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ORIGINAL RESEARCH

Etanercept in Axial Spondyloarthritis, Psoriatic Arthritis, and Plaque Psoriasis: Real-World Outcome Data from German Non-interventional Study ADEQUATE

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ABSTRACT

Introduction: For chronic diseases such as axial spondyloarthritis (axSpA), psoriatic arthritis (PsA), and plaque psoriasis (PsO), treatment goals include remission or at least low disease activity (LDA) by 12 weeks. Improvements in symptoms such as pain and fatigue should also be treatment goals.

Methods: ADEQUATE was a German, prospective, non-interventional study to evaluate the proportion of patients with rheumatoid arthritis, PsA, axSpA, or PsO who, in routine clinical practice, benefit from the continuation of treatment with etanercept (ETN) beyond 12 weeks, even when their treatment goals have not yet been reached. Patient-reported outcomes (PROs) and changes in concomitant glucocorticoid use were also recorded. This article focuses on results for patients with axSpA and PsA; data for patients with PsO are described briefly.

Results: In total, 305, 254, and 70 patients with axSpA, PsA, and PsO, respectively, were included. Rates of remission at week 12 and week 24, respectively, were 19% and 18% for axSpA, 38% and 51% for PsA, and 7% and 19% for PsO. Rates of LDA at week 12 and week 24, respectively, were 39% and 45% for axSpA, 50% and 60% for PsA, and 34% and 51% for PsO. Extending treatment up to 52 weeks was associated with stable rates of or further increases in remission and LDA rates. Improvements in pain, fatigue, and depression (axSpA, PsA, and

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PsO) and reductions in concomitant glucocorticoid use (axSpA and PsA) were observed. No new safety signals were detected.
Conclusion: These findings confirm the effectiveness and safety of ETN in routine clinical practice for several indications and highlight potential benefits of continuing ETN treatment in patients who have not reached their treatment goals after 12 weeks. Additional benefits included improvements in PROs and reduction of concomitant glucocorticoids.
Trial Registration: ClinicalTrials.gov NCT0248 6302.

PLAIN LANGUAGE SUMMARY

Axial spondyloarthritis is a disorder that causes joint pain mainly in the spine and can cause deformation of the spine. Psoriatic arthritis and plaque psoriasis are disorders that cause dry, itchy, and raised skin patches. Psoriatic arthritis also causes swollen, stiff, and painful joints. Etanercept is a treatment used to reduce the symptoms of axial spondyloarthritis, psoriatic arthritis, and plaque psoriasis. The aim of treatment is remission, or low disease activity after 12 weeks. In this study, people received etanercept for up to 52 weeks from their usual doctors in Germany. A total of 305 people with axial spondyloarthritis, 254 people with psoriatic arthritis, and 70 people with plaque psoriasis took part in the study. After 12 weeks of treatment, 19 in 100 people with axial spondyloarthritis were in remission and 39 in 100 people had low disease activity. In addition, 38 in 100 people with psoriatic arthritis were in remission and 50 in 100 people had low disease activity. Finally, 7 in 100 people with plaque psoriasis were in remission and 34 in 100 people had low disease activity. These numbers remained mostly stable until the end of the study. People also reported less pain, fatigue, and depression. Most people were able to use less glucocorticoids. The number and types of unwanted side effects were similar to those seen in other studies of etanercept in people with axial spondyloarthritis, psoriatic arthritis, or plaque psoriasis.

Keywords: Axial spondyloarthritis; Etanercept; Plaque psoriasis; Psoriatic arthritis; Real world; Remission

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Key Summary Points

Why carry out this study?

Goals of treatment for rheumatic diseases and plaque psoriasis (PsO) generally include remission or at least low disease activity (LDA) after 12 weeks of treatment.

The objective of this non-interventional study conducted in Germany was to evaluate the proportion of patients with axial spondyloarthritis (axSpA; n = 305), psoriatic arthritis (PsA; n = 254), and PsO (n = 70) who benefit from treatment with the tumor necrosis factor alpha inhibitor etanercept (ETN) beyond 12 weeks despite not having reached remission or LDA by week 12.

What were the study outomes?

In this study, 19% and 18% of patients with axSpA, 38% and 51% of patients with PsA, and 7% and 19% of patients with PsO achieved disease remission after 12 and 24 weeks of treatment with ETN, respectively; 39% and 45% of patients with axSpA, 50% and 60% of patients with PsA, and 34% and 51% of patients with PsO achieved LDA after 12 and 24 weeks, respectively.

What was learned from the study?

Rates of remission and LDA remained stable until or continued to increase up to week 52 of treatment, suggesting that some patients may benefit from extending treatment with ETN beyond 12 weeks.

INTRODUCTION

For patients with chronic diseases such as axial spondyloarthritis (axSpA), psoriatic arthritis (PsA), and plaque psoriasis (PsO), treatment goals usually include attaining remission preferably within the first 12 weeks of treatment [1–3]. In instances where disease remission is unlikely, current recommendations state that achieving low disease activity (LDA) can be an acceptable alternative. If remission or LDA has not been reached after 12 weeks, current treatment should be adjusted [4–9]. Patients showing some improvement in disease activity in this time period, but who have not yet achieved the treatment target, may continue with current treatment if they are expected to reach their goal by 24 weeks [10, 11]. Patients with chronic diseases can experience pain, fatigue, low or depressed mood, and adverse effects of concomitant glucocorticoid use; therefore, another treatment target should be improvement in patient quality of life [3, 11].

Previous studies in rheumatic diseases and PsO have demonstrated the benefits, with regards to disease remission rates, of treating beyond 12 weeks [12, 13]. The primary aim of this prospective, non-interventional study was to evaluate the proportion of patients with rheumatoid arthritis (RA), axSpA, PsA, or PsO who, in routine clinical practice, benefit from the continuation of treatment with etanercept (ETN) beyond 12 weeks, even in cases where the defined treatment goal has not been formally attained by week 12. Patient-reported outcomes were also recorded. Results for patients with RA have been published previously [14]. This article presents data from patients with axSpA, PsA, or PsO. As a result of the small number of patients with PsO, those data are only described briefly, with further details and figures provided as supplementary material.

METHODS

Study Design

ADEQUATE was a prospective, multicenter, non-interventional study conducted in Germany. It was designed to evaluate the effectiveness of ETN in patients with RA, PsA, axSpA, or PsO after 12, 24, 36, and 52 weeks of routine treatment. The study design has been described in detail previously [14].

ETN was prescribed in accordance with the Summary of Product Characteristics (SmPC).

