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# Pain mechanisms and ultrasonic inflammatory activity as prognostic factors in patients with psoriatic arthritis: protocol for a prospective, exploratory cohort study

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## ABSTRACT

**Introduction:** Persistent pain is a major concern for patients with psoriatic arthritis (PsA). Pain may be due to inflammatory activity or augmented central pain processing. Unawareness of the origin and mechanisms of pain can lead to misinterpretation of disease activity (by composite scores) and erroneous treatments. Ultrasonography (US) is a highly sensitive method to detect tissue inflammation. Evaluating pain mechanisms in relation to US measures may prove valuable in predicting response to treatment in PsA.

**Aims:** To study the association and prognostic value of pain mechanisms, ultrasonic activity and clinical outcomes in patients with PsA who intensify antirheumatic treatment.

**Methods and analyses:** 100 participants >18 years of age with PsA who initiate or switch antirheumatic treatment (biologicals and/or conventional synthetic disease-modifying antirheumatic drugs (DMARDs)) will be prospectively recruited from outpatient clinics in Copenhagen. All data (demographics, clinical, imaging, blood samples and patient-reported outcomes) will be collected at baseline and after 4 months. Pain is assessed by the PainDETECT Questionnaire, Visual Analogue Scale for pain, Swollen to Tender Joint Count Ratio, Widespread Pain Index and tender point examination. The association between pain variables and clinical/US characteristics will be described by correlation analyses. The predictive value of pain measures and baseline US scores on treatment response will be analysed with regression models. Outcomes are composite and clinical, as well as patient reported.

**Ethics and dissemination:** The study is approved by the ethics committee of the Capital Region of Denmark (H-15009080) and has been designed in cooperation with patient research partners. The study is registered at clinicaltrials.gov (number NCT02572700). Results will be disseminated through publication in international peer-reviewed journals.

**Trial registration number:** NCT02572700, Pre-results.

## Strengths and limitations of this study

- Prospective and comprehensive investigation of psoriatic arthritis (PsA) manifestations, ultrasonography and pain mechanisms in relation to treatment outcomes.
- Focus on patient-reported outcomes in 'real-life' observational settings.
- Involvement of several specialties and patient research partners.
- Results should be interpreted in the context of the explorative study design and the use of outcome measures that are not (sufficiently) validated for PsA.
- Heterogeneity of the study population may limit the analyses.

## INTRODUCTION

Psoriatic arthritis (PsA) is a heterogeneous disease with a wide clinical spectrum and diverse outcomes.[1] Disease-modifying antirheumatic drugs (DMARDs), including biological treatments, have improved the management of PsA substantially during the past decades.[2] Nevertheless, only around half of the patients experience a sufficient response from these drugs in routine care.[3] Research of prognostic factors and treatment response modifiers in PsA has provided valuable knowledge that could theoretically improve treatment strategies and overall prognosis.[3–13] Nevertheless, the majority of patients with PsA still consider their disease to be severe and perceive the treatment options as limited or burdensome.[14] Presumably, assessment of prognostic profiles has to be more comprehensive

