



BMJ Open Efficacy of tofacitinib in reduction of inflammation detected on MRI in patients with Psoriatic Arthritis presenting with axial involvement (PASTOR): protocol of a randomised, double-blind, placebo-controlled, multicentre trial

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ABSTRACT

Introduction Psoriatic arthritis (PsA) is an inflammatory disease characterised by synovitis, enthesitis, dactylitis and axial involvement. The prevalence of axial involvement ranges from 25% to 70% in this patient group. Treatment recommendations for axial PsA were mainly extrapolated from guidelines for axial spondyloarthritis, and the main treatment options are non-steroidal anti-inflammatory drugs and biological disease-modifying antirheumatic drugs (tumour necrosis factor, IL-17 and IL-23 inhibitors). Tofacitinib was approved for the treatment of PsA and its efficacy on axial inflammation has been demonstrated in a phase II study of ankylosing spondylitis (AS). This prospective study aims to evaluate the efficacy of tofacitinib in reducing inflammation in the sacroiliac joints (SIJs) and spine on MRI in patients with axial disease of their PsA presenting with active axial involvement compatible with axial PsA.

Methods and analyses This is a randomised, double-blind, placebo-controlled, multicentre clinical trial in patients with axial PsA who have evidence of axial involvement, active disease as defined by a Bath AS Disease Activity Index score of ≥ 4 and active inflammation on MRI of the SIJs and/or spine as assessed by an independent central reader. The study includes a 6-week screening period, a 24-week treatment period, which consists of a 12-week placebo-controlled double-blind treatment period followed by a 12-week active treatment period with tofacitinib for all participants, and a safety follow-up period of 4 weeks. At baseline, 80 subjects shall be randomised (1:1) to receive either tofacitinib or matching placebo for a 12-week double-blind treatment period. At week 12, an MRI of the whole spine and SIJs will be performed to evaluate the primary study endpoint.

Ethics and dissemination The study will be performed according to the ethical principles of the Declaration of Helsinki and the German drug law. The independent ethics committees of each centre approved the ethical, scientific

Strengths and limitations of this study

- This is the first prospective randomised controlled trial to investigate the efficacy of a Janus kinase inhibitor (tofacitinib) in patients with psoriatic arthritis (PsA) presenting with active axial involvement.
- The primary endpoint is the improvement of the total Berlin MRI score in the sacroiliac joints and spine on MRI as compared with baseline after 12 weeks as an objective measure of reduction of inflammatory activity.
- A potential limitation of this study could be that the study uses a definition of active axial disease in PsA that has never been evaluated in other studies.
- Another limitation is related to the sample size calculation. The assumption for this calculation was done based on results from a phase II study with tofacitinib in patients with radiographic axial spondyloarthritis.
- The last limitation is that the study is conducted only in one country (Germany).

and medical appropriateness of the study before it was conducted.

Trial registration number NCT04062695; ClinicalTrials.gov and EudraCT No: 2018-004254-22; European Union Clinical Trials Register.

INTRODUCTION

Psoriatic arthritis (PsA) is a chronic inflammatory disease associated with psoriasis (PSO). Data from cohort studies suggest that up to 30% of patients with PSO develop PsA characterised by peripheral (synovitis, enthesitis and dactylitis) and/or axial (sacroiliac joints (SIJ), spine) musculoskeletal involvement.^{1 2} There



is a natural overlap between the CLASSification criteria for Psoriatic ARthritis (CASPAR) classification criteria for PsA³ and Assessment of Spondyloarthritis International Society (ASAS) classification criteria for spondyloarthritis—SpA (both axial and peripheral), resulting from the pathophysiological proximity of the diseases. Depending on the definition used, the prevalence of the axial disease varies from 25% to 70% in patients with PsA.^{4–7}

MRI has been widely used as a diagnostic instrument to detect inflammatory affection of the axial skeleton in SpA and is being increasingly used to detect axial involvement in PsA.^{8,9} MRI can detect both active inflammatory (bone marrow oedema/osteitis) and structural (postinflammatory) changes (such as, fat lesions, erosions, sclerosis, new bone formation/ankylosis) in the SIJ and the spine. MRI findings in patients with PsA and axial involvement are largely similar to those in patients with axSpA, although an isolated spinal involvement (without SIJ), asymmetrical lesions, involvement of cervical spine seem to be more common in PsA than in idiopathic axial SpA.^{10–12}

Treatment guidelines for axial disease in PsA (European League Against Rheumatism¹³/Group for Research and Assessment of Psoriasis and Psoriatic Arthritis)¹⁴ were mainly extrapolated from axial SpA guidelines and recommend treating patients with axial PsA in a similar way as patients with primary axial SpA, despite some differences in disease characteristics and missing clinical trial evidence for the efficacy on axial disease in PsA.^{11 12 15 16} According to the above-mentioned international guidelines, the first-line treatment options in patients with PsA presenting with axial involvement are non-steroidal anti-inflammatory drugs (NSAIDs). When adequate efficacy is not achieved, tumour necrosis factor (TNF) or IL-17 inhibitors might be considered.^{17 18} It is, however, currently unclear whether treatment response in patients with PsA with axial involvement can be extrapolated from the data generated in primary axial SpA since only a few studies have been conducted so far in patients with PsA and axial affection.^{19 20}