The specified contraindications, warnings and precautions for use, undesirable effects, interactions, and posology and method of administration were followed at each investigator's discretion. After regular initiation of treatment with ETN, patient information was documented for up to 52 weeks. Initial treatment decisions were taken prior to enrollment into the study, and documentation was performed at five regular 12-weekly study visits over the course of the 52-week observation period. Written informed consent was obtained by the treating physician or a designated person prior to patients entering the study. This non-interventional study was conducted in accordance with the Declaration of Helsinki and is registered with the Federal Institute for Drugs and Medical Devices, the Federal Association of Statutory Health Insurance Physicians, and the Head Association of Health Insurers. It is also registered on ClinicalTrials.gov (NCT02486302). The final protocol and subject information and informed consent documentation were reviewed and approved by the Ethics Committee of the Faculty of Medicine of the Goethe University of Frankfurt am Main, Germany (432/14).

Inclusion and Exclusion Criteria

Inclusion criteria were a confirmed diagnosis of RA, axSpA, PsA, or PsO, no prior treatment with ETN (prior treatment with other biologics was permitted), treatment according to the ETN SmPC, and age $\geq$ 18 years. Exclusion criteria were the contraindications and the special warnings and precautions in the SmPC.

Primary and Secondary Endpoints

The primary endpoints for this study were the proportion of patients achieving remission at week 12 and week 24 of treatment, and the proportion of patients achieving LDA at week 12 and week 24. The criteria for remission and LDA used in this study are listed in Supplementary Table S1 [1, 15, 16]. Secondary endpoints were the proportion of patients continuing treatment with ETN despite not achieving remission at week 12, overall incidence of adverse events (AEs), and PROs, e.g., patient global assessment, depression (evaluated using the Patient Health Questionnaire-2 [PHQ-2]), and fatigue and pain (measured by the visual analog scale [VAS]).

Data Collection and Statistical Analyses

Treating physicians collected data at each visit using a case report form. Categorical data were presented as relative frequencies (absolute and adjusted) and numerical data were presented as mean ($\pm$ standard deviation) or median (range, 25% and 75% quartiles). Missing values were not imputed unless otherwise stated.

Analysis sets were defined as "all documented" (all documented patients), "treated set" (all patients with $\geq$ 1 post-baseline value including documentation of an AE), and "per protocol set" (all patients without major protocol deviations).

RESULTS

Patients

Patient disposition for the overall study has been published previously [14]. A total of 333 patients with documented axSpA and 265 with documented PsA entered the study, of whom 305 (91.6%) and 254 (95.8%), respectively, were included in the treated set (Fig. 1). A total of 182 (59.7%) and 152 (59.8%) in the axSpA and PsA groups, respectively, completed the study, while 83 (27.2%) and 73 (28.7%), respectively, discontinued prematurely. Documentation was not completed for 40 (13.1%) and 29 (11.4%) patients with axSpA and PsA, respectively. The most common reason for treatment discontinuation in patients with axSpA was AEs (n = 33 [10.8%]); the main reason for discontinuation in patients with PsA was insufficient efficacy (n = 43 [16.9%]). Seventy-five patients with PsO entered the study, of whom 70 (90.3%) were included in the treated set and 43 (61.4%) completed the study. Patient disposition for the PsO group is shown in Supplementary Fig. S1.

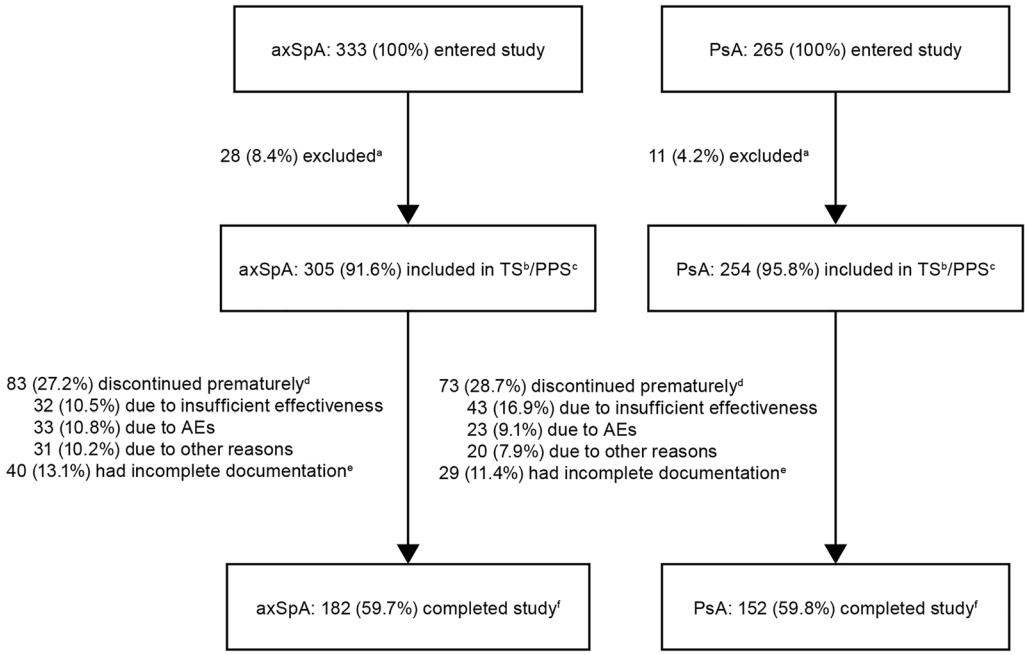

Fig. 1 Disposition of patients with axSpA and PsA. [a]Possible reasons: consent withdrawn; center excluded; deviation between therapy start and baseline visit; never took study medication; excluded owing to lack of post-baseline values. [b]All treated patients with ≥ 1 post-baseline value including documentation of an AE. [c]TS patients who adhered to the protocol without any major protocol deviation. [d]Non-completer with treatment discontinuation, multiple reasons possible. [e]Non-completer with or without treatment discontinuation. [f]Completed week 52 and treatment not discontinued. *AE* adverse event, *PPS* per-protocol set, *TS* treated set, *axSpA* axial spondyloarthritis, *PsA* psoriatic arthritis

Baseline Characteristics

The proportion of female patients with axSpA and PsA was 44.3% and 55.5%, respectively, and mean age was 45.8 and 53.1 years (Table 1). The median disease duration was 4.2 years in the axSpA group and 3.4 years in the PsA group (Table 1).