and include patient-related concerns, motives and psychological aspects in order to optimise the clinical benefit. Seen from this aspect, the focus on pain seems relevant. Pain has been endorsed as a core domain in the assessment of PsA by the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) and Outcome Measures in Rheumatology (OMERACT) initiative.[15] Patients with PsA report pain to be their utmost priority and major health concern, while this symptom may be underestimated by clinicians.[16–18] Little is known about pain mechanisms in PsA.[19–22] The complex disease spectrum and lack of valid inflammatory biomarkers challenge the clinical evaluation and interpretation of pain reporting in PsA in which the widespread and persistent pain may be caused by augmented pain processing as a consequence of central sensitisation (CS).[22] Clinically CS is thought to account for neuropathic pain features such as secondary hyperalgesia, burning and prickling sensation, allodynia, pain attacks/electric shocks and pain evoked by slight pressure. These are also common pain qualities in patients with fibromyalgia[23] and frequently reported by rheumatic patients.[24–26] In some individuals, CS seems to develop into a state of chronic widespread pain (CWP) fully uncoupled from inflammatory activity. The mechanisms behind CWP is sparsely elucidated but may involve maladaptive neuroplasticity and cortical reorganisation of the somatosensory and motor systems,[26 27] aberrant peripheral inputs to central nervous system,[28] modulation of glia cell function,[29] and disruption of descending inhibitory and facilitating control.[30 31] An alternative explanation for ongoing pain could be obscure, untargeted inflammation of psoriatic loci not (always) assessed in routine rheumatology care such as entheses, skin and tendons. Besides, these manifestations seem less responsive to conventional disease-modifying drugs than synovitis of the joints.[2 32] High-frequency ultrasound is increasingly being used for the evaluating of inflammatory arthritis, including PsA, since this method exhibits sensitivity for assessing disease activity and structural damage compared with clinical examination.[33–36] Synovial hypertrophy and effusions are examined by grey scale (GS) ultrasound and the neovascularisation within the inflamed structures can be visualised by ultrasound Doppler activity (USD). In PsA, the value of ultrasonography (US) as a prognostic factor has been sparsely investigated to date. In patients with psoriasis, studies have documented that US activity in entheses, for example, is associated with an increased risk of developing PsA.[37–39] In rheumatoid arthritis (RA), subclinical arthritic activity determined by US seems to provide valuable prognostic insight into the risk of structural damage[40] as well as the chance of treatment response,[41] and recent studies have emphasised the benefit of US compared with composite clinical scores in the clinical evaluation of RA with concomitant fibromyalgia.[42 43]

## RATIONALE AND THEORETICAL CONSIDERATIONS

Incomplete awareness of underlying pain mechanisms may influence the assessment and management of PsA in several ways. Augmented central pain processing in PsA generates continuous reporting of high pain, disability and overall poor health.[16 44–46] This may specifically lead to misinterpretation of composite disease outcome measures, which then increases the risk of redundant conventional synthetic and/or biologicals DMARD (cs/bDMARD) treatment and insufficient pain management. In other cases, poor patient-reported outcomes and ongoing pain may be generated by untargeted (subclinical) psoriatic disease activity, which should not be interpreted as a 'chronic pain syndrome'. A thorough examination of pain mechanisms combined with an evaluation of inflammatory activity by US imaging and clinical examination may improve our interpretation of PsA disease expressions.

*Aims*: The primary aim is to investigate pain mechanism in PsA, and elucidate associations between pain outcome measures and clinical characteristics, with a special emphasis on US inflammatory activity. The study further aims to explore response rates to cs/bDMARD therapy in PsA subgroups (eg, according to pain profile, baseline US scores or treatment intervention), and analyse the predictive value of US scores and pain mechanisms on response to cs/bDMARD treatment.

We hypothesise that US assessment will be a valuable tool to improve the interpretation of pain outcome measures in PsA, and that pain mechanisms and/or US scores are of value in predicting response to anti-inflammatory treatment

## PATIENTS RESEARCH PARTNERS (PRPS)

The observational, clinical settings of the study ensure a high external validity. Furthermore, the study is designed with assistance from a professional, international PRP (co-author MdW) and two Danish PRPs (Connie Haugaard (CH) and co-author KB). Collaboration between patients and professionals in developing and disseminating research projects is relatively new. Nevertheless, this project follows the EULAR recommendations[47] for the inclusion of patient representatives in the contemporary scientific process by adhering to eight important aspects as depicted in table 1.

