follow-up from a phase 3 study. Arthritis Rheumatol 2018;70 (suppl 10).

Coates LC, Fransen J, Helliwell PS. Defining minimal disease activity in psoriatic arthritis: a proposed objective target for treatment. Ann Rheum Dis 2010;69:48–53.

Coates LC, Helliwell PS. Defining low disease activity states in psoriatic arthritis using novel composite disease instruments. J Rheumatol 2016;43:371–5.

Mease P, Roussou E, Burmester GR, Goupille P, Gottlieb A, Moriarty S, et al. Safety of ixekizumab in patients with psoriatic arthritis: results from a pooled analysis of three clinical trials. Arthritis Care Res (Hoboken) 2019;71:367–78.

Coates LC, Helliwell PS. Treat to target in psoriatic arthritis-evidence, target, research agenda. Curr Rheumatol Rep 2015;17:517.

Coates LC, Strand V, Wilson H, Revicki D, Stolshek B, Samad A, et al. Measurement properties of the minimal disease activity criteria for psoriatic arthritis. RMD Open 2019;5:e001002.

Ajeganova S, Huizinga T. Sustained remission in rheumatoid arthritis: latest evidence and clinical considerations. Ther Adv Musculoskelet Dis 2017;9:249–62.

Tanaka Y, Takeuchi T, Mimori T, Saito K, Nawata M, Kameda H, et al. Discontinuation of infliximab after attaining low disease activity in patients with rheumatoid arthritis: RRR (remission induction by Remicade in RA) study. Ann Rheum Dis 2010;69:1286–91.
25 Baraliakos X, Listing J, Brandt J, Zink A, Alten R, Burmester G, et al. Clinical response to discontinuation of anti-TNF therapy in patients with ankylosing spondylitis after 3 years of continuous treatment with infliximab. Arthritis Res Ther 2005;7:R439–44.

26 Brandt J, Listing J, Haibel H, Sörensen H, Schwebig A, Rudwaleit M, et al. Long-term efficacy and safety of etanercept after readministration in patients with active ankylosing spondylitis. Rheumatology (Oxford) 2005;44:342–8.

27 Sebastian A, Wojtala P, Lubinski L, Mimier M, Chlebicki A, Wiland P. Disease activity in axial spondyloarthritis after discontinuation of TNF inhibitors therapy. Reumatologia 2017;55:157–62.

28 Song IH, Althoff CE, Haibel H, Hermann KGA, Poddubnyy D, Listing J, et al. Frequency and duration of drug-free remission after 1 year of treatment with etanercept versus sulfasalazine in early axial spondyloarthritis: 2 year data of the ESTHER trial. Ann Rheum Dis 2012;71:1212–5.
|                                | Open-label population | Randomized withdrawal ITT population |
|--------------------------------|-----------------------|--------------------------------------|
|                                | IXE Q2W | IXE Q2W withdrawal | IXE Q2W |
|                                | N=394   | N=79                | N=79    |
| Age (years), mean (SD)         | 47 (11.4) | 43 (10.5)           | 44 (10.8) |
| Male, n (%)                    | 182 (46)  | 40 (51)             | 47 (60)  |
| BMI (kg/m\(^2\)), mean (SD)   | 29 (6.3)  | 29 (7.2)            | 28 (5.0) |
| Time since PsA onset (years), mean (SD) | 7.9 (7.1) | 7.5 (7.5)          | 7.1 (6.3) |
| Current csDMARD use\(^a\), n (%) | 291 (74)  | 60 (76)              | 59 (75)  |
| TJC (68 joints), mean (SD)     | 21 (14.3) | 16 (12.3)           | 17 (11.5) |
| SJC (66 joints), mean (SD)     | 10 (8.1)  | 9.0 (5.6)           | 9.4 (7.4) |
| HAQ-DI total score, mean (SD)  | 1.2 (0.6)  | 1.0 (0.5)           | 1.1 (0.6) |
| Pain VAS, mean (SD)            | 61 (18.0)  | 59 (18.9)           | 60 (19.4) |
| PatGA, mean (SD)               | 62 (18.9)  | 61 (19.5)           | 59 (19.4) |
| PASI total score\(^b\), mean (SD) | 7.1 (9.5)  | 7.6 (10.2)          | 8.4 (8.2) |
| BSA\(^c\), mean (SD)          | 14 (17.6)  | 14 (17.8)           | 17 (18.2) |
| LEI score >0, n (%)            | 276 (70.1) | 47 (59.5)           | 48 (60.8) |
| LEI total score\(^d\), mean (SD) | 2.6 (1.5)  | 2.5 (1.3)          | 2.4 (1.3) |
| Enthesitis SPARCC score >0, n (%) | 330 (83.8) | 57 (72.2)         | 62 (78.5) |
| Enthesitis SPARCC score\(^e\), mean (SD) | 5.3 (3.7)  | 4.4 (3.3)          | 4.6 (3.1) |