More than half (60.9%) of patients with axSpA had received no previous conventional disease-modifying antirheumatic drugs (DMARDs). The majority of patients with PsA had previously received one or two conventional DMARDs (cDMARDs) (Table 1). Non-steroidal anti-inflammatory drugs were the most common prior therapy in patients with axSpA (47.2%), while methotrexate was the most frequent prior therapy in patients with PsA (87.4%) (Table 1). The concomitant medications most often used by patients with axSpA were etoricoxib (17.7%), methotrexate (12.1%), ibuprofen (11.8%), and pantoprazole (11.8%); patients with PsA most often used methotrexate (37.4%), prednisolone (15.7%), and ibuprofen (12.6%).

The most recorded concomitant diseases at baseline for patients with axSpA were hypertension (25.9%), obesity (5.9%), and osteoarthritis (5.2%); for patients with PsA, these were hypertension (29.9%), osteoarthritis (9.1%), and depression (7.9%).

Baseline characteristics for patients with PsO are shown in Supplementary Table S2. Thirty-nine percent of these patients were female and the mean age was 51.9 years. The most common prior medication was fumarate (68.6%) and most frequent concomitant medication was calcipotriol/betamethasone (20.0%). Of concomitant diseases, hypertension and obesity were recorded the most (27.1% and 4.3%, respectively).

Table 1 Patient demographics and baseline disease characteristics

Characteristic	axSpA (n = 305)	PsA (n = 254)
Female, n (%)	135 (44.3)	141 (55.5)
Age, years, mean ± SD	45.8 ± 13.4	53.1 ± 12.7
BMI, kg/m^2, mean ± SD	27.5 ± 5.5	28.6 ± 5.7
Duration of disease, years, median (range)	4.2 (0.0–49.7)	3.4 (0.0–55.6)
Baseline disease characteristics		
RF+, n (%)	14 (5.6)	23 (10.4)
ACPA, > 20 U/ml, n (%)	4 (1.3)	4 (1.6)
HLA-B27+, n (%)	223 (75.9)	N/D
DAS28, median (Q1; Q3)	N/D	4.1 (3.2; 5.1)
ASDAS-CRP, median (Q1; Q3)	3.3 (2.8; 3.8)	N/D
BASDAI score, median (Q1; Q3)	5.3 (3.6; 7.0)	N/D
FFbH score, median (Q1; Q3)	69.4 (52.8; 83.3)	72.2 (50.0; 86.1)
Pain (VAS) score, median (Q1; Q3)	67.0 (48.0; 80.0)	65.0 (45.0; 80.0)
Fatigue (VAS) score, median (Q1; Q3)	65.0 (36.0; 84.0)	62.5 (31.0; 81.0)
No depression (PHQ-2 = 0), n (%)	24 (8.1)	19 (7.6)
Radiologically/MRT confirmed sacroiliitis, n (%)	173 (59.5)	–
Radiological sacroiliitis according to modified New York criteria, n (%)	168 (57.7)	–
Axial manifestations, n (%)	1 (0.3)	2 (0.8)
≥ 1 extraspinal symptom[a], n (%)	60 (19.7)	134 (52.8)
Psoriasis	18 (5.9)	127 (50.0)
Uveitis/iritis	27 (8.9)	2 (0.8)
Crohn's disease/ulcerative colitis	1 (0.3)	1 (0.4)
Other/unknown	16 (5.2)	10 (3.9)
Enthesitis, n (%)	22 (7.2)	77 (30.3)
Psoriasis BSA %, mean ± SD	–	10.6 ± 16.4
Nail involvement, mean ± SD	–	6.7 ± 5.1
Prior medication		
Previous cDMARD, n (%)		
0	185 (60.9)	19 (7.5)
1	81 (26.6)	104 (40.9)
2	34 (11.2)	97 (38.2)
≥ 3	4 (1.3)	34 (13.4)
Type of previous cDMARD, n (%)		
Methotrexate	64 (21.0)	222 (87.4)
Cyclosporine	3 (1.0)	12 (4.7)
Leflunomide	8 (2.6)	95 (37.4)
Sulfasalazine	82 (26.9)	63 (24.8)
Others	18 (5.9)	25 (9.8)

Table 1 continued

Characteristic	axSpA (n = 305)	PsA (n = 254)
bDMARD, n (%)	65 (21.3)	46 (18.1)
NSAID, n (%)	144 (47.2)	99 (39.0)
COX2 inhibitor, n (%)	84 (27.5)	53 (20.9)
Glucocorticoids		
n (%)	87 (87.9)	144 (94.7)
Average daily dose, mg/day, mean ± SD	6.2 ± 5.7	6.3 ± 5.1

ACPA anti-citrullinated protein antibody, *ASDAS-CRP* ankylosing spondylitis disease activity score with C-reactive protein, *axSpA* axial spondyloarthritis, *BASDAI* Bath ankylosing spondylitis disease activity index, *b/cDMARD* biological/conventional disease-modifying antirheumatic drug, *BMI* body mass index, *BSA* body surface area, *COX2* cyclooxygenase 2, *DAS28* disease activity score in 28 joints, *FFbH* Hannover functional questionnaire, *HLA-B27* human leukocyte antigen B27, *N/D* not determined, *NSAID* non-steroidal anti-inflammatory drugs, *PHQ-2* patient health questionnaire-2, *PsA* psoriatic arthritis, *PsO* psoriasis, *RF* rheumatoid factor, *SD* standard deviation, *VAS* visual analog scale

[a]More than one possible

Effectiveness

After 12 weeks of ETN treatment, 19.0% (38/200) of patients with axSpA achieved disease remission (Fig. 2a) according to Ankylosing Spondyloarthritis Disease Activity Score (ASDAS) of < 1.3 (Supplementary Table S1). This proportion remained stable at week 24 (18.4% [28/152]), increased to 26.7% (35/131) at week 36, and remained approximately stable (23.4% [32/137]) at week 52. Among patients with PsA, 38.3% (92/240) achieved disease remission at week 12, i.e., a Disease Activity Score in 28 joints (DAS28) < 2.6 or minimal disease activity criteria met (Supplementary Table S1; Fig. 2a). This proportion increased steadily over time for patients who remained on study drug, with 51.0% achieving remission at both week 24 (106/209) and week 36 (93/181) of treatment, and 54.0% (87/161) achieving it at week 52.

At week 12, 38.6% (100/259) of patients with axSpA achieved LDA (Fig. 2b). This proportion increased to 45.4% (93/205) at week 24 and to 50.3% (94/187) at week 36; it then decreased slightly, to 45.3% (81/179), at week 52. In the PsA group, 50.0% (120/240) of patients achieved LDA at week 12 (Fig. 2b). This proportion increased to 60.3% (126/209) at week 24 and remained approximately stable at week 36 (59.7% [108/181]) and week 52 (57.8% [93/161]).

