

# Differences and similarities between the EULAR/ASAS-EULAR and national recommendations for treatment of patients with psoriatic arthritis and axial spondyloarthritis across Europe



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The Lancet Regional Health - Europe 2023;33: 100706  
Published Online xxx  
<https://doi.org/10.1016/j.lanep.2023.100706>

## Summary

This is the first report comparing EULAR and national treatment recommendations for PsA patients across Europe, and the first this decade to compare ASAS-EULAR and national treatment recommendations in axSpA patients. An electronic survey was completed from October 2021–April 2022 by rheumatologists in 15 European countries. One and four countries followed all EULAR and ASAS-EULAR recommendations, respectively. Five countries had no national treatment recommendations for PsA and/or axSpA, but followed other regulations. In several countries, national treatment recommendations predated the most recent EULAR/ASAS-EULAR recommendations. Entry criteria for starting biologic/targeted synthetic disease-modifying anti-rheumatic drugs varied considerably. In several countries, for PsA patients with significant skin involvement, interleukin-17 inhibitors were not given preference. The positioning of Janus Kinase inhibitors differed and Phosphodiesterase-4 inhibitors were not in use/reimbursed in most countries. This study may motivate European countries to update their national treatment recommendations, to align them better with the latest international recommendations.

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**Keywords:** Health policy; Psoriatic arthritis; Axial spondyloarthritis; Treatment recommendations

## Introduction

International treatment recommendations serve as an important basis for evidence-based therapeutic decision-making, aiming to achieve equally good patient care, independent of country.<sup>1,2</sup> Treatment recommendations provide guidance to physicians and patients and help to standardize care across different healthcare providers and settings, as well as serve as a basis for development of national treatment recommendations.

In Europe, the European Alliance of Associations for Rheumatology (EULAR) recommendations for the treatment of patients with PsA and the Assessment of SpondyloArthritis international Society (ASAS)-EULAR treatment recommendations for patients with axSpA are pivotal and regularly updated.<sup>1,2</sup>

However, most countries establish their own national treatment recommendations, which overlap to varying degrees with international recommendations.<sup>3</sup> This could potentially result in heterogeneity across countries in terms of eligibility criteria for treatment and available treatment options.<sup>4,5</sup> Awareness of such heterogeneity is important from public health and health economic perspectives, as well as in the investigation of patient outcomes across different countries in multinational registry collaborations such as the European Spondyloarthritis (EuroSpA) Research Collaboration Network (RCN), a scientific collaboration between SpA registries across Europe.

Therefore, this study aimed to examine differences and similarities between the most recent EULAR and ASAS-EULAR recommendations for the treatment of PsA and axSpA, respectively, and the most recent national PsA and axSpA treatment recommendations from countries within the EuroSpA RCN.

## Methods

The EuroSpA includes 16 European observational SpA registries, and seeks to investigate various research

questions relevant to the routine management of these patients.<sup>6,7</sup> A Research Electronic Data Capture (REDCap)<sup>8,9</sup> survey was completed by 15 registries between October 11, 2021 and April 7, 2022: ATTRA (Czech Republic), DANBIO (Denmark), BSRBR-AS (United Kingdom (UK)), ESRBTR (Estonia), ROB-FIN (Finland), ICEBIO (Iceland), GISEA (Italy), ARC (Netherlands), NOR-DMARD (Norway), Reuma.pt (Portugal), RRBR (Romania), biorx.si (Slovenia), BIOBADASER (Spain), SRQ (Sweden), and SCQM (Switzerland). The survey respondents were leading experts and researchers in the field of rheumatology appointed by the scientific committee in each of the participating registries/countries.

Through this survey, we first identified the available national treatment recommendations for PsA and axSpA. Second, we compared the most recent national PsA and axSpA treatment recommendations in each country with the “EULAR recommendations for the management of PsA with pharmacological therapies: 2019 update” and the “2016 update of the ASAS-EULAR recommendations for axSpA”.<sup>1,2</sup> At the time of the survey, the 2022 ASAS-EULAR recommendations for axSpA were in development.<sup>10</sup> The 2019 EULAR recommendations contains twelve recommendations for the management of PsA and the 2016 ASAS-EULAR recommendations thirteen recommendations for the management of axSpA, which were compared with the national treatment recommendations.<sup>1,2</sup> In countries without national treatment recommendations, other national regulations for treatment as reported by the survey respondents were compared with the international recommendations. The processed data based on the REDCap survey was sent to respondents of the survey and to co-authors (mainly rheumatologists from the participating countries) to ensure accuracy. Since the healthcare arrangements differ across the nations of the UK, the study focused on the recommendations applicable for England and Wales. As advised by

EULAR, we use the term recommendations throughout the paper, although some of the countries have published their recommendations as guidelines.<sup>11</sup>

## Results

### National treatment recommendations for PsA patients

By 2021, all participating countries except Estonia, the Netherlands, Slovenia, and Switzerland had published national treatment recommendations for PsA, with publication years varying from 2012 to 2021 (Table 1).

In Estonia, EULAR recommendations were largely followed alongside the regulations from the Estonian Health Insurance Fund (due to economic restrictions) for the initiation of biologic Disease-Modifying Anti-Rheumatic Drugs (biologics), with their latest update in 2021. In the Netherlands, national treatment recommendations were under development, and EULAR recommendations were followed. In Slovenia, recommendations were agreed upon in 2015, but not published (mainly because there are fewer than 40 rheumatologists in the country). In Switzerland, there were drug-class specific summaries, but no national disease-specific summaries.<sup>12</sup> In Norway, national treatment recommendations were available, but the EULAR recommendations were also expected to be followed at a group level. In several countries (Denmark, Estonia (intravenous infliximab and rituximab), Iceland, Norway, and Sweden), tender processes performed yearly or every other year give guidance on the recommended sequence of biologics and targeted synthetic Disease-Modifying Anti-Rheumatic Drugs (tsDMARDs) based on the price of the different drugs. In all countries except Finland, Norway, Spain, Sweden, and Switzerland, the prescribing doctor was required to adhere to national recommendations/regulations in order to prescribe biologics/tsDMARDs. Deviations were accepted if indicated on a case-by-case basis in several countries.

### National treatment recommendations vs. EULAR recommendations—PsA

Table 1 compares the latest EULAR<sup>1</sup> and national treatment recommendations for PsA. For countries with no national treatment recommendations by October 2021, differences between the EULAR recommendations and other national regulations for treatment as reported by the survey respondents are listed. Notably, some national recommendations predated the latest update by EULAR. Only Netherlands followed all EULAR recommendations (Table 1 and Fig. 1a). Most differences were found in Portugal, Switzerland and UK (Fig. 2a).