## METHODS
### Study design

A cohort of patients with PsA initiating antirheumatic treatment in routine care will prospectively be enrolled in the Non-Intervention-Study (NIS) framework. All participants will be assessed at baseline and after 4 months (follow-up). The baseline visit is defined as the time window from 14 days before until 7 days after initiation/switch of cs/bDMARD treatment. The enrolment period will be from 17 September 2015 to 1 February 2017. Follow-up will be completed by 15 June 2017. All

**Table 1** PRP involvement according to EULAR recommendations

1  PRPs (CH KB and MdW) have voluntarily participated in the process of designing and preparing the study protocol. They have acknowledged the protocol in its current form.
2  The PRPs have acknowledged the idea and purpose of the study, and participated in discussions of ethics, design, relevance and feasibility of the content and investigation programme. They have revised all patient information prior to distribution. PRPs and primary investigator (PH) will meet approximately every 6th month until the study is finalised to discuss the process.
3  The PrPs suffer from psoriasis and concomitant psoriatic arthritis. One is young (20 years), while the others are middle aged.
4  The 2 Danish PRPs were identified during routine care. Prior to their decision of participation, they received a written and oral task description that clarified their roles and expected contributions.
5  The PRP exhibited immense interest in the research collaboration and showed good communication skills.
6  The primary investigator will continuously consider the specific needs of the PRP, including educational aspects. A safe and respectful environment is highly prioritised and the PRP may contact the research group whenever needed.
7  The investigators provide information and appropriate training, including awareness of ethical issues continuously throughout the study.
8  The PRP work voluntarily and have been offered coauthorship according to the International Committee of Medical Journal Editors criteria.

PRP, patient research partner.

examinations will be carried out at The Parker Institute, Frederiksberg Hospital, the Capital Region of Denmark.

## Participants

Patients with a diagnosis of PsA who may be considered for inclusion will be identified during routine care at Departments of Rheumatology in the Capital Region of Denmark. The primary study investigator will determine whether the eligibility criteria are fulfilled. Patients of at least 18 years of age and diagnosed with PsA by a rheumatologist and fulfil the CASPAR classification criteria[48] are considered for inclusion if they present with peripheral joint involvement and are about to initiate or switch csDMARD or bDMARD treatment due to active PsA. Written informed consent is acquired. Patients are excluded in case of pregnancy, peripheral neuropathy, demyelinating disease, recent stroke or other rheumatic inflammatory diseases. Patients who suffer from axial PsA without peripheral manifestations are excluded and patients treated with oral, intra-articular or intramuscular glucocorticoids within the past 3 weeks, centrally acting analgesics (opioids, antidepressants, anticonvulsants) during the past week or mild analgesics (non-steroidal anti-inflammatory drugs, acetylsalicylic acid, acetaminophen) 24 h prior to baseline are not includable. During the study period, the patients will receive routine care as decided by their treating rheumatologist, with prospective registrations in the Danish DANBIO registry according to Danish standard for clinical practise.[49] All relevant interventions will be registered in the study.

## Variables and outcome measures

Participants will undergo an examination programme to assess the variables of interest (table 2).

## Clinical examination

Two trained healthcare professionals will perform the interview and clinical examination, which consist of (table 2): a 66/68 swollen/tender joint count ad modum EULAR; the Spondyloarthritis Research Consortium of Canada enthesitis score (SPARCC)[50] evaluating tenderness in 18 entheses sites, with a maximum score of 16; number of fingers and toes affected by dactylitis (present/not present); tender point examination according to the 1990 American College of Rheumatology (ACR) criteria for fibromyalgia;[51] psoriatic nail disease (yes/no, y/n); psoriasis body surface area (BSA); type of psoriasis and Psoriatic Area Severity Index (PASI) in psoriasis vulgaris. Height and weight will be measured as well. An Assessment of Motor and Process Skills (AMPS test) will be performed by a calibrated occupational therapist who has attended a specialised training course in the standardised AMPS administration procedures.[52]

## Blood samples

Blood samples, as specified in table 2, will be collected and processed by a trained laboratory technician and analysed according to standard procedures. All samples will be anonymised by a coding procedure and destroyed at study completion.