Among patients with axSpA achieving remission at week 12 and week 24, respectively, 42.3% (11/26) and 56.5% (13/23) maintained this up to week 52; and 57.9% (44/76) and 64.9% (50/77) of patients achieving LDA at week 12 and week 24, respectively, maintained this up to week 52 (Fig. 2c, d). Among patients with PsA, 52.2% (36/69) and 66.7% (58/87) of those achieving remission at week 12 and week 24, respectively, and 57.3% (55/96) and 70.5% (74/105) of those achieving LDA at week 12 and week 24, respectively, maintained this up to week 52 (Fig. 2c, d). Of the patients with axSpA and those with PsA who did not reach their treatment goal at week 12, 7.8% and 35.8%, respectively, did so at week 24.

At week 12, 7.1% (5/70) of patients with PsO attained remission. This proportion increased over time, to 18.6% (11/59) at week 24, 27.1% (13/48) at week 36, and 31.8% (14/44) at week 52 (Supplementary Fig. S2a). For patients with PsO achieving LDA, 34.3% (24/70) did so at week 12, and this increased to 50.8% (30/59) at week 24, 52.1% (25/48) at week 36, and 54.5% (24/44) at week 52 (Supplementary Fig. S2b). Seventy-five percent and 87.5% of patients achieving remission at week 12 and week 24, respectively, maintained this up to week 52; and 72.2% and 81.0% of those reaching LDA at week 12 and week 24, respectively, maintained this up to week 52 (Supplementary Fig. S2c, d).

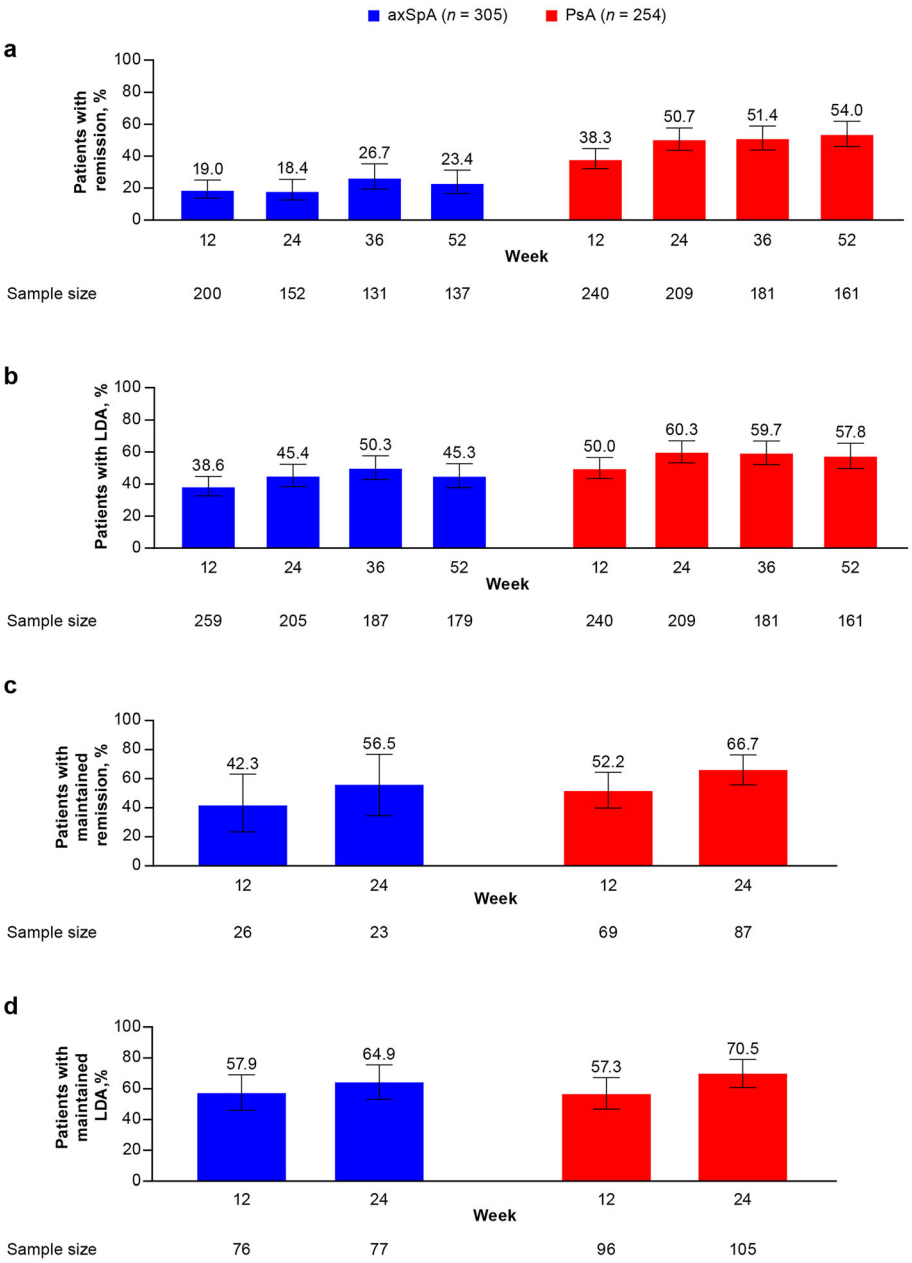

Fig. 2 Percentage of patients achieving **a** remission, **b** LDA, **c** remission at week 12 and week 24 and maintaining it until week 52, and **d** LDA at week 12 and week 24 and maintaining it until week 52. Error bars show 95% CI. Data are based on observed cases. *n* refers to the number of patients included in the per-protocol set. Sample sizes exclude missing values, based on the number of patient documentations available at the indicated visit. Remission was defined as ASDAS < 1.3 for axSpA, and DAS28 < 2.6 or MDA criteria met for PsA. LDA was defined as BASDAI: 50% relative difference or absolute difference of 2 points (scale 0–10) and expert opinion on treatment continuation for axSpA, and DAS28 $\leq$ 3.2 for PsA. *ASDAS* ankylosing spondylitis disease activity score, *axSpA* axial spondyloarthritis, *BASDAI* Bath ankylosing spondylitis disease activity index, *CI* confidence interval, *DAS28* disease activity score in 28 joints, *DLQI* dermatology life quality index, *LDA* low disease activity, *MDA* minimal disease activity, *PsA* psoriatic arthritis

Patient-Reported Outcomes

Over the course of the study, a clinically relevant reduction in pain was observed in patients with axSpA and those with PsA (Fig. 3a). For both groups, clinically relevant reductions in fatigue and mean PHQ-2 scores were also observed, with the most pronounced reductions observed during the first 12 weeks of treatment with ETN (Fig. 3b, c). The proportion of patients without depression (PHQ-2 = 0) increased steadily throughout the study: in the axSpA group, 8.1% had depression at baseline versus 29.7% at week 52; and the corresponding rates for the PsA group were 7.6% at baseline and 30.9% at week 52.