**EULAR recommendation number 1**, “Treatment should be aimed at reaching the target of remission or, alternatively, low disease activity, by regular disease activity

assessment and appropriate adjustment of therapy,” differed from national treatment recommendations in Finland, Slovenia, and Sweden. In Finland, use of a conventional synthetic DMARD (csDMARD) was required prior to starting a biologics/tsDMARD, including cases presenting with enthesitis and axial disease. In Slovenia, a reduction of DAS28 > 1.2 or specific reduction in swollen joint count after 6 months was suggested as the minimum response to continue biologics/tsDMARDs. In Sweden, a treat-to-target (T2T) approach was less clearly emphasized, although it was indirectly advocated.

**EULAR recommendation number 2**, “Non-steroidal anti-inflammatory drugs may be used to relieve musculo-skeletal signs and symptoms,” differed according to the Portuguese recommendations, for which it was specified that NSAIDs *should* be used as treatment for enthesitis, dactylitis and axial manifestations.

**EULAR recommendation number 3**, “Local injections of glucocorticoids should be considered as adjunctive therapy in psoriatic arthritis; systemic glucocorticoids may be used with caution at the lowest effective dose,” differed from the UK recommendations, which did not mention systemic steroids.

**EULAR recommendation number 4**, “In patients with polyarthritis, a csDMARD should be initiated rapidly, with methotrexate preferred in those with relevant skin involvement,” differed for Finland, Portugal, Sweden, Switzerland, and UK. In Portugal and Switzerland, the preference for methotrexate in patients with skin involvement was not included. In Finland and Sweden, methotrexate was preferred before sulfasalazine and leflunomide for all patients (i.e., not only for those with relevant skin involvement). In the UK, no comment on polyarthritis was provided.

**EULAR recommendation number 5**, “In patients with monoarthritis or oligoarthritis, particularly with poor prognostic factors such as structural damage, high erythrocyte sedimentation rate/C-reactive protein, dactylitis or nail involvement, a csDMARD should be considered.” This differed from the Portuguese recommendations, where in case of mono/oligoarthritis, intra-articular corticosteroids should be considered. Furthermore, in Switzerland, in the drug-specific summaries, no distinctions were made between polyarthritis and monoarthritis or oligoarthritis.

**EULAR recommendation number 6**, “In patients with peripheral arthritis and an inadequate response to at least one csDMARD, therapy with a bDMARD should be commenced; when there is relevant skin involvement, an interleukin (IL)-17 inhibitor (i) or IL-12/23i may be preferred.” This recommendation was different for Estonia, Iceland, Norway, Portugal, Romania, Sweden, Switzerland, and UK. According to the Estonian health insurance rules, two csDMARDs were required prior to biologics, followed by two TNFi (prior to any another type of biologics). In Iceland, one to two TNFi were

Czech Republic	Denmark	Estonia <sup>a</sup>	Finland	Iceland	Italy	Netherlands <sup>a</sup>	Norway	Portugal	Romania	Slovenia <sup>a</sup>	Spain	Sweden	Switzerland <sup>a</sup>	UK
<b>Are there national treatment recommendations in your country for starting a b/tsDMARD in PsA?</b>														
Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	No	Yes
<b>When were your most recent national recommendations for patients with PsA made available?</b>														
2016	2018	NA	2021	2019	2017	NA	2019	2015	2021	NA	2018	2021	NA	2012
<b>EULAR recommendations number 1:</b> Treatment should be aimed at reaching the target of remission or, alternatively, low disease activity, by regular disease activity assessment and appropriate adjustment of therapy:														
=	=	=	D	=	=	=	=	=	=	D	=	D	=	=
<b>EULAR recommendations number 2:</b> Non-steroidal anti-inflammatory drugs may be used to relieve musculoskeletal signs and symptoms:														
=	=	=	=	=	=	=	=	D	=	=	=	=	=	=
<b>EULAR recommendations number 3:</b> Local injections of glucocorticoids should be considered as adjunctive therapy in psoriatic arthritis; systemic glucocorticoids may be used with caution at the lowest effective dose:														
=	=	=	=	=	=	=	=	=	=	=	=	=	=	D
<b>EULAR recommendations number 4:</b> In patients with polyarthritis, a csDMARD should be initiated rapidly, with methotrexate preferred in those with relevant skin involvement:														
=	=	=	D	=	=	=	=	D	=	=	=	D	D	D
<b>EULAR recommendations number 5:</b> In patients with monoarthritis or oligoarthritis, particularly with poor prognostic factors such as structural damage, high erythrocyte sedimentation rate/C reactive protein, dactylitis or nail involvement, a csDMARD should be considered:														
=	=	=	=	=	=	=	=	D	=	=	=	=	D	=
<b>EULAR recommendations number 6:</b> In patients with peripheral arthritis and an inadequate response to at least one csDMARD, therapy with a bDMARD should be commenced; when there is relevant skin involvement, an IL-17 inhibitor or IL-12/23 inhibitor may be preferred:														
=	=	D	=	D	=	=	D	D	D	=	=	D	D	D
<b>EULAR recommendations number 7:</b> In patients with peripheral arthritis and an inadequate response to at least one csDMARD and at least one bDMARD, or when a bDMARD is not appropriate, a JAK inhibitor may be considered:														
D	D	D	=	=	D	=	D	D	D	=	D	D	D	D
<b>EULAR recommendations number 8:</b> In patients with mild disease and an inadequate response to at least one csDMARD, in whom neither a bDMARD nor a JAK inhibitor is appropriate, a PDE4 inhibitor may be considered:														
=	D	D	=	D	D	=	D	D	D	=	=	=	D	D
<b>EULAR recommendations number 9:</b> In patients with unequivocal enthesitis and insufficient response to NSAIDs or local glucocorticoid injections, therapy with a bDMARD should be considered:														
=	D	D	D	=	=	=	=	=	=	D	=	D	D	D
<b>EULAR recommendations number 10:</b> In patients with predominantly axial disease which is active and has insufficient response to NSAIDs, therapy with a bDMARD should be considered, which according to current practice is a TNF inhibitor; when there is relevant skin involvement, IL-17 inhibitor may be preferred:														
=	=	D	D	D	=	=	D	D	D	=	=	D	D	D
<b>EULAR recommendations number 11:</b> In patients who fail to respond adequately to or are intolerant of a bDMARD, switching to another bDMARD or tsDMARD should be considered, including one switch within a class:														
=	=	=	=	D	D	=	D	D	=	=	=	=	D	=
<b>EULAR recommendations number 12:</b> In patients in sustained remission, cautious tapering of DMARDs may be considered:														
=	=	=	D	D	D	=	D	=	=	=	=	=	=	D

The survey was conducted October 2021–April 2022 and thus, reflects the situation at that time. <sup>a</sup>Other national regulations, please see text for details; bDMARD, biologic DMARD (biologics); csDMARD, conventional synthetic DMARD; DMARD, disease-modifying anti-rheumatic drug; tsDMARD, targeted synthetic DMARD (understood as tsDMARDs available at the time the recommendations were published); D, Differences exist; =, Concordance; EULAR, European Alliance of Associations for Rheumatology; IL, interleukin; JAK, Janus Kinase; PDE4, Phosphodiesterase-4.