## Assessment of pain mechanisms

Characterisation of pain profiles will be based on the following assessment tools:

1. The PainDETECT Questionnaire (PDQ) was developed and validated in 2006 for the purpose of establishing a patient-administered screening tool to detect the likelihood of a neuropathic pain component in patients with low back pain.[46] Research of neuropathic pain features in other chronic pain and rheumatic conditions has expanded the applicability of PDQ.[23 24 53 54] The PDQ consists of nine items of which seven are somatosensory descriptor items, and two items relate to the spatial (radiating) and temporal pain characteristics. For screening purposes, PDQ cut-off scores ≤12 (a neuropathic component is unlikely) and ≥19 (a neuropathic component is likely) have been found to be appropriate.[46]

**Table 2** Examination and interview at baseline and follow-up

| | Baseline | 4 Months |
|---|:---:|:---:|
| **Demographics and disease-related characteristics (interview)** | | |
| Sex(M/F) | X | |
| Age (years) | X | |
| Diagnosed with spinal involvement (y/n) | X | |
| Disease duration of psoriatic arthritis (months) | X | |
| Symptom duration prior to diagnosis (months) | X | |
| Disease duration of psoriasis (months) | X | |
| Educational level | X | |
| Smoking (current/previous/never) | X | |
| Alcohol consumption (number per week) | X | |
| Diabetes (y/n) | X | |
| Cardiovascular disease (y/n) | X | |
| Dyslipidaemia (or treatment for this) (y/n) | X | |
| Mental disorder (depression, anxiety) (y/n) | X | |
| **Medication (interview)** | | |
| Use of mild analgesics, including NSAIDs (dosage) | X | X |
| Use of opioids, antidepressants or anticonvulsants during the study period (dosage) | | X |
| Cumulated dose of oral prednisolone during the last month | X | X |
| Medication history (current and previous cs/bDMARD) | X | |
| Interval (days) between study baseline visit and initiation of new treatment | X | |
| Date for treatment termination of new drug | | X |
| Reason for treatment withdrawal during the study period (lack of effect, adverse events, other) | | X |
| **Clinical examination** | | |
| VAS physician (0–100) | X | X |
| Height (cm) | X | |
| Weight (kg) | X | |
| Swollen joint count (66)(number) | X | X |
| Tender joint count (68)(number) | X | X |
| Manual tender point examination (number), only scores ≥2 are interpreted as a tender point. | X | X |
| SPARCC | X | X |
| Dactylitis (number) | X | X |
| Psoriatic body surface area (%) | X | X |
| Subtype of psoriasis | X | |
| Psoriatic nail lesions (number) | X | X |
| PASI (if psoriasis vulgaris) | X | X |
| **Patient-reported outcomes** | | |
| PDQ score | X | X |
| HAQ Disability Index (HAQ, including VAS for pain and global) | X | X |
| Medical Outcomes Study Questionnaire (SF-36, mental and physical) | X | X |
| PsAID | X | X |
| DLQI | X | X |
| VAS fatigue (0–100) | X | X |
| AMPS | X | X |
| WPI | X | X |
| GAD-10 | X | X |
| Trans-Q score | | X |
| BASFI | X | X |
| BASDAI | X | X |
| **Imaging** | | |
| X-ray hands and feet | X | |
| Ultrasonographic examination | X | X |
| **Blood samples (maximum 54 mL at each time point)** | | |
| *Blood samples will be analysed for*: C reactive protein, ALAT, alkaline phosphatase, erythrocytes, erythrocytes volume fraction, erythrocyte MCV, haemoglobin, erythrocyte MCHC, leucocytes and leucocyte types, reticulocytes, thrombocytes, potassium, sodium, creatinine, cobalamin (B12), VitD (P-25(OH)D cholesterol (total), LDL, HDL, glucose, HbA1C, inflammatory biomarkers. | X | X |