\(^a\)Current csDMARD use reported in open-label population and at time of randomization (methotrexate, sulfasalazine, leflunomide, hydroxychloroquine, or cyclosporine); \(^b\)In patients with baseline PASI >0; \(^c\)In patients with baseline BSA >0; \(^d\)In patients with baseline LEI >0; \(^e\)Based on 16-point entheseal point assessment in patients with baseline enthesitis SPARCC >0. BMI = body mass index; BSA = body surface area; csDMARD = conventional synthetic disease-modifying antirheumatic drug; HAQ-DI = Health Assessment Questionnaire-Disability Index; IXE
Q2W = ixekizumab 80 mg every 2 weeks; LEI = Leeds Enthesitis Index; N = number of patients in analysis population; PASI = Psoriasis Area and Severity Index; PatGA = Patient’s Global Assessment of Disease Activity; PsA = psoriatic arthritis; SD = standard deviation; SJC = swollen joint count; SPARCC = Spondyloarthritis Research Consortium of Canada; TJC = tender joint count; VAS = Visual Analog Scale.
Table 2. Safety results in the SPIRIT-P3 study

|                      | Randomized withdrawal | All IXE combined |
|----------------------|-----------------------|------------------|
|                      | ITT population<sup>a</sup> |                  |
| IXE Q2W withdrawal   |                       |                  |
| N                    | 79                    | 79               |
| **Exposure, person years** | 42.1               | 71.0             | 631.1           |
| **TEAE (≥1), n (%)**  |                       |                  |
| Mild                 | 30 (38.0)             | 24 (30.4)        | 156 (39.6)      |
| Moderate             | 9 (11.4)              | 14 (17.7)        | 144 (36.5)      |
| Severe               | 1 (1.3)               | 2 (2.5)          | 25 (6.3)        |
| **Serious AE, n (%)**| 2 (2.5)               | 1 (1.3)          | 28 (7.1)        |
| **Discontinuations due to AE, n (%)** | 1 (1.3) | 0 | 21 (5.3) |
| **Deaths**           | 0                     | 0                | 2 (0.5)         |
| **Most frequent TEAEs<sup>c</sup>** |                   |                  |
| Nasopharyngitis      | 4 (5.1)               | 11 (13.9)        | 70 (17.8)       |
| Upper respiratory tract infection | 4 (5.1) | 9 (11.4) | 65 (16.5)       |
| Injection site reaction | 0               | 1 (1.3)          | 62 (15.7)       |
| Bronchitis           | 1 (1.3)               | 4 (5.1)          | 34 (8.6)        |
| Urinary tract infection | 3 (3.8)         | 1 (1.3)          | 21 (5.3)        |
| Sinusitis            | 1 (1.3)               | 0                | 20 (5.1)        |
| **Adverse events of special interest<sup>d</sup>** |                   |                  |
| Infections           | 20 (25.3)             | 29 (36.7)        | 243 (61.7)      |
| Serious infections   | 1 (1.3)               | 0                | 5 (1.3)         |
| Injection-site reactions | 0           | 2 (2.5)          | 80 (20.3)       |
| Hepatic event        | 3 (3.8)               | 6 (7.6)          | 37 (9.4)        |
| Allergic reactions/hypersensitivities<sup>e</sup> | 0 | 3 (3.8) | 25 (6.3) |
| Cytopenias           | 1 (1.3)               | 5 (6.3)          | 21 (5.3)        |
| Condition                                | AE Count | IXE Count | TEAE Count |
|-----------------------------------------|----------|-----------|------------|
| Depression                              | 0        | 0         | 13 (3.3)   |
| Cerebrocardiovascular events\(f\)      | 0        | 0         | 3 (0.8)    |
| Malignancies                            | 0        | 0         | 2 (0.5)    |
| Inflammatory bowel disease\(f\)        | 0        | 0         | 1 (0.3)\(g\) |

\(a\) Randomization to relapse or week 104; \(b\) Patients who had at least 1 dose of IXE; \(c\) \(\geq\)5\% in the all IXE combined group; \(d\) Reported as adverse events according to the high-level term in MedDRA, V.21.1. Groups of adverse events of special interest are shown; no events of interstitial lung disease were reported in any group; \(e\) No allergic reactions/hypersensitivity events were anaphylaxis events; \(f\) Adjudicated event; \(g\) Crohn’s disease. AE = adverse event; IXE = ixekizumab; MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment emergent adverse event.
FIGURE LEGENDS