**Table 1: Differences between the “2019 update of the EULAR recommendations for the management of PsA with pharmacological therapies” and the national treatment recommendations/regulations for the treatment of patients with PsA across Europe.**

recommended before IL-17i or IL-12/23i. In Portugal and Switzerland, no differentiation between biologics classes were made. In Norway and Romania, no preference for IL-17i or IL-12/23i was given. In Sweden, TNFi were recommended as first-line biologics irrespective of skin involvement. In the UK, two csDMARDs were required before start of biologics. Furthermore, the latest UK recommendations predated the availability of IL-17i and IL-12/23i.

**EULAR recommendation number 7,** “In patients with peripheral arthritis and an inadequate response to at least one csDMARD and at least one bDMARD, or when a bDMARD is not appropriate, a Janus Kinase inhibitor (JAKi) may be considered,” differed in Czech Republic,

Denmark, Estonia, Italy, Norway, Portugal, Romania, Spain, Sweden, Switzerland, and UK.

In Estonia, two csDMARDs and two TNFi should have failed before treatment with a JAKi. The latest Czech, Danish, Portuguese, Norwegian, Spanish and UK recommendations did not mention JAKi. The latest Italian recommendations reviewed the use of JAKi, but did not include it among the therapeutic options. In Romania, JAKi were positioned at the same level as biologics.

In Sweden, a TNFi was recommended as first-line biologics. In case of inadequate response/side effects, a second TNFi, an IL-17i or JAKi was recommended. If inadequate response/side effects, further switches

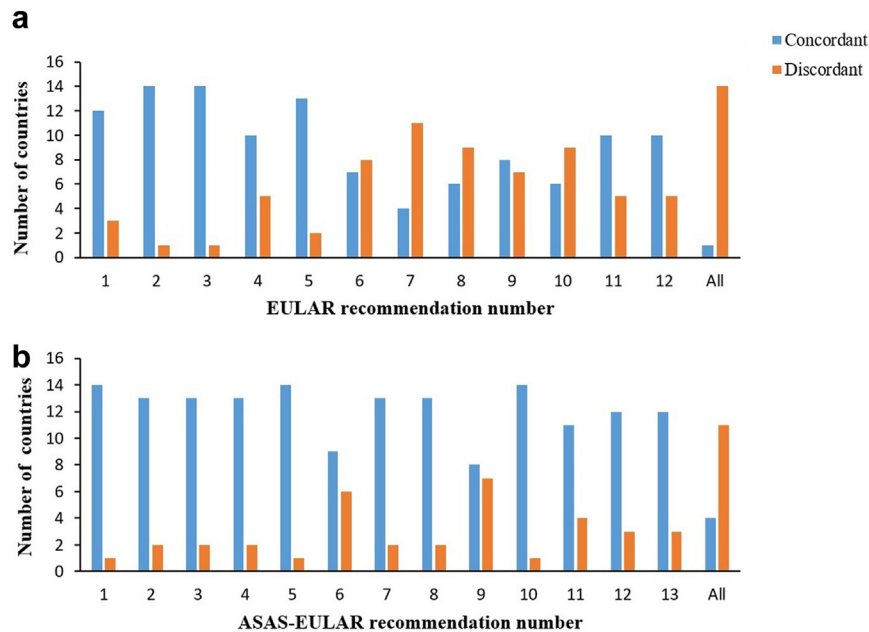


Fig. 1: Differences and similarities between national (survey October 2021–April 2022) and international treatment recommendations, a) for PsA (EULAR) and b) for axSpA (ASAS-EULAR).

within these three classes were recommended. Guselkumab, ustekinumab, abatacept, and apremilast were only recommended as ‘alternative biologics/tsDMARDs’ for selected cases. Specific comments were provided: A) if severe skin psoriasis, an IL-17i or guselkumab could be considered prior to a second TNFi or a JAKi, B) ustekinumab is effective on skin psoriasis and inflammatory bowel disease (IBD), C) abatacept has no effect on skin psoriasis, D) apremilast could be considered if milder disease, inadequate csDMARD response and unsuitability for biologics/JAKi.

In Switzerland, JAKi were approved as equal to biologics for all patients. However, a critical benefit-risk evaluation was recommended, in particular for patients aged >65 years.

**EULAR recommendation number 8**, “In patients with mild disease and an inadequate response to at least one csDMARD, in whom neither a bDMARD nor a JAKi is appropriate, a Phosphodiesterase-4 inhibitor (PDE-4i) may be considered,” differed in Denmark, Estonia, Iceland, Italy, Norway, Portugal, Romania, Switzerland, and UK. According to the Danish treatment recommendations, PDE-4i was an alternative in patients who had failed TNFi, but it was not on the list of recommended drugs based on the tender. In Estonia and Romania, PDE-4i were not reimbursed. In Iceland, PDE-4i were recommended after one to two TNFi. In UK, Norway and Portugal, JAKi and PDE-4i were not available when the latest recommendations were published. In Italy, PDE-4i (apremilast) was recommended as alternative first biologic/tsDMARD in patients with non-erosive

arthritis, enthesitis, or dactylitis. Apremilast was only reimbursed for csDMARD inadequate responders who were not eligible for treatment with biologics. In Switzerland, PDE-4i was approved on the same line as biologics.

**EULAR recommendation number 9**, “In patients with unequivocal enthesitis and insufficient response to NSAIDs or local glucocorticoid injections, therapy with a bDMARD should be considered,” differed in Denmark, Estonia, Finland, Slovenia, Sweden, Switzerland, and UK. In the Danish recommendations, enthesitis was not mentioned as a specific reason for biologics/tsDMARD start or change. In Estonia, it was not allowed to use biologics for enthesitis without arthritis. In Finland, a csDMARD, preferably methotrexate, should always precede initiation of any biologics. In Sweden, use of methotrexate could be considered for enthesitis prior to initiating a biologics/tsDMARD. In Switzerland, there was no distinction between different disease manifestations in the formal approval of biologics. The UK recommendations did not include any recommendation for the treatment of enthesitis.