ALAT, alanine aminotransferase; AMPS, Assessment of Motor and Process Skills; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; cs/bDMARD, conventional synthetic and/or biologicals disease-modifying antirheumatic drugs; DLQI, Dermatology Life Quality Index; GAD-10, Generalised Anxiety Disorder Self-Assessment Questionnaire; HAQ, Health Assessment Questionnaire; HbA1C, glycated haemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; M/F, male/female; MCHC, mean corpuscular haemoglobin concentration; MCV, mean cell volume; PASI, Psoriatic Area Severity Index; PDQ, PainDETECT Questionnaire; PsAID, Psoriatic Arthritis Impact of Disease score; SPARCC, Spondyloarthritis Research Consortium of Canada enthesitis score; Trans-Q, Transition Questionnaire; VAS, Visual Analogue Scale; WPI, Widespread Pain Index; y/n, yes/no.

2. The Widespread Pain Index (WPI) constitutes part of the 2010 diagnostic criteria for fibromyalgia. From a list of 19 body parts supported by an explanatory body diagram, patients are able to indicate in which of the 19 areas they have had pain during the last week, corresponding to a WPI score between 0 and 19. A score above 7 is interpreted as a widespread pain indicium.[55]

3. The Swollen to Tender Joint Count Ratio (SJ/TJ) has been explored in a cohort of >2500 patients with RA who initiated anti-tumour necrosis factor-alpha treatment. Patients presenting with a SJ/TJ count ratio >0.5 were 2–3 times more likely to respond to treatment.[56] The relevance of SJ/TJ ratio has not been investigated in PsA before. The SJ/TJ ratio in this study will be based on maximum 66 SJ and 66 TJ (excluding tenderness of the hips).

4. The tender point count is part of the 1990 ACR criteria for fibromyalgia (FM), where the cut-off is 11 of the 18 tender points (in combination with pain in 3 body quadrants).[51] A study of PsA found that features with the greatest discriminating power for FM were a tender point count ≥8 tender points and ≥6 FM-associated symptoms.[22]

## Imaging

No gold-standard ultrasound (US) algorithm has yet been accepted for assessing disease activity in PsA. With the purpose of achieving a visualised measure of the composite psoriatic disease activity, we will apply a systematic US examination that assesses inflammatory changes in 26 joints (13 unilateral) of upper and lower extremities, and 12 entheses/tendons (6 unilateral) as shown in table 3. US examination of wrists, knees and metacarpophalangeal (MCP), metatarsophalangeal (MTP), proximal (PIP) and distal (DIP) interphalangeal joints of hands and feet will be performed by two experienced sonographers blinded to the patients clinical and laboratory data. The images of all patients will be saved in a digital archiving computer system for subsequent scoring. The scoring of US pathology will follow a prespecified procedure made in accordance with the OMERACT definitions and previously published scoring systems.[57–60] Joints will be assessed for synovial hypertrophy, Doppler activity and erosions, whereas scoring of entheses/tendons will adhere to the Madrid Sonographic Enthesitis Index (MASEI) algorithm.[61] Scanning will be performed with a General Electric Logiq E9 (Milwaukee, Wisconsin, USA) using a linear array matrix transducer with a 15 MHz centre frequency.

The interobserver reliability of the two sonographers will be investigated by double scans of patient 6–35. US assessment will occur on the same day as the clinical examination.

Radiographic images (X-rays) of the hands and feet will be taken at study start and evaluated for psoriatic changes by a radiologist, unless radiographic images and descriptions from the past 6 months are available from the hospital files.

## Patient demographics and patient-reported outcomes

Patient demographics and medication profile will be collected from the participants through the interview and from the patients' files. Patient-reported outcomes will be obtained from electronic questionnaires (table 2) accessible from computer touch screens at the study site.[62] Besides pain assessment questionnaires, the following questionnaires will be presented to the participants.