Over the last 20 years, knowledge of the intracellular pathways downstream of cytokine receptors has considerably increased and the inhibition of intracellular enzymes such as receptor-associated kinases become a novel alternative to inhibit various cytokines. The Janus kinases/signal transducers and activators of transcription signalling pathway is essential for immunity that controls the cellular and antibody-related immune response.²¹ Tofacitinib—a pan-JAK inhibitor—has been investigated in a number of autoimmune diseases and received approval in the European Union, the USA and many other countries for the treatment of adult patients with rheumatoid arthritis (RA), PsA and ulcerative colitis. The efficacy of tofacitinib in the treatment of peripheral PsA has been demonstrated in Oral Psoriatic Arthritis Trial (OPAL)-Broaden and OPAL-Beyond trials that included patients who were either TNFi-naïve or had a history of treatment with TNFi, respectively.^{22 23} Similar to tofacitinib, the

selective JAK1 inhibitors filgotinib and upadacitinib were found effective in a phase II/ III trials for the treatment of active PsA.^{24–26} In addition to these positive results in PsA, tofacitinib was found clinically effective in a phase II clinical trial in patients with radiographic axial SpA.²⁷ Recently, data from phase II/III studies of two selective JAK1 inhibitors, filgotinib and upadacitinib, demonstrated benefit in patients with active radiographic axial SpA supporting further use of this mode of action in axial inflammation.^{28 29} However, there are no data on efficacy of JAK blockade in patients with PsA presenting with axial involvement.

The objective of this prospective study is to evaluate the efficacy of tofacitinib in reducing inflammation in the SIJs and spine on MRI in patients with PsA presenting with active axial disease.

METHODS AND ANALYSIS

Study design

This is a randomised, double blind, placebo-controlled, multicentre clinical trial. The study will include a 6-week screening period, a 24-week treatment period, which will consist of a 12-week placebo-controlled double-blind treatment period followed by a 12-week active treatment period with tofacitinib for all participants, and a safety follow-up period of 4 weeks (figure 1). During the screening period, patients will be assessed for study eligibility and will undergo procedures outlined in the assessment schedule (table 1). The baseline MRI of the whole spine and SIJs will be performed according to the study protocol within this period to confirm the presence of active inflammation (bone marrow oedema) compatible with SpA as assessed by an independent central reader.^{30–33} Briefly, the central eligibility reading is performed by one out of three MRI readers (two radiologists and one rheumatologist), who are experts in the field and have a long-standing experience in imaging in axial SpA otherwise not involved in the study activities. A calibration to assure agreement on the interpretation of the used definitions took place before the study starts. The patient is considered eligible if active inflammation fulfilling the ASAS definition and deemed indicative of axial involvement is present in the SIJs and/or spine.^{30–33}

At baseline visit (week 0), subjects will be randomised on a 1:1 ratio to receive either tofacitinib 5 mg two times per day or matching placebo two times per day for a 12-week double-blind treatment period. A biostatistician independent of the clinical study team created the randomisation list by a fixed block size of 4. The previous history of treatment with biological or targeted synthetic disease-modifying antirheumatic drugs is applied for stratification.

At week 12, an MRI of the whole spine and SIJs will be performed to evaluate the primary study endpoint. After week 12, all patients will receive tofacitinib 5 mg orally two times per day open-label for another 12 weeks. After the last tofacitinib dose at week 24 or in case of

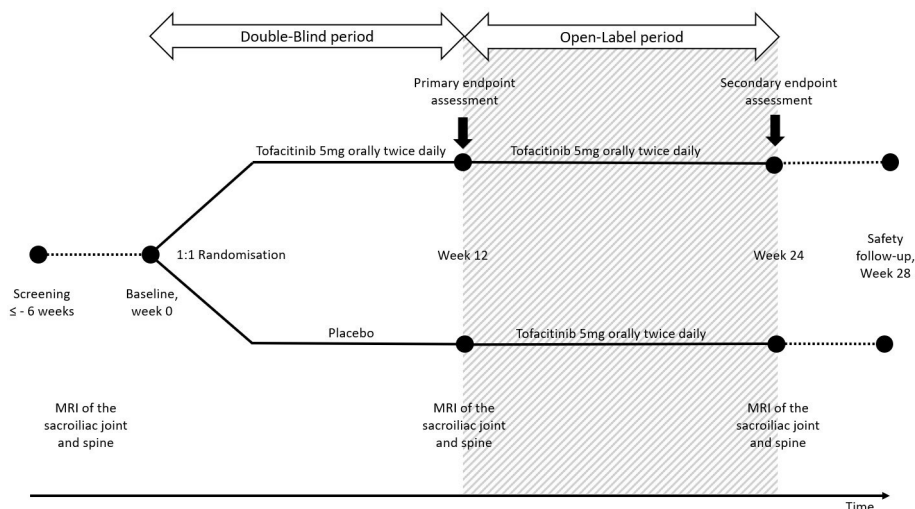


Figure 1 Study design of the PASTOR study. PASTOR, Psoriatic Arthritis presenting with axial involvement.

early termination, MRI of the whole spine and SIJs will be evaluated.