Similar trends were observed for patients with PsO (Supplementary Fig. S3a–c).

Concomitant Glucocorticoid Treatment in Rheumatologic Indications

The proportions of patients with axSpA and PsA who received concomitant glucocorticoid treatment decreased over the course of the study (Fig. 4a), and the mean daily concomitant glucocorticoid dose was reduced compared with baseline and previously reported doses (Fig. 4b). The mean daily dose reduction compared with baseline was most pronounced at week 12 and remained stable or decreased further up until week 52. This apparent trend was seen in the overall study population, as well as in patients achieving remission or LDA at a later timepoint (week 36 or week 52), or not at all by week 52 (data on file). Among patients who had previously received biological DMARD (bDMARD) therapy, the proportion taking glucocorticoids at baseline was slightly higher compared with patients who were bDMARD-naïve, and this remained higher throughout the study (84.8% vs. 82.5%); the mean daily dose of glucocorticoids decreased to a lesser extent for those who had received bDMARD therapy compared with those who had not. Rates of remission and LDA were numerically higher among patients with axSpA who did not receive any glucocorticoids prior to initiation of ETN and up to week 12 or 24 compared with those who had received at least one dose (Supplementary Fig. 5). In patients with PsA, rates of remission and LDA were numerically lower or similar in patients who did not receive any prior or concomitant glucocorticoids compared with those you had received at least one dose by week 12 or 24. No relationship between mean daily glucocorticoid dose and AEs was observed (data on file)

Subsequent Treatment After Discontinuation of ETN

In patients with axSpA, of the 83 who discontinued ETN, subsequent therapy was specified for 60 patients. While 12 (20.0%) received no further treatment, three (5.0%) were treated with an ETN biosimilar, 18 (30.0%) with another tumor necrosis factor (TNF) inhibitor, and 11 (18.3%) with a biologic with a different mode of action. In patients with PsA, of the 73 who discontinued ETN, subsequent therapy was specified for 54 patients. While 13 (24.1%) received no further treatment, 17 (31.5%) were treated with another TNF inhibitor and 15 (27.8%) were treated with a biologic with a different mode of action. In the PsO group, subsequent therapy was specified for 10 of the 12 patients who discontinued. Of these, three (30.0%) patients received no further treatment, four (40.0%) were treated with secukinumab, and one patient (10%) each received adalimumab, ustekinumab, or psoralen plus longwave ultraviolet light.

Safety

A total of 152 (49.8%) patients with axSpA, 122 (48.0%) with PsA, and 21 (30.0%) with PsO experienced at least one treatment-emergent AE (TEAE) during the observational period. The most common TEAEs are shown in Table 2 and Supplementary Table S3.

In the axSpA group, the most common TEAEs were drug ineffective (9.8%), nasopharyngitis (7.2%), and condition aggravated, injection-site erythema, and injection-site reaction (2.6% each). The most common TEAEs in the PsA group were drug ineffective (15.4%), nasopharyngitis (5.1%), and condition

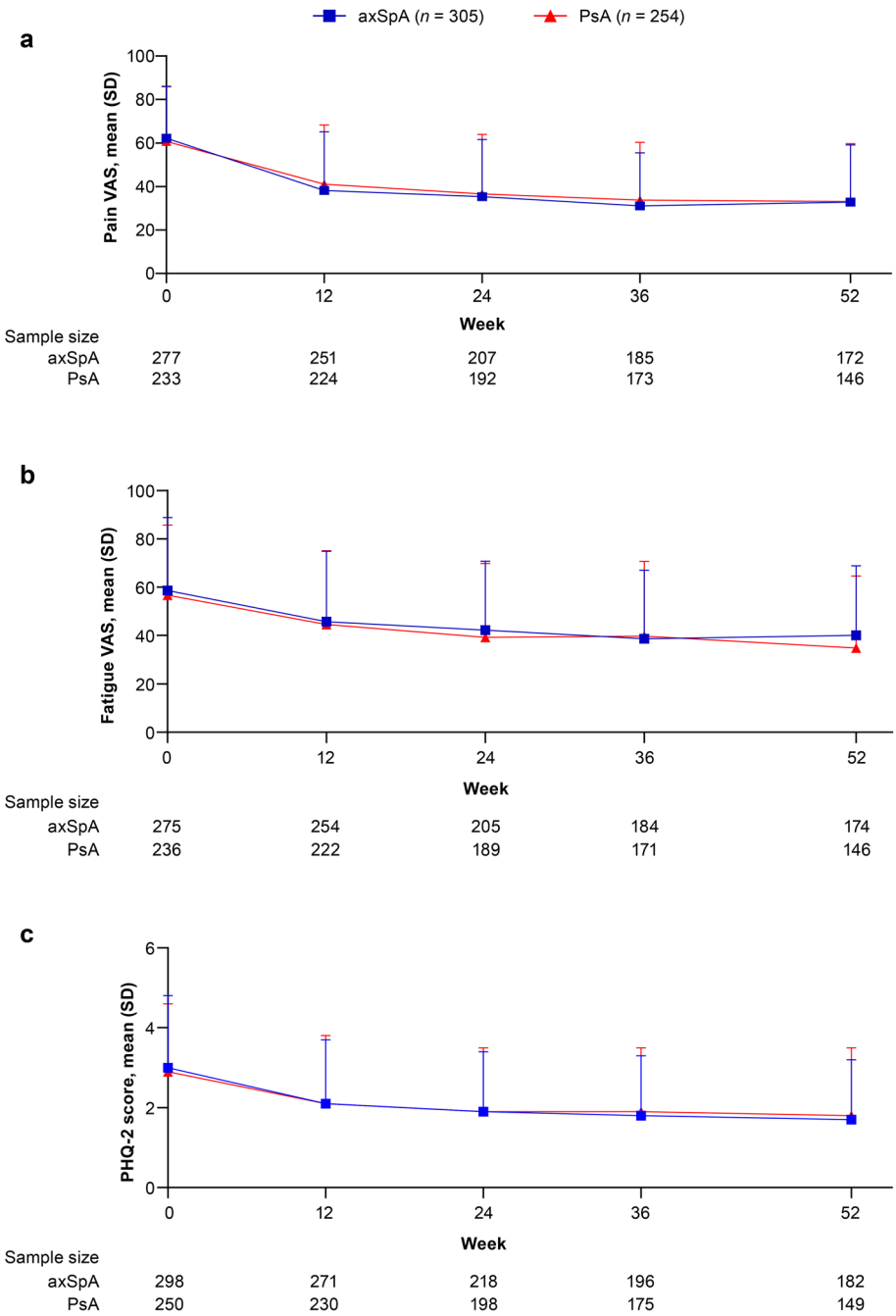

Fig. 3 Global assessment of **a** pain, **b** fatigue, and **c** PHQ-2 score for depression. Error bars show SD. Data are based on observed cases. *n* refers to the number of patients included in the per-protocol set. Sample sizes exclude missing values, based on the number of patient documentations available at the indicated visit. *axSpA* axial spondyloarthritis, *MDA* minimal disease activity, *PHQ-2* patient health questionnaire-2, *PsA* psoriatic arthritis, *SD* standard deviation, *VAS* visual analog scale