The Psoriatic Arthritis Impact of Disease score (PsAID) is a newly developed, prevalidated patient-derived and patient-reported outcome measure (0–10 scale) for assessment of pain, skin, fatigue, work/leisure activities, function, discomfort, sleep, coping and anxiety.[18]

The Medical Outcomes Study SF-36 (SF-36) is a generic health status questionnaire developed as a tool to compare various aspects of health status across a general and broad patient population. We will use the Danish version of SF-36 which uses a 4-week recall period. Both the Physical Component Summary (PCS) and the Mental Component Summary (MCS) scores will be assessed.[63]

The Health Assessment Questionnaire (HAQ) is used for assessing limitations in daily living activities. It

**Table 3** Ultrasonographic assessment of joints, tendons and entheses

| Tendons and joints | | Entheses | |
|---|---|---|---|
| Assessments (scores) | Loci | Assessments (scores) | Loci (mm*) |
| Synovial hypertrophy (0–3) | MCP 2–3 (D/V) | Structure (±) | Quadriceps ligament (<6.1) |
| Synovial Doppler (0–3), | PIP 2–3 (D/V) | Thickness (±) | Patella proximal ligament |
| Tendon thickness (±), | DIP 2–3 (D/V) | Calcification (0–3) | (<4) Patella distal ligament (<4) |
| Tendon Doppler (±), | Wrist (D/V) | Doppler (0–3) | Fascia plantaris (<4.4) |
| Erosions (0–3). | Knee (M/L) | Bursitis (±). | Achilles tendon (<5.29) |
| | MTP-D 1–3 | | Triceps tendon (<4.3) |
| | DIP-D 2–3 (foot) | | |

*Normal tendon thickness.
D, dorsal; DIP, distal interphalangeal; L, lateral; M, medial; MCP, metacarpophalangeal; MTP, metatarsophalangeal; PIP, proximal interphalangeal; V, volar.

consists of 20 questions addressing eight different areas of functional ability, and yields a total score between 0 and 3, with a higher score representing increasing disability.[64] It was originally developed for RA, but is now validated and widely used in PsA.[65][66]

Dermatology Life Quality Index (DLQI) is a dermatology-specific health-related quality of life questionnaire. It consists of 10 questions concerning symptoms and feelings, daily activities, leisure, work, personal relationships and treatment. Each question is scored 0–3, giving a sum ranging from 0 (no impairment of life quality) to 30 (maximum impairment) for the total score.[67]

The Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) comprises six Visual Analogue Scale (VAS) items regarding fatigue, pain and stiffness. It was developed for assessment of spinal disease in ankylosing spondylitis, but has been adopted in the evaluation of axial PsA disease.[68] The Bath Ankylosing Spondylitis Functional Index (BASFI) is a validated index to determine functional limitation in patients with ankylosing spondylitis and has subsequently been implemented for the assessment of spondyloarthropathies. It comprises of 10 questions regarding everyday life activities.

The Generalised Anxiety Disorder Self-Assessment Questionnaire (GAD-10) is a 10-item questionnaire developed from the Hamilton six-item anxiety scale. The instrument measures generalised anxiety according to a severity scale ranging from 0 to 50. A score of 15–19, 20–29 and 30–50 points indicate mild, moderate and severe anxiety, respectively.[69]

The Transition Questionnaire (Trans-Q) consists of three main questions addressing whether there has been an improvement, deterioration or no change regarding pain, function and overall condition between the two visits.[70]

### Exploratory outcomes and response criteria

Response to treatment during the 4-month study period will be assessed by various outcome variables covering composite, clinician-reported and patient-reported measures. Some of these outcomes are not validated for PsA, but are included based on their extensive use in trials and routine care of PsA. These are described in the following section. Clinician-reported and patient-reported outcomes are shown in table 4.