**EULAR recommendation number 10**, “In patients with predominantly axial disease which is active and has insufficient response to NSAIDs, therapy with a bDMARD should be considered, which according to current practice is a TNF inhibitor; when there is relevant skin involvement, IL-17 inhibitor may be preferred,” differed in Estonia, Finland, Iceland, Norway, Portugal, Romania, Sweden, Switzerland, and UK. In Estonia, two TNFi had to be tried before an IL-17i could be used. In Finland, a



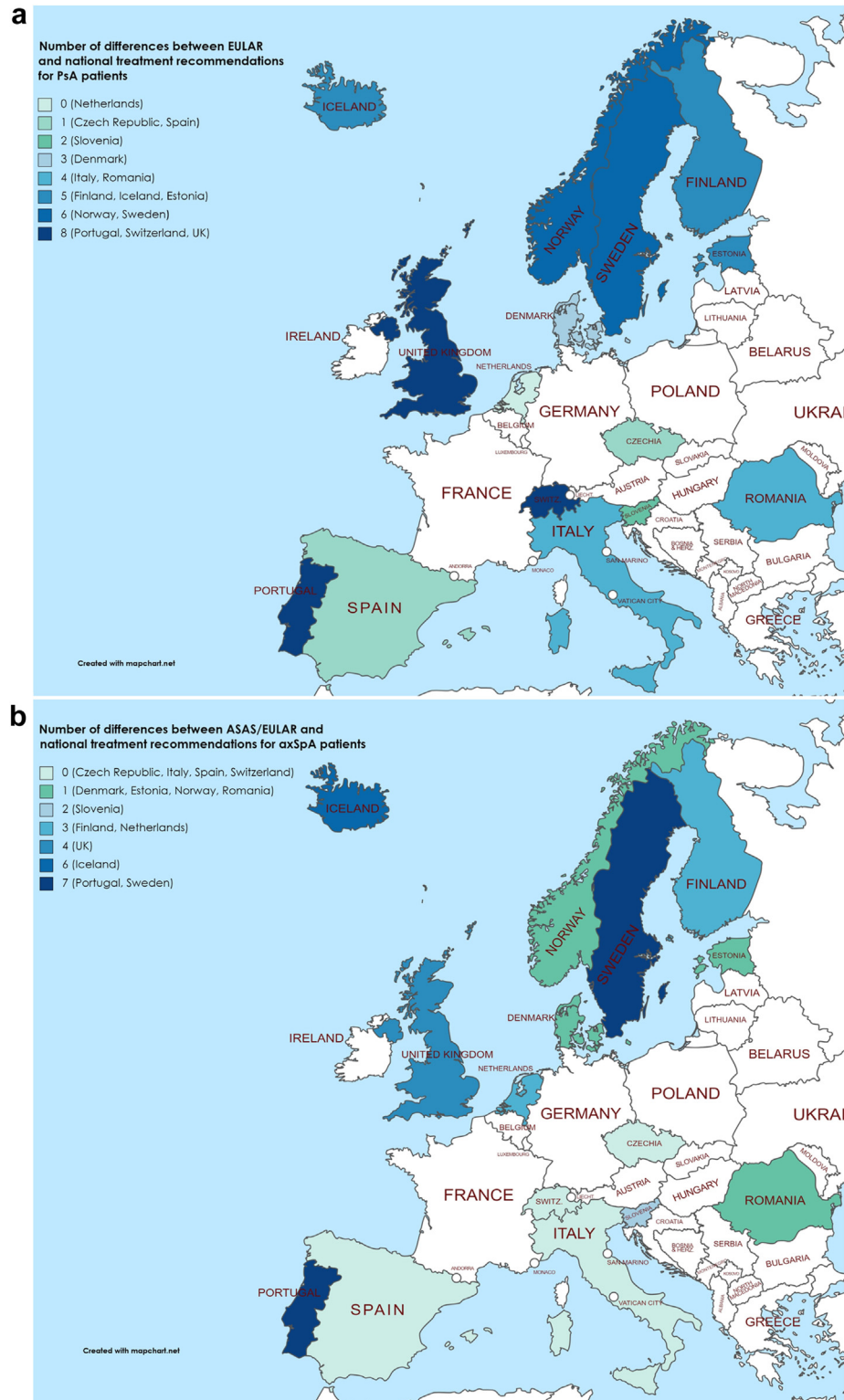


Fig. 2: Number of differences between national treatment recommendations and EULAR and ASAS-EULAR recommendations for patients with a) PsA and b) axSpA in each of the European countries.

csDMARD, preferably methotrexate, sulfasalazine or leflunomide, should always precede the initiation of any biologics. In Iceland, one to two TNFi were recommended before IL-17i and IL-12/23i. In Norway and Portugal, the use of IL-17i for relevant skin involvement was not included. In Sweden, use of IL-17i when relevant skin involvement was not included for first-line biologics, but for second-line treatment. In Romania, IL-17i were positioned at the same level as TNFi. In Switzerland, no distinction was made between disease manifestations in the formal approval for reimbursement; therefore, failure of a csDMARD was required before biologics could be tried. This also applied to PsA patients with predominantly axial disease. In the UK, the latest recommendations predated the availability of IL-17i.

**EULAR recommendation number 11**, “*In patients who fail to respond adequately to, or are intolerant of a bDMARD, switching to another bDMARD or tsDMARD should be considered, including one switch within a class,*” differed in Iceland, Italy, Norway, Portugal, and Switzerland. In Iceland, one to two TNFi were recommended before IL-17i and IL-12/23i. In Italy, Norway, and Portugal, JAKi were not available when the latest national treatment recommendations were published. In Switzerland, there was no limitation on the number of switches within a class.

**EULAR recommendation number 12**, “*In patients in sustained remission, cautious tapering of DMARDs may be considered,*” was not included in the Finnish, Icelandic, Italian, Norwegian, and UK treatment recommendations. In Switzerland, tapering was included in the drug-specific summaries in 2021, but only for biologics.

### National treatment recommendations for axSpA patients

By 2021, all countries except Estonia, Finland, Slovenia, and Switzerland had published national treatment recommendations for start of biologics/tsDMARDs in axSpA patients, with publication years varying from 2014 to 2021 (Table 2).

In Estonia, the ASAS-EULAR recommendations were followed with changes as required by the Estonian Health Insurance Fund regulations (due to economical restrictions), with their latest update in 2021.

Finland had no official recommendations for axSpA, but expert recommendations adapted from the ASAS-EULAR recommendations. Slovenia had unpublished recommendations from 2012, and, in general, followed the ASAS-EULAR recommendations. In Switzerland, there were no national recommendations to treat axSpA, and ASAS-EULAR recommendations were followed. In the Netherlands, the latest recommendations were published in 2014, with the addition of a point-of-view/position document in 2017, regarding newer drugs. In Norway, although there were national treatment recommendations, the ASAS-EULAR recommendations

were expected to be followed at a group level. In UK, the British Society of Rheumatology (BSR) recommendations from 2016 and the National Institute for Health and Care Excellence (NICE) recommendations from 2017 were followed. In Sweden, the national treatment recommendations only concerned pharmacologic therapy, and did not include other aspects of care. Regarding tender processes and requirements to follow national treatment recommendations/regulations, the same applied for axSpA as stated for PsA above.

### National treatment recommendations vs. ASAS-EULAR recommendations—axSpA

In Table 2, differences between the (at the time of this study) latest ASAS-EULAR recommendations and the most recent national treatment recommendations/regulations are listed.<sup>2</sup> All ASAS-EULAR recommendations were followed in four of the fifteen countries: Czech Republic, Italy, Spain, and Switzerland (Fig. 1). Most differences were found in Portugal and Sweden (Fig. 2b).