aggravated (3.5%) (Table 2). In patients with PsO, the most frequent TEAEs were drug ineffective (11.4%), nasopharyngitis (4.3%), and cardiac disorder (4.3%) (Supplementary Table S3).

Treatment-emergent serious AEs (TESAEs) were reported in 34 (11.1%) patients with axSpA, 19 (7.5%) patients with PsA, and five (7.1%) patients with PsO. The most common TESAEs are listed in Table 3 and Supplementary Table S4.

The most commonly reported TESAEs in patients with axSpA were cardiac disorder (1.3%), intervertebral disc protrusion (1.0%), gastrointestinal disorders (1.0%), and hepatobiliary disorders (1.0%). In patients with PsA, the most common TESAEs were condition aggravated (1.2%), injury, poisoning, and procedural complications (0.8%), cardiac disorders (0.8%), gastrointestinal disorders (0.8%), and neoplasms (benign, malignant, or unspecified; 0.8%) (Table 3). In patients with PsO, the TESAEs most reported were osteoarthritis, intervertebral disc protrusion, bronchitis, atrial fibrillation, skin and subcutaneous tissues disorders, nervous system disorders, and immune system disorders (1.4% each) (Supplementary Table S4). Overall, one patient with PsA (none in the axSpA and PsO groups) died during the observational period; this was deemed unrelated to the study drug and the cause of death was unknown.

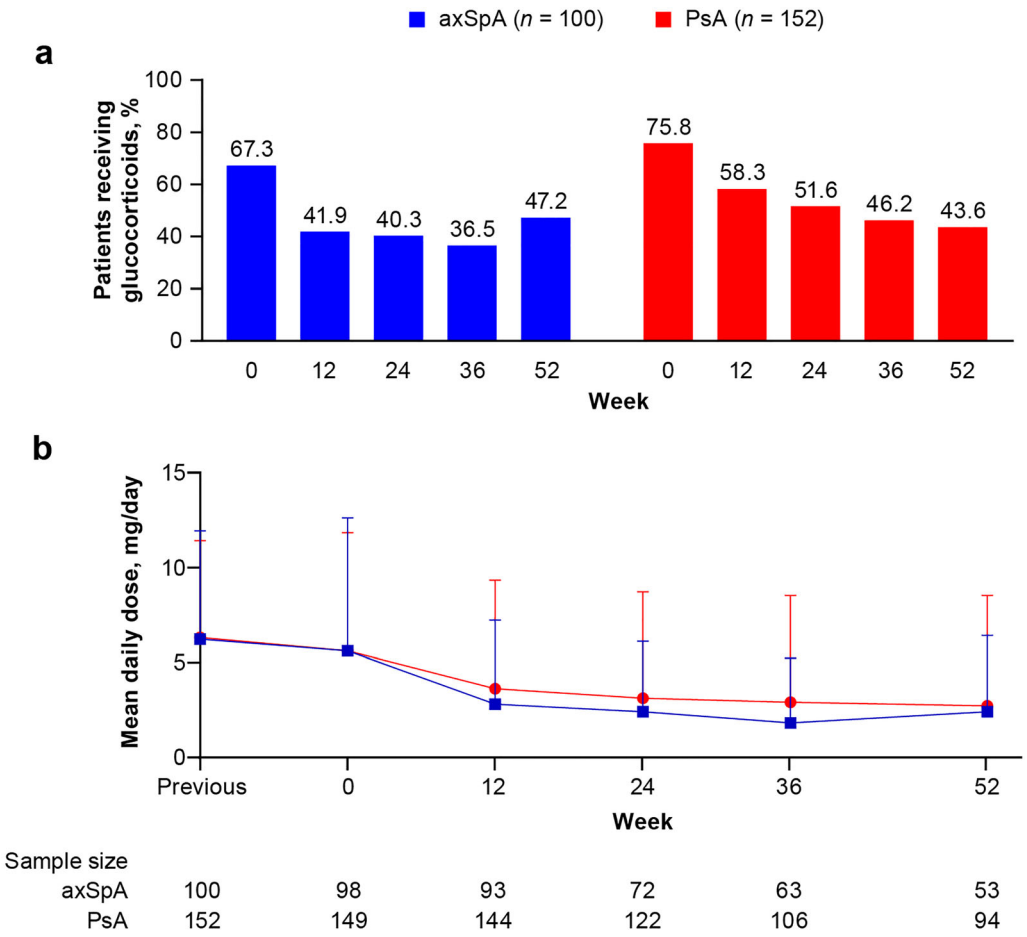

Fig. 4 **a** Concomitant glucocorticoid use and **b** mean daily glucocorticoid dose. Error bars show SD. Data are based on observed cases. *n* refers to the number of patients included in the per-protocol set. Sample sizes exclude missing values, based on the number of patient documentations available at the indicated visit. *axSpA* axial spondyloarthritis, *PsA* psoriatic arthritis, *SD* standard deviation

Table 2 Treatment-emergent AEs by SOC and preferred term, as reported in at least 1% of patients (including select AEs of special interest in less than 1% of patients)

Primary SOC Preferred term (MedDRA)	axSpA (*n* = 305)	PsA (*n* = 254)
≥ 1 treatment-emergent AE	152 (49.8)	122 (48.0)
General disorders and administration-site conditions	67 (22.0)	68 (26.8)
Drug ineffective	30 (9.8)	39 (15.4)
Condition aggravated	8 (2.6)	9 (3.5)
Injection-site erythema	8 (2.6)	6 (2.4)
Injection-site reaction	8 (2.6)	4 (1.6)
Infections and infestations	49 (16.1)	33 (13.0)
Nasopharyngitis	22 (7.2)	13 (5.1)
Bronchitis	5 (1.6)	4 (1.6)
Herpes zoster	1 (0.3)	–
Pneumonia	2 (0.7)	–
Urinary tract infection	1 (0.3)	2 (0.8)
Musculoskeletal and connective tissue disorders	22 (7.2)	17 (6.7)
Osteoarthritis	2 (0.7)	3 (1.2)
Skin and subcutaneous tissue disorders	17 (5.6)	22 (8.7)
Pruritus	1 (0.3)	2 (0.8)
Gastrointestinal disorders	17 (5.6)	5 (2.0)
Injury, poisoning, and procedural complications	9 (3.0)	3 (1.2)
Nervous system disorders	5 (1.6)	9 (3.5)
Respiratory, thoracic, and mediastinal disorders	7 (2.3)	4 (1.6)
Cardiac disorders	7 (2.3)	2 (0.8)
Investigations	3 (1.0)	5 (2.0)