Psoriatic Arthritis Disease Activity Score (PASDAS)[71] is a weighted index comprising assessments of joints, function, acute-phase response, quality of life, and patient and physician global disease evaluation by VAS. The score range of the PASDAS is 0–10, with worse disease activity represented by higher scores. Cut-off values for a PASDAS good/moderate/poor response has been elaborated.[72] In the current study, the original PASDAS will be slightly modified (mPASDAS) by substituting assessment of the entheses at the medial femur condyle with that of the proximal patella. The latter site is included in the SPARCC (already part of the examination

**Table 4** Outcome measures assessed 4 months' after baseline

| | |
|---|---|
| Composite outcome | ACR 20%/50%/70% response |
| | MDA |
| | DAPSA |
| | DAPSA 50%/75%/85% response |
| | Δ CDAI |
| | Δ DAS28 |
| | mPASDAS good response |
| | Δ mPASDAS |
| Clinical outcomes | Δ SPARCC enthesitis score |
| | Δ Dactylitis (number) |
| | Δ Number of tender and swollen joints |
| | Δ PASI |
| | Δ CRP level |
| | Δ Physician's global assessment (VAS global) |
| | Δ Ultrasonic score |
| | Δ AMPS |
| Patient-reported outcomes | Δ VAS-fatigue, Δ VAS-pain, Δ patient VAS-global |
| | Δ PSAID |
| | Δ BASDAI |
| | Δ BASFI |
| | Δ SF-36 physical and mental summary scores (PCS, MCS) |
| | Δ HAQ-DI scores |
| | Δ DLQI |
| | Δ WPI |
| | Δ GAD-10 |
| | Trans-Q score |

Δ, change; ACR, American College of Rheumatology response criteria; AMPS, Assessment of Motor and Process Skills; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; CDAI, Clinical Disease Activity Index; CRP, C reactive protein; DAPSA, Disease Activity Index for Psoriatic Arthritis; DAS28, Disease Activity Score 28; DLQI, Dermatology Life Quality Index; GAD-10, Generalised Anxiety Disorder Self-Assessment Questionnaire; HAQ-DI, Health Assessment Questionnaire Disability Index; MDA, Minimal Disease Activity; mPASDAS, modified Psoriatic Arthritis Disease Activity Score; PASI, Psoriatic Area Severity Index; SF-36, 36-Item Short Form Health Survey; SPARCC, Spondyloarthritis Research Consortium of Canada enthesitis score; Trans-Q, Transition Questionnaire; VAS, Visual Analogue Scale; WPI, Widespread Pain Index.

programme) and does not overlap with the location of a tender point. Both the change in mPASDAS as well as achievement of mPASDAS good response (score <3.2 and an improvement in score of >1.6) will be evaluated.

The Disease Activity index for Psoriatic Arthritis (DAPSA) is the summation of the following five variables: Patient's global assessment, Patient's pain assessment (both on 10 cm VAS scales), Swollen joint count (0–66), Tender joint count (0–68) and C-reactive protein (CRP). DAPSA was originally developed for reactive arthritis (named 'DAREA'), but evidence has been provided for the utility and validity of the DAPSA for PsA disease activity assessment.[73] Furthermore, DAPSA correlates with ultrasound disease activity,[59] and the cut-offs for disease activity states and treatment response criteria have recently been provided.[74]

The ACR response criteria[75] were developed as measures of treatment response in trials of RA and has been adopted in PsA, where it has shown good discriminatory capacity.[76] It has a dichotomous outcome (y/n) based on the percentage of improvement in tender and swollen joint counts, and in at least three of the following five parameters: patients assessment, physician assessment, pain scale, physical function, and acute-phase reactant (CRP). The patient may fulfil a 20%, 50% or 70% improvement in these variables.

Minimal disease activity (MDA) criteria has been developed and validated with the objective of implementing treat-to-target strategies and achieving remission in PsA.[77] A patient is classified as having MDA when they meet five of seven of the following criteria: tender joint count ≤1, swollen joint count ≤1, PASI≤1 or BSA≤3 patient pain VAS≤15 mm (0–100 mm), patient global activity VAS≤20 mm, HAQ≤0.5, tender entheseal points ≤1.