**ASAS-EULAR recommendation number 1**: “*The treatment of patients with axSpA should be individualised according to the current signs and symptoms of the disease (axial, peripheral, extra-articular manifestations) and the patient characteristics including comorbidities and psychosocial factors,*” was included in all national treatment recommendations except for Portugal.

**ASAS-EULAR recommendation number 2**: “*Disease monitoring of patients with axSpA should include patient-reported outcomes, clinical findings, laboratory tests and imaging, all with the appropriate instruments and relevant to the clinical presentation. The frequency of monitoring should be decided on an individual basis depending on symptoms, severity and treatment,*” was included in all national treatment recommendations except for those from Portugal and the UK.

**ASAS-EULAR recommendation number 3**: “*Treatment should be guided according to a predefined treatment target,*” differed in the Netherlands and Sweden. In the Dutch recommendations, T2T was not explicitly mentioned. In the Swedish recommendations, a T2T approach was not this clearly emphasized in axSpA, although it was indirectly indicated.

**ASAS-EULAR recommendation number 4**: “*Patients should be educated about axSpA and encouraged to exercise on a regular basis and stop smoking; physical therapy should be considered,*” was not mentioned in the Portuguese and Swedish recommendations, although it was considered part of standard clinical practice.

**ASAS-EULAR recommendation number 5**: “*Patients suffering from pain and stiffness should use an NSAID as first-line drug treatment up to the maximum dose, taking risks and benefits into account. For patients who respond well to NSAIDs continuous use is preferred if symptomatic otherwise,*” differed in Sweden, where NSAIDs should be used in the lowest possible dose that provides relief of

Czech Republic	Denmark	Estonia <sup>a</sup>	Finland <sup>a</sup>	Iceland	Italy	Netherlands	Norway	Portugal	Romania	Slovenia <sup>a</sup>	Spain	Sweden	Switzerland <sup>a</sup>	UK
<b>Are there recommendations in your country for starting a b/tsDMARD in patients with axSpA?</b>														
Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes
<b>When were your most recent national treatment recommendations for patients with axSpA made available?</b>														
2021	2021	NA	NA	2017	2021	2014/2017	2021	2017	2021	NA	2018	2021	NA	2017
<b>ASAS-EULAR recommendation number 1:</b> The treatment of patients with axSpA should be individualized according to the current signs and symptoms of the disease (axial, peripheral, extra-articular manifestations) and the patient characteristics including comorbidities and psychosocial factors:														
=	=	=	=	=	=	=	=	D	=	=	=	=	=	=
<b>ASAS-EULAR recommendation number 2:</b> Disease monitoring of patients with axSpA should include patient-reported outcomes, clinical findings, laboratory tests and imaging, all with the appropriate instruments and relevant to the clinical presentation. The frequency of monitoring should be decided on an individual basis depending on symptoms, severity and treatment:														
=	=	=	=	=	=	=	=	D	=	=	=	=	=	D
<b>ASAS-EULAR recommendation number 3:</b> Treatment should be guided according to a predefined treatment target:														
=	=	=	=	=	=	D	=	=	=	=	=	D	=	=
<b>ASAS-EULAR recommendation number 4:</b> Patients should be educated about axSpA and encouraged to exercise on a regular basis and stop smoking; physical therapy should be considered:														
=	=	=	=	=	=	=	=	D	=	=	=	D	=	=
<b>ASAS-EULAR recommendation number 5:</b> Patients suffering from pain and stiffness should use an NSAID as first-line drug treatment up to the maximum dose, taking risks and benefits into account. For patients who respond well to NSAIDs continuous use is preferred if symptomatic otherwise:														
=	=	=	=	=	=	=	=	=	=	=	=	D	=	=
<b>ASAS-EULAR recommendation number 6:</b> Analgesics, such as paracetamol and opioid-(like) drugs, might be considered for residual pain after previously recommended treatments have failed, are contraindicated, and/or poorly tolerated:														
=	D	=	=	D	=	D	=	D	=	=	=	D	=	D
<b>ASAS-EULAR recommendation number 7:</b> Glucocorticoid injections directed to the local site of musculoskeletal inflammation may be considered. Patients with axial disease should not receive long-term treatment with systemic glucocorticoids:														
=	=	=	=	D	=	=	=	=	=	D	=	=	=	=
<b>ASAS-EULAR recommendation number 8:</b> Patients with purely axial disease should normally not be treated with csDMARDs; sulfasalazine may be considered in patients with peripheral arthritis:														
=	=	=	D	=	=	=	D	=	=	=	=	=	=	=
<b>ASAS-EULAR recommendation number 9:</b> bDMARDs should be considered in patients with persistently high disease activity despite conventional treatments; current practice is to start with TNF therapy:														
=	=	=	D	D	=	=	=	D	D	D	=	D	=	D
<b>ASAS-EULAR recommendation number 10:</b> If TNFi therapy fails, switching to another TNFi or IL-17i therapy should be considered:														
=	=	D	=	=	=	=	=	=	=	=	=	=	=	=
<b>ASAS-EULAR recommendation number 11:</b> If a patient is in sustained remission, tapering of a bDMARD can be considered:														
=	=	=	D	D	=	D	=	=	=	=	=	=	=	D
<b>ASAS-EULAR recommendation number 12:</b> Total hip arthroplasty should be considered in patients with refractory pain or disability and radiographic evidence of structural damage, independent of age; spinal corrective osteotomy in specialised centres may be considered in patients with severe disabling deformity:														
=	=	=	=	D	=	=	=	D	=	=	=	D	=	=
<b>ASAS-EULAR recommendation number 13:</b> If a significant change in the course of the disease occurs, causes other than inflammation, such as a spinal fracture, should be considered and appropriate evaluation, including imaging, should be performed:														
=	=	=	=	D	=	=	=	D	=	=	=	D	=	=

The survey was conducted October 2021–April 2022 and thus, reflects the situation at that time. <sup>a</sup>Other national regulations, please see text for details; ASAS, Assessment of SpondyloArthritis international Society; bDMARD, biologic DMARD (biologics); csDMARD, conventional synthetic DMARD; DMARD, disease-modifying anti-rheumatic drug; D, Differences exist; =, Concordance; EULAR, European Alliance of Associations for Rheumatology; IL-17i, interleukin-17 inhibitor; TNFi, tumor necrosis factor inhibitor.

**Table 2: Differences between the ASAS-EULAR treatment recommendations and the most recent national treatment recommendations/regulations for patients with axSpA across Europe.**

symptoms, i.e., use ‘when needed’ was preferred over continuous use.