Data are shown as *n* (%)
AE adverse event, *axSpA* axial spondyloarthritis, *MedDRA* Medical Dictionary for Regulatory Activities, *PsA* psoriatic arthritis, *SOC* system organ class

Table 3 Treatment-emergent SAEs by SOC and preferred term, as reported in at least five patients (including select SAEs of special interest in fewer than five patients)

Primary SOC Preferred term (MedDRA)	axSpA (*n* = 305)	PsA (*n* = 254)
≥ 1 treatment-emergent SAE	34 (11.1)	19 (7.5)
Musculoskeletal and connective tissue disorders	8 (2.6)	4 (1.6)
Osteoarthritis	2 (0.7)	1 (0.4)
Intervertebral disc protrusion	3 (1.0)	–
General disorders and administration-site conditions	7 (2.3)	5 (2.0)
Condition aggravated	2 (0.7)	3 (1.2)
Drug ineffective	1 (0.3)	1 (0.4)
Death	–	1 (0.4)
Infections and infestations	6 (2.0)	5 (2.0)
Pneumonia	1 (0.3)	–
Cardiac disorders	4 (1.3)	2 (0.8)
Injury, poisoning, and procedural complications	2 (0.7)	2 (0.8)
Gastrointestinal disorders	3 (1.0)	2 (0.8)
Skin and subcutaneous tissue disorders	1 (0.3)	3 (1.2)
Neoplasms[a]	–	2 (0.8)
Vascular disorders	2 (0.7)	1 (0.4)
Nervous system disorders	1 (0.3)	1 (0.4)
Hepatobiliary disorders	3 (1.0)	1 (0.4)
Respiratory, thoracic, and mediastinal disorders	–	1 (0.4)

Data are shown as *n* (%)
axSpA axial spondyloarthritis, *MedDRA* Medical Dictionary for Regulatory Activities, *PsA* psoriatic arthritis, *SAE* serious adverse event, *SOC* system organ class
[a]Benign, malignant, and unspecified (including cysts and polyps)

DISCUSSION

In this non-interventional study of patients with axSpA, PsA, or PsO treated with ETN in

routine clinical practice, a considerable proportion of patients reached the treatment goal of remission or LDA after 12 weeks of treatment, and this was maintained for up to 52 weeks of treatment. In addition, improvements in PROs such as pain and fatigue were observed across all indications.

These findings are generally in agreement with results for patients with RA from the same study [14] and are in line with previous real-world observations for TNF inhibitors and other biologics. In a prospective observational study of golimumab as a second-line TNF inhibitor, 33% of patients with axSpA and 59% with PsA achieved ASDAS and DAS28 remission, respectively, at 6 months [17]. Data from an observational study of patients with PsA showed that a significantly greater proportion of patients receiving ETN monotherapy versus ETN plus cDMARD achieved LDA based on DAS28 < 2.6 (21.1% vs. 24.4%; $p < 0.05$) at 52 weeks [18]. Overall, for patients receiving monotherapy or combination therapy, DAS28 remission criteria were attained after 12 weeks and remained stable through to week 52 in this patient population. In a post hoc analysis of the non-interventional, prospective GO-NICE study of golimumab as first-, second-, or third-line treatment, 50–76% of patients with PsA were in Psoriatic Arthritis Response Criteria remission [19]. In another study that pooled data from patients with PsA enrolled in 12 European registries and receiving TNF inhibitors, the remission (DAS28 < 2.6) rate at 6 months was 56% [20]. In the real-world PsABio study, the interleukin-12/23 inhibitor ustekinumab was compared to TNF inhibitors. After 1 year's treatment, 22% of patients receiving ustekinumab were in clinical Disease Activity Index for Psoriatic Arthritis remission, compared with 31% of patients receiving TNF inhibitors [21]; LDA rates were 56% and 67%, respectively.

Similarly, the PRISTINE study showed that 37.2% of patients with PsO treated once weekly with 50 mg of ETN achieved a Psoriasis Area and Severity Index (PASI) 75 (PASI75) response after 12 weeks (62.4% achieved PASI75 when ETN 50 mg was administered twice weekly). The proportion of patients attaining a PASI75 response increased to 59.9% after 24 weeks (78.2% when treated with 50 mg ETN twice weekly) [7]. In a Spanish study of patients with PsO treated with ETN, an increase in the proportion of patients reaching PASI75 was observed, from 59.0% at 12 weeks to 66.3% at 24 weeks [22]. In addition, a comparison of infliximab, adalimumab, and ETN in Greek patients with RA showed an increase in DAS28 response beyond 24 weeks and up to 8 years of treatment [23].

While there were numerical increases in the proportion of patients achieving remission or LDA throughout the course of the current study, 15% of patients discontinued treatment because of insufficient response. This observation, along with the high proportion of patients subsequently receiving another bDMARD, suggests that investigators based their treatment decisions on the treatment goals detailed in the relevant guidelines [3, 15, 24]. Nevertheless, a sizable proportion of patients received ETN until the end of the study despite not reaching their treatment target. These patients were seen to have improvements in PROs such as depression, fatigue, and pain. This indicates that for some patients, objective assessment of disease activity may not be the only reason for treatment continuation in clinical practice; patients may benefit from staying on a particular treatment simply because of substantial improvements in PROs. Although switching treatment when treatment goals have not been reached after 12–24 weeks has been shown to be a beneficial approach [25–29], switching is not always possible because of patient comorbidities or contraindications.

The current study demonstrates that extending treatment with ETN beyond 12 weeks has the potential to expand the proportion of patients achieving the treatment goal of remission or LDA. Indeed, for some patients, this did not happen until after 24 weeks of treatment. These findings, together with the improvements in PROs seen in patients who reached treatment goal at a later point in the study, indicate that continuing treatment with ETN can be of benefit to patients with a range of rheumatic diseases and PsO, even for those who do not reach treatment goals after 12 or 24 weeks.