Disease Activity Score 28 (DAS28) is widely used to assess PsA disease activity in clinical settings and has shown good discriminatory capacity in PsA studies, although this composite score was originally developed for RA.[76 78] DAS28-CRP includes a 28 swollen joint and tender joint count in addition to CRP level and a global health scale.

Clinical Disease Activity Index (CDAI) is a simple measure of disease activity that sums the patient's and physician's global assessments, and a swollen and a tender joint count. It is formally validated for RA, but not for PsA.[79] As with DAS28, the regular assessment of CDAI in routine PsA care makes it relevant as an exploratory outcome in the current study.

## ANALYSES AND STATISTICS
### Sample size considerations
Owing to the exploratory design, no statistical power calculation has been performed. The study period is limited to 17 months, which presumably allows us to enrol 100 patients.

### Descriptive statistics and main analyses
The study results will be reported in accordance with the STROBE statement.[80] Missing data at follow-up will be imputed by a non-responder assumption (applying baseline observation carried forward technique for continuous data). Baseline variables will be described for all participants and in relevant subgroups (eg, according to treatment, pain profile or US activity). Means and SDs or medians and IQRs will be calculated depending on data distribution and comparisons will be performed by $\chi^2$ test for categorical data and Mann-Whitney or Kruskal-Wallis test for continuous data. p Values <0.05 are considered to be statistically significant. The total number of participants with recorded values will be reported. Correlations will be explored by Spearman's rank-order correlation.

Achievement of patient, clinician and composite response measures will be described for all patients and in subgroups (eg, according to treatment, pain profile, US activity). Regression models will be applied to study if pain measurements and/or ultrasonic activity have an impact on the treatment response measures (table 4). Crude and adjusted estimates will be reported.

## DISCUSSION
Patients suffering a chronic (rheumatic) disease need to be aware of how various factors might influence their prognosis in order to understand their disease course. This insight will encourage patients and healthcare providers to intervene against modifiable adverse factors and optimise/personalise treatment strategies based on shared decision-making. The proposed study will explore and provide insight into the presence and prognostic impact of aberrant pain processing, and US assessed inflammatory load in PsA. Pain is a dominant and persistent symptom in PsA and is not uniformly correlated to routine measures of inflammatory activity. Investigating the underlying mechanisms responsible for this phenomenon will help clinicians to comprehend reasons for persistent pain, interpret composite disease activity scores, optimise patient counselling, and select the most optimal treatment strategies. To the best of our knowledge the impact of pain mechanisms in combination with US inflammatory assessment of treatment response constitute a novel prognostic research focus in PsA. A detailed study programme based on interview, multidisciplinary clinical examination, imaging and questionnaires will provide a thorough evaluation of the PsA cohort and include, among other factors, the core domains endorsed by OMERACT in 2006 for PsA assessment in randomised control trial and observational studies. The PsA core outcome set is currently undergoing a revision (according to the OMERACT filter 2.0) in order to enhance patients' perspectives and reflect recent insight into PsA disease. As part of this process, an overview of the measurement properties and feasibility of instruments used for PsA will be performed with the aim of endorsing at least one appropriate measurement instrument per core domain.[81–83] The current study complies with the intention of GRAPPA and OMERACT to incorporate patients' perspectives into the assessment and evaluation of PsA[47 83–85] by examining various patient-reported outcomes and by the participation of PRPs. Nevertheless, our study also reflects the need for valid instruments (gold standards) to assess PsA; several of the included outcome measures are not validated for PsA, which is a limitation that must be kept in mind when interpreting the results. However, we find this strategy acceptable and appropriate given the lack of gold standards, the multifaceted nature of PsA and the limited knowledge currently available in this research field. In conclusion, the proposed study will shed light on associations and prognostic impact of pain mechanisms, and US-assessed inflammatory activity in patients with PsA followed in routine care.

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