**ASAS-EULAR recommendation number 6:** “Analgesics, such as paracetamol and opioid-(like) drugs, might be considered for residual pain after previously recommended treatments have failed, are contraindicated, and/or poorly tolerated,” differed in Denmark, Iceland, Netherlands, Portugal, Sweden, and the UK. In Denmark, opioid-like drugs were not recommended. In Iceland, Netherlands, Portugal, Sweden, and the UK, analgesics were not mentioned in the national treatment recommendations.

**ASAS-EULAR recommendation number 7:** “Glucocorticoid injections directed to the local site of musculoskeletal inflammation may be considered. Patients with axial disease should not receive long-term treatment with systemic glucocorticoids,” was not mentioned in the Icelandic and Slovenian recommendations.

**ASAS-EULAR recommendation number 8:** “Patients with purely axial disease should normally not be treated with csDMARDs; sulfasalazine may be considered in patients with peripheral arthritis,” differed from Finnish and Norwegian recommendations. In Finland, use of a



csDMARD, preferably sulfasalazine or methotrexate, was recommended to always precede start of a biologics. In Norway, sulfasalazine or methotrexate were recommended as first choice in axSpA patients with peripheral arthritis.

**ASAS-EULAR recommendation number 9:** “bDMARDs should be considered in patients with persistently high disease activity despite conventional treatments (as shown in the corresponding ASAS/EULAR figure); current practice is to start with TNFi therapy,” differed in Finland, Iceland, Portugal, Romania, Slovenia, Sweden, and the UK.

In Finland, a csDMARD was required to precede initiation of a biologics.

In Iceland, positive MRI or radiographic sacroiliitis was not mentioned in order to start a TNFi.

In Portugal, axSpA patients with peripheral arthritis should have attempted adequate csDMARD treatment (at least three months with full dose, preferably sulfasalazine), unless contraindicated, intolerance or side-effects. In case of monoarthritis/oligoarthritis at least one intra-articular steroid injection should have been tried, and for symptomatic enthesitis, at least one local steroid injection, if not contraindicated.

In Romania, Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) > 6 at two successive evaluations at least four weeks apart and Ankylosing Spondylitis Disease Activity Score (ASDAS) ≥ 2.5, or erythrocyte sedimentation rate > 28 mm/h and/or C-reactive protein above 3 times the upper reference limit, was required to start biologics.

In Slovenia, ASDAS was not used as an entry criterion for biologics therapy.

In Sweden, start of TNFi was recommended for patients with high disease activity as assessed by clinical judgement of a rheumatologist (including evaluation of axial/peripheral disease, IBD, uveitis, and psoriasis), for patients with previously insufficient response to at least two NSAIDs during at least three months in total, and optional prior attempts with glucocorticoid injections in the sacroiliac joints. In predominantly peripheral disease, attempts with glucocorticoid injections were additionally required before TNFi start and optionally also at least four months of sulfasalazine. The use of validated measures of axial disease activity were recommended (ASDAS ≥ 2.1 or BASDAI ≥ 4).

In UK, ASDAS/BASDAI were not specified for eligibility.

**ASAS-EULAR recommendation number 10:** “If TNFi therapy fails, switching to another TNFi or IL-17i therapy should be considered,” differed in Estonia, where the second biologics was also required to be a TNFi.

**ASAS-EULAR recommendation number 11:** “If a patient is in sustained remission, tapering of a bDMARD can be considered,” was not included in the Dutch (although common clinical practice), Finnish, Icelandic, and UK recommendations.

**ASAS-EULAR recommendation number 12:** “Total hip arthroplasty should be considered in patients with refractory pain or disability and radiographic evidence of structural damage, independent of age; spinal corrective osteotomy in specialised centres may be considered in patients with severe disabling deformity,” was not included in the Icelandic, Portuguese (total hip arthroplasty), and Swedish recommendations.

**ASAS-EULAR recommendation number 13:** “If a significant change in the course of the disease occurs, causes other than inflammation, such as a spinal fracture, should be considered and appropriate evaluation, including imaging, should be performed,” was not included in the Icelandic, Portuguese, and Swedish recommendations.

## Discussion

In this report, only a minority of the national treatment recommendations in fifteen countries across Europe were in line with all EULAR recommendations for the treatment of patients with PsA and all ASAS-EULAR recommendations for the treatment of patients with axSpA.<sup>1,2</sup> Some countries had stricter requirements to start biologics/tsDMARDs, which could impact access to these treatments for some patients. Not all countries had published national treatment recommendations, but rather had other rules or regulations to follow. In Slovenia, recommendations were generally agreed upon, but not published, and in the Netherlands recommendations for PsA were under development, whereas recommendations for axSpA had been published. In Switzerland, there were drug-class-specific recommendations from the Clinical Affairs Committee of the Swiss Society of Rheumatology, which also included the status of health insurance coverage, and in Estonia the health insurance fund regulations were to be followed. Finland had official treatment recommendations for PsA and expert recommendations for axSpA adapted from the ASAS/EULAR recommendations.

Several of the differences between national and international treatment recommendations were explained by the national recommendations pre-dating the international publications and hence, not always including recently developed treatment options, such as IL-17i, IL-12/23i and JAKi. More differences were found between the national treatment recommendations for PsA and the EULAR recommendations, than between the national treatment recommendations for axSpA and the ASAS-EULAR recommendations.<sup>2</sup> Contributing to the better agreement between the ASAS-EULAR recommendations and national treatment recommendations for patients with axSpA, may be that the first ASAS recommendations for treatment of patients with ankylosing spondylitis (AS) were published several years before (2003) the first EULAR recommendations for treatment of patients with PsA (2011).<sup>13</sup> Furthermore,

the first ASAS-EULAR recommendations for the treatment of patients with AS were published in 2005.<sup>14</sup>

Several of the differences between national treatment recommendations/regulations and international recommendations seemed to be of minor clinical importance. However, in some countries, there were more marked differences, such as for PsA patients in Finland and Switzerland, where the use of a csDMARD was required prior to initiation of a biologics/tsDMARD, even in patients with predominantly enthesal involvement or axial disease. In Estonia, for patients with PsA, two csDMARDs and two TNFi should have failed before initiation of treatment with other biologics/tsDMARDs. Entry criteria for start of biologics varied across countries and were the most stringent in Romania, where BASDAI > 6 and ASDAS ≥ 2.5 were part of the eligibility criteria for starting biologics in axSpA patients.

In PsA patients with significant skin involvement, no preference for an IL-17i or IL-12/23i was given in several countries, which is in contrast to EULAR recommendation numbers 6 and 10. The positioning of JAKi in PsA differed across countries, i.e., JAKi were positioned either at the same level as biologics or recommended after failure of biologics. PDE-4i were not in use or not reimbursed in several countries. In contrast to ASAS-EULAR recommendation number 6, analgesics were not specifically mentioned in several of the national treatment recommendations for axSpA, which is surprising given that pain is a major challenge for patients.<sup>15</sup>

Regarding standardization of treatment practices across the world, evidence-based international treatment recommendations may form an important basis for the development of national treatment recommendations and practices. On the other hand, countries may have a need for national treatment recommendations due to e.g., economic restrictions in the prescription of costly drugs, other regulatory restrictions or language barriers. Yet, the national recommendations still lean heavily on international recommendations, which underline their importance.