Figure 1. SPIRIT-P3 study design. aEncompassed week 0 (study baseline) up to week 36. bBetween weeks 36 and 64 (inclusive), patients treated with IXE Q2W for at least 36 weeks who had achieved 4 consecutive visits of meeting MDA were eligible for randomization at the visit at which these criteria were met. Patients were randomized 1:1 to IXE Q2W or Withdrawal (PBO). Patients remained in their treatment arms up to week 104, or until relapse (no longer met MDA), at which point they received IXE Q2W up to week 104. cPatients who did not meet the randomization eligibility criteria by week 64 remained on IXE Q2W uninterrupted up to week 104. dPatients were discontinued from the study if they failed to achieve ≥20% improvement in tender joint count and swollen joint count at week 24 or at any subsequent visit through week 104, except from the point of randomization until the visit after relapse for patients in the randomized double-blind withdrawal period. IXE Q2W = ixekizumab 80 mg every 2 weeks; MDA = minimal disease activity; PBO = placebo.

Figure 2. Time to relapse (loss of MDA) in the randomized withdrawal intent-to-treat population. p<0.0001 vs. IXE Q2W Withdrawal. CI = confidence interval; NE = not estimable.

Figure 3. Time to loss of response of individual components of MDA in the randomized withdrawal intent-to-treat population. p-value is from adjusted log-rank test stratified by geographic region and csDMARD use. CI = confidence interval; MDA = minimal disease activity; NE = not estimable; Nx = the number of patients who met the MDA component at randomization and subsequently lost the response.

Figure 4. Time to re-achieving A, MDA following relapse or B, sustained MDA (≥4 visits over three consecutive months) following relapse. A, Week 0 represents retreatment, and there are no data after week 40. B, Week 0 represents retreatment, and there are no data after week 60.
APPENDIX A: MEMBERS OF THE SPIRIT-P3 STUDY GROUP

Members of the SPIRIT-P3 Study Group are as follows: Khalid Ahmed, Nicholas Barkham, Linda Belhorn, Daniela Bichovska, Michaela Blahova, Ladislav Bortlik, Johannes Breedt, Michael Brooks, Paul Caldron, Silvia Ciernik, Stefan Daniluk, Roger Diegel, Pavol Dobrovodsky, Eva Dokoupilova, Leobardo Teran Estrada, Francisco Javier Blanco Garcia, Olena Garmish, Iurii Gasanov, Mariela Geneva-Popova, David Goddard, Oleksandr Golovchenko, Katarzyna Gruszecka, Tomas Hala, Jolana Hejlova, Mary Howell, Elena Ilivanova, Ramina Jajoo, Ewa Kaliszuk-Kaminska, Nadezhda Kapandjieva, Steven Klein, Mariusz Korkosz, Milan Krcpicar, Dolores Alonso Martinez, Nomawethu Hejlova, Mary Howell, Elena Ilivanova, Ramina Jajoo, Ewa Kaliszuk-Kaminska, Nadezhda Kapandjieva, Steven Klein, Mariusz Korkosz, Milan Krcpicar, Dolores Alonso Martinez, Nomawethu Matsiliza, Marcin Mazurek, Malgorzata Miakisz, Eric Mueller, Rauli Muller, Leysan Myasoutova, Oleh Nadashkevych, Antonio Fernandez Nebro, Petr Nemec, Clark Neuwelt, Meera Oza, Margus Pail, Iris Colunga Pedraza, Dimitar Penev, Lucie Podrazilova, Jennifer-Anne Potts, Grazyna Pulka, Eve-Kai Raussi, Riteesha Reddy, Dmytro Rekalov, Maria Rell-Bakalarska, Juan Cruz Rizo Rodriguez, Euthalia Roussou, Anna Rychlewska-Hanczewska, Federico Navarro Sarabia, Liliana Sedova, Shadi Shahouri, Sergii Shevchuk, David Sikes, Lubomira Simova, Andrea Skublova, Malgorzata Socik-Pojawa, Sheldon Solomon, Catherine Spargo, Mykola Stanislavchuk, Helena Stehlikova, Zuzana Stejfova, Maria Stopinska-Polaszewska, Katarzyna Swierkocka, Hasan Tahir, Sandra Talli, Gareth Tarr, Cesar Francisco Pacheco Tena, Erika Timanikova, Vira Tseluyko, Zuzana Urbanova, Ivo Valter, Edgar Hernandez Vargas, Viktoria Vasylets, Federico Galvan Villegas, Petr Vitek, Monika Wronisz, and Hana Zelenkova.