Notable AEs related to glucocorticoid treatment include decreased quality of life and cardiovascular effects, which are generally dose-dependent [30]. In the current study, while there was a decrease in concomitant glucocorticoid use across all patient populations, half of those with axSpA and PsA remained on long-term, low-dose glucocorticoid treatment throughout the study. This highlights the need for improved disease management in accordance with new treatment guidelines. Systemic glucocorticoid treatment should be used with caution and at the lowest effective dose in patients with PsA [24]. Long-term treatment with systemic glucocorticoids is not recommended in patients with axSpA [1].

Numerically, rates of remission and LDA were higher in patients with axSpA who had not received any prior or concomitant glucocorticoids compared with patients who had received at least one dose. This indicates that responses in patients with axSpA may be mostly due to the effect of ETN. While we cannot explain the numerically lower rates in patients who received prior or concomitant glucocorticoids, it is important to note the low number of patients in this group preventing definite conclusions based on these results alone. In patients with PsA who had not received any prior or concomitant glucocorticoids, rates of remission were numerically lower at week 12 but similar at week 24. Rates of LDA were similar in both groups at week 12 and week 24. This indicates that glucocorticoids may have had a small add-on effect on response and LDA rates in patients with PsA. However, without a comparator group receiving glucocorticoids alone and studies designed to detect glucocorticoid treatment effects, the exact effects of glucocorticoids are difficult to determine. Response rates observed at 12 weeks of treatment with ETN were highest in patients with PsA, followed by those with axSpA. This observation may have been an artifact of the chosen disease activity score. DAS28 was used for PsA, in line with guidelines at the time of study conception [15, 24]; however, the American College of Rheumatology/European League Against Rheumatism guidelines now recommend using the Simplified Disease Activity Index and the Clinical Disease Activity Index scores to measure remission and LDA [11]. However, these scores tend to yield lower rates of remission than DAS28, as observed in this study. Similarly, the Disease Activity in PsA score, which is now recommended for assessing responses in patients with PsA [3], may yield different rates of remission or LDA compared with DAS28.

In this study, the proportion of patients with PsO who achieved remission at 12 or 24 weeks was markedly lower than that observed in previous studies with ETN or other TNF inhibitors [31]; this is likely due to the definition of remission used here (PASI75 and Dermatology Life Quality Index [DLQI] $\leq$ 1; Supplementary Table S1). DLQI $\leq$ 1 is more likely to be achieved by patients with PASI90, suggesting that the definition used for remission in PsO is important when interpreting results. Absolute PASI score $\leq$ 2 (corresponding with PASI90 and representing Physician's Global Assessment clear/almost clear) is now frequently used to inform treatment decisions for PsO in the clinical setting [27]. In the current study, a sizable proportion of patients with PsO achieved PASI75 at week 12 and week 24 (34% and 57%, respectively; Supplementary Fig. S4), indicating good responses to ETN in this patient population.

Study Limitations

Inherent limitations of non-interventional, observational studies are the risk of selection/ascertainment bias and the inability to attribute causation. As a result of the current study's duration of 52 weeks, no conclusions on long-term outcomes can be drawn. A further limitation is the decreasing number of observations over time. Reasons for discontinuation included switching to a different treatment because of AEs or insufficient effectiveness; in addition, some patients were lost to follow-up. This leads to a potential risk of bias due to missing data. However, randomized controlled trials usually have much stricter inclusion and exclusion criteria, and are therefore not representative of the general population of patients eligible for a certain medication. Data from the German

biologics registry RABBIT showed that only 21–33% of patients included in the registry would have been eligible for a randomized controlled trial [32]. Remission and LDA criteria were defined on the basis of guidelines available at the time of study conception. Since then, updated guidelines for axSpA [5, 6], PsA [4, 7–9], and PsO [7, 8] have been published. A decrease in the number of patients over time (due to discontinuation of treatment or lost to follow-up) is common in non-interventional studies [22, 23]. Finally, documentation may be incomplete as only routine clinical investigations are included because of the non-interventional nature of the study, which may vary from practice to practice.

CONCLUSIONS

This study demonstrated that decision-making relating to the continuation or switching of therapy in rheumatic diseases is complex. Treatment decisions should always consider patient preferences. While switching treatment when treatment goals have not been reached has been proven to have clinical benefit, some patients may benefit from prolonged treatment with ETN, i.e., beyond 12 weeks, before a switch is considered. This study confirms the effectiveness and safety of ETN in a real-world setting and highlights the potential benefits of continuing treatment with ETN in patients with axSpA and PsA who have not reached their treatment goal after 12 weeks. These results mirror those from the same study in patients with RA, demonstrating benefits of extended ETN treatment across a range of rheumatic diseases [14].

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Data Availability. Upon request, and subject to review, Pfizer will provide the data that support the findings of this study. Subject to certain criteria, conditions, and exceptions, Pfizer may also provide access to the related individual de-identified participant data. See https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information.

Declarations

Conflict of Interest. Eugen Feist received consulting/speaker fees from AbbVie, BMS, Celgene, Galapagos, Lilly, Medac, Novartis, Pfizer, Roche, Sanofi, Sobi, and UCB. Xenofon Baraliakos received honoraria or grants from AbbVie, Amgen, Biocad, BMS, Celltrion, Chugai, Gilead, Janssen, Lilly, Novartis, Pfizer, Roche, Sandoz, and UCB. Frank Behrens received research grants from Bionorica, Celgene, Chugai, Janssen, Pfizer, and Roche; and consulting/speaker fees from AbbVie, Amgen, Boehringer Ingelheim, Celgene, Chugai, Janssen, Genzyme, Gilead, Lilly, MSD, Novartis, Pfizer, Roche, Sandoz, Sanofi, and UCB. Diamant Thaçi was consultant, investigator, and speaker, and has participated in advisory boards for AbbVie, Almirall, Amgen, Biogen Idec, BMS, Celgene, Janssen-Cilag, LEO Pharma, Lilly, MSD, Novartis, Pfizer, Regeneron, Sanofi, and UCB; and has received research/educational grants from AbbVie, Leo-Pharma Celgene Corp, and Novartis. Anja Plenske, Pascal Klaus, and

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Ethical Approval. This non-interventional study was conducted in accordance with the Declaration of Helsinki and is registered with the Federal Institute for Drugs and Medical Devices, the Federal Association of Statutory Health Insurance Physicians, and the Head Association of Health Insurers. Written informed consent was obtained by the treating physician or a designated person prior to patients entering the study. The final protocol and subject information and informed consent documentation were reviewed and approved by the Ethics Committee of the Faculty of Medicine of the Goethe University of Frankfurt am Main, Germany (432/14).

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