The 2022 ASAS/EULAR recommendations for axSpA were in development at the time of this comparison.<sup>10</sup> They are, however, mostly in line with the 2016 recommendations assessed in this report. The most important differences are two newly formulated recommendations: number 10 on the preference of TNF monoclonal antibodies for treatment of recurrent uveitis and IBD, and number 11 concerning prompt reevaluation of diagnosis and consideration of comorbidities in patients with treatment failure. Furthermore, in recommendation number 9, TNFi, IL-17i or JAKi (previously bDMARDs) should be considered in patients with persistently high disease activity despite conventional treatment; current practice is to start a TNFi or IL-17i (previously TNFi). In previous recommendation number 10 (now 12) also a JAKi, and not only TNFi or

IL-17i, should be considered in case of failure of a first biologics/tsDMARD (previous TNFi). However, even given these differences, the conclusions of this paper remain valid.

At the EULAR Annual Meeting June 2023 the yet-to-be-published “EULAR recommendations for the management of psoriatic arthritis: 2023 update” were presented, including one completely new recommendation: “The choice of the mode of action should reflect non-musculoskeletal manifestations related to PsA; with clinically relevant skin involvement, preference should be given to an IL-17A or IL-17A/F or IL-23 or IL-12/23 inhibitor; with uveitis to an anti-TNF monoclonal antibody; and with IBD to an anti-TNF monoclonal antibody or an IL-23i or IL-12/23i or a JAKi.” Furthermore, the last part of recommendation number 3, “systemic glucocorticoids may be used with caution at the lowest effective dose” will no longer be included, and biologics in current recommendation number 10 will be specified as IL-17Ai, TNFi, IL17-A/Fi or JAKi. Also to note, in recommendation number 11, tsDMARDs will be specified as JAKi. Apart from this, only minor differences from the current recommendations were presented. Hence, also taking this information into account, the conclusions of this paper remain valid.

To our knowledge, this is the first study to compare EULAR and national treatment recommendations for patients with PsA across Europe. In axSpA, only one similar study was published more than a decade ago.<sup>16</sup> Additionally, a review focusing on pharmacological treatment of PsA and axSpA including national and international recommendations was published in 2014.<sup>5</sup> As in the previous studies, we discovered in some countries stricter eligibility criteria for disease activity and previous treatment failures in order to start biologics, which could impact access to biologics/tsDMARD therapy across countries.

Our study is limited by its focus on the EULAR and ASAS-EULAR recommendations, without reference to the “American College of Rheumatology/Spondylitis Association of America/Spondyloarthritis Research and Treatment Network recommendations for axSpA”<sup>17</sup> or the “Group for the Assessment for Psoriasis and Psoriatic Arthritis (GRAPPA)” recommendations.<sup>18</sup> The EULAR and ASAS-EULAR recommendations were considered particularly relevant in a European setting, also taking into consideration that our national rheumatology organizations are part of EULAR. Of note, GRAPPA uses different methodology than EULAR in their recommendations, and has a more recent update, leading to some differences in the proposed sequential use of drugs (Supplementary Table S1).<sup>1,18</sup> Nevertheless, we acknowledge the importance of all these sets of recommendations. A further limitation of the study is that we did not collect information on the penetration of national treatment recommendations in different regions of the countries.

### Search strategy and selection criteria

The international treatment recommendations and comparisons of national and international treatment recommendations in this narrative review were identified through searches of PubMed with the search terms “recommendations”, “guidelines”, “psoriatic arthritis”, “axial spondyloarthritis”, “ankylosing spondylitis”, “spondyloarthropathy”, “comparison”, “comparability”, “differences” and “similarities.” The final reference list was generated on the basis of the most recent EULAR and ASAS/EULAR treatment recommendations and any comparison of national and international treatment recommendations for patients with PsA and/or axSpA written in English. The national treatment recommendations across Europe were identified and collated through an electronic survey completed by leading experts in the field of rheumatology from the Czech Republic, Denmark, Estonia, Finland, Iceland, Italy, the Netherlands, Norway, Portugal, Romania, Slovenia, Spain, Sweden, Switzerland, and the United Kingdom between October 2021 and April 2022.

In conclusion, only a minority of the national treatment recommendations in fifteen countries across Europe were completely in line with all EULAR recommendations for treatment of patients with PsA and all ASAS-EULAR recommendations for the treatment of patients with axSpA. In some countries, eligibility criteria for biologics/tsDMARD treatment were more stringent, limiting access to these treatments for some patients. This report may motivate some European countries to update their national treatment recommendations for patients with PsA and axSpA, to be more aligned with newer treatment options and the latest international treatment recommendations.

### Contributors

Conceptualisation: BM, MØ, MJN, AC, BMö, LMØ, MLH; Methodology: BM, MØ, MJN, AC, BMö, LMØ, MLH; Software: BM; Validation: All authors; Formal analysis: BM; Investigation: All authors; Resources: MØ, MLH; Data curation: BM, MØ, MLH; Writing (original draft): BM; Writing (Review and editing): All authors. Visualisation: BM; Supervision: MØ, MLH; Project administration: BM, MØ, MLH; Funding acquisition: BM, MØ, MLH. The CRediT statement is found in the supplementary file.

### Editor note

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### Declaration of interests

BM, research grant from Novartis (for the present manuscript, paid to employer), Centre for treatment of Rheumatic and Musculoskeletal Diseases (REMEDY) is funded as a Centre for Clinical Treatment Research by The Research Council of Norway (project 328657); MØ, Funding for the present manuscript from Novartis (paid to institution), The EuroSpA Research Collaboration Network was financially supported by Novartis Pharma AG, research grants from Abbvie, BMS, Merck, Novartis, UCB, consulting fees from Abbvie, BMS, Celgene, Eli-Lilly, Galapagos, Gilead, Janssen, MEDAC, Merck, Novartis, Pfizer, Sandoz, UCB, payment or

honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Abbvie, BMS, Celgene, Eli-Lilly, Galapagos, Gilead, Janssen, MEDAC, Merck, Novartis, Pfizer, Sandoz, UCB, support for attending meetings and/or travel from UCB; MJN, grant from Novartis (payment to institution), consulting fees from AbbVie, Eli-Lilly, Janssen, Novartis, Pfizer (payment to institution), payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from AbbVie, Eli-Lilly, Janssen, Novartis, Pfizer (payment to institution), support for attending meetings and/or travel from Janssen, UCB (payment to institution), participation on a Data Safety Monitoring Board or Advisory Board from Eli-Lilly, Janssen, Novartis, Pfizer (payment to institution), scientific member of the SCQM registry and the EuroSpA collaboration (unpaid), ASAS-EULAR taskforce member (unpaid); AC, payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Abbvie, Merck-Sharp & Dohme, Novartis; BMö, payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Abbvie, Janssen, Novartis, Pfizer, support for attending meetings and/or travel from Abbvie, Janssen, Novartis, Pfizer; LMØ, research grant from Novartis (for the present manuscript, paid to employer); JZ, payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Abbvie, Eli-Lilly, Sandoz, Novartis, Egis, UCB, Sanofi, Astra Zeneca, support for attending meetings and/or travel from Abbvie, Pfizer, Astra Zeneca, participation on a data safety monitoring board or advisory board from Abbvie, UCB, Sobi; BGLi, Research grants from Pfizer, AbbVie, BMS (payments made to institution); AM; payment for work done in relation to research questions for this project from the University of Aberdeen, speakers fees for educational events from Galapagos; KL, Honoraria for lectures from Pfizer, Abbvie, Novartis, Janssen, support for attending meetings from Abbvie, Pfizer; DN, Consulting fees from BMS, Lilly, MSD, Novartis, Pfizer, UCB, payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Pfizer, support for attending meetings and/or travel from Pfizer; BGu, consulting fees from Novartis, speaker bureaus from Novartis, Nordic Pharma; FI, payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Abbvie, BMS, Galapagos, Eli-Lilly, Pfizer, UCB, support for attending meetings and/or travel from Pfizer, UCB; PH, research grant (payments made to employer) from Novartis; TKK, consulting fees from AbbVie, Gilead, Janssen, Novartis, Pfizer, Sandoz, UCB, payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Grünenthal, Janssen, Sandoz, participation on a data safety monitoring board or advisory board from Abbvie, grants or contracts from AbbVie, BMS, Galapagos, Novartis, Pfizer, UCB; AMR, payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Abbvie, Amgen, Novartis, support for attending meetings and/or travel from Amgen, Nordic, Theramex, grants or contracts from Novartis, Pfizer, Amgen, Astra Zeneca, Abbvie, MSD, Lilly, Boehringer Ingelheim; CC, None; ZR, Consulting fees from AbbVie, Janssen, Novartis, MSD and Lek Sandoz, payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Eli Lilly, Janssen, Abbvie, Pfizer, Boehringer Ingelheim, support for attending meetings and/or travel from Gedeon Richter, Pfizer, SOBI (payments made to employer), participation on data safety monitoring board or advisory board from Abbvie, Pfizer, Astra Zeneca, Janssen, Eli Lilly, Novartis and Boehringer Ingelheim; ICF, consulting fees from Pfizer, Galapagos, payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from BMS, Eli-Lilly, Gilead, Janssen, Novartis, MSD, Pfizer, GSK, support for attending meetings and/or travel from Pfizer, Eli-Lilly; JKW, Research support from Abbvie, Amgen, Eli Lilly, Novartis, Pfizer (unrelated to the present work, payment made to Lund University), speakers bureaus from Abbvie and Amgen (paid to Skåne University Hospital), acting co-chair of the Swedish Society for Rheumatology's working group annually updating Swedish treatment recommendations for axial spondyloarthritis and psoriatic arthritis (unpaid, fiduciary assignment); JV, support for the present manuscript from the Czech Ministry of Health—Conceptual Development of Research Organization 00023728 (Institute of Rheumatology), payment to institution,

consulting fees from Eli Lilly, payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Abbvie, Biogen, Eli Lilly, Gilead, MSD, Novartis, Pfizer, Roche, Sanofi, UCB, support for attending meetings and/or travel from Abbvie (payment to institution), participation on a data safety monitoring board or advisory board from Abbvie, Gilead, Pfizer, UCB, grants or contracts from Abbvie (payment to institution); AGL, Consulting fees from Janssen-Cilag A/S, Lilly Nordics, UCB, payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Novartis Healthcare A/S, Pfizer, support for attending meetings and/or travel from Pfizer, UCB, participation on a data safety monitoring board or advisory board from Janssen-Cilag A/S, Lilly Nordics, UCB; MH; None; SV, None; AMH, Research grant from MSD, grant for attending meeting from Janssen, Pfizer, support for travel cost from Janssen; GG, None; MS, support for the present manuscript from Lilly and Boehringer-Ingelheim, payment or honoraria for lectures, presentations, speaker's bureaus, manuscript writing or educational events from Pfizer, Boehringer-Ingelheim, GSK, participation on data safety or advisory board from Janssen-Cilag, support for attending meetings and/or travel from Janssen-Cilag; MvdS, Research support/grant from UCB, Eli Lilly, Novartis, Janssen (payments made to institution, AMR Medical Research BV), consulting fees from Novartis, UCB, Abbvie (payments made to institution), payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Novartis, UCB, Janssen (payments made to institution), support for attending meetings and/or travel from UCB; EKK, None; MJS, payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Abbvie, Janssen, Lilly, Novartis, Pfizer, support for attending meetings and/or travel from Janssen, Viartis, Medac and receipt of equipment, materials, drugs, medical writing, gifts or other services from Vifor; CM, None; MT, payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Abbvie, Amgen, Boehringer, Pfizer, Sanofi-Aventis, Roche, Lek-Sandoz, Janssen, Medis, Novartis, participation on data safety or advisory board from Astra Zeneca, Eli Lilly, Janssen, Boehringer, MSD, Novartis, Roche; FDG, payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Abbvie, Galapagos, Janssen, and support for attending meetings and/or travel from Pfizer, Astra Zeneca; DDG, None; MLH, payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Pfizer, Medac, Sandoz, research grants from Abbvie, Biogen, BMS, Celltrion, Eli Lilly, Janssen Biologics B.V, Lundbeck Foundation, MSD, Pfizer, Roche, Samsung Biopies, Sandoz, Novartis, Nordstar (payment to institution). MLH has chaired the steering committee of the Danish Rheumatology Quality Registry (DANBIO, DRQ), which receives public funding from the hospital owners and funding from pharmaceutical companies. MLH co-chairs EuroSpA, which generates real-world evidence of treatment of psoriatic arthritis and axial spondyloarthritis based on secondary data and is partly funded by Novartis.

## Acknowledgements

The EuroSpA Research Collaboration Network was financially supported by Novartis Pharma AG. Novartis had no influence on the data collection, analyses, manuscript preparation or decision to submit the manuscript.

Role of funding source: The EuroSpA Research Collaboration Network was financially supported by Novartis Pharma AG. Novartis had no influence on the data collection, analyses, manuscript preparation or decision to submit the manuscript. The authors were not precluded from assessing data in the study, and they accept responsibility to submit for publication.

## Appendix A. Supplementary data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.janep.2023.100706>.

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