Safety assessments will be included in the regular visits and a follow-up visit will be performed 4 weeks after the last visit (ie, week 28) for patients completing the study according to the protocol. This protocol is described using the 2013 Standard Protocol Items Recommendations for Interventional Trials guidelines on standard protocol items for clinical trials.³⁴

Study population

A total of 80 patients with the clinical diagnosis of axial PsA presenting with axial involvement as confirmed by the presence of active inflammation in the SIJ or spine on MRI according to current consensus definitions,^{30–33} who are ≥ 18 and < 65 years of age at screening from either sex, fulfilling the CASPAR criteria for PsA,³ with active disease (Bath Ankylosing Spondylitis Disease Activity Index) and a history of an inadequate response to at least two NSAIDs, and who are able and willing to give written informed consent will be included. Key and full lists of inclusion and exclusion criteria of the Psoriatic Arthritis presenting with axial involvement (PASTOR) trial are shown in table 2 and online supplemental table 1, respectively.

Patients will be recruited in 20 study centres (both university and community-based) across Germany, which has been selected based on feasibility of recruitment and ability to comply with the MRI protocol. We anticipate an overly recruitment duration of 18 months.

Study endpoints

The primary endpoint is the improvement of the total Berlin MRI score (for SIJ and spine^{35–38} as compared with baseline after 12 weeks of therapy with tofacitinib or placebo. The Berlin MRI score is based on semiquantitative grading of lesions according to the extent of the subchondral bone marrow and vertebral units affection, for SIJ quadrant/entire sacroiliac or and spine, respectively. While active inflammation, erosions and fatty

lesions are assessed both for SIJs and spine, sclerosis and ankylosis are assessed for SIJs and bone proliferation active inflammation of the posterior segments evaluated for the spine.

Specifically, the active inflammatory and structural lesions will be assessed as follows:

- ▶ Sacroiliac joints
 - Bone marrow oedema—0–3 per quadrant, 0–24 in total.
 - Fat bone marrow deposition—0–3 per quadrant, 0–24 in total.
 - Erosions—0–3 per quadrant, 0–24 in total.
 - Subchondral sclerosis—0–1 per joint, 0–2 in total.
 - Ankylosis—0–1 per joint, 0–2 in total.
- ▶ Spine
 - Bone marrow oedema—0–3 per vertebral unit, 0–69 in total.
 - Fat bone marrow deposition—0–3 per vertebral unit, 0–69 in total.
 - Erosions—0–3 per vertebral unit, 0–69 in total.
 - Bone proliferation—0–3 per vertebral unit, 0–69 in total.
 - Inflammation of the posterior segments—0–2 per vertebral unit, 0–46 in total.

The secondary endpoints are the improvement of the total Berlin MRI score for SIJs and spine at week 24 as compared with baseline and to week 12, change in disease activity, function, axial mobility, quality of life and psoriatic skin involvement. For the MRI endpoints, MRI images will be assessed by three trained and calibrated readers (see above) blinded for the time point and for all clinical information. The final Berlin MRI SIJ/spine score will be calculated as a mean of three readers.

The primary and the main secondary study endpoints are summarised in box 1.

Site monitoring, quality control and data management

All procedures will be documented in the patient's charts and in the patient's electronic case report forms.

Table 1 Assessment schedule of the PASTOR trial

	Screening ≤6 weeks	Baseline (Day 1)	Week 2*	Week 4*	Week 8*	Week 12*	Week 14*	Week 16*	Week 20*	Week 24*/ ET†	Week 28*/FU‡
Study procedures	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11
Informed consenta	X										
Inclusion/exclusion criteria	X	X§				X§					
Randomisation		X									
Demographics	X										
Medical/surgical history	X	X §									
Vaccination status	X										
Prior/concomitant medication	X	X	X	X	X	X	X	X	X	X	
Vital signs ¶	X	X	X	X	X	X	X	X	X	X	
Weight and height **		X				X				X	
Smoking assessment ††		X				X				X	
Physical examination	X	X	X	X	X	X	X	X	X	X	X
Enthesitis assessment (MASES)		X		X		X		X		X	
Dactylitic finger/toe count		X		X		X		X		X	
PASI (only in cases with ≥3% BSA involvement at baseline)		X		X		X		X		X	
DAPSA (calculated, includes tender and swollen joint counts)		X		X		X		X		X	
MDA (calculated)				X		X		X		X	
ASDAS-CRP (calculated)		X		X		X		X		X	
BASDAI	X	X		X		X		X		X	
BASFI	X	X		X		X		X		X	
BASMI10, chest expansion		X				X				X	
Physician Global Assessment (PhGA+PhASS)	X	X		X		X		X		X	
Patient Global Assessment (PGA+PASS)	X	X		X		X		X		X	
HAQ-DI		X		X		X		X		X	
ASAS Health Index		X		X		X		X		X	
Blood chemistry ††	X	X	X	X	X	X	X	X	X	X	
Lipid profile (fasting samples) §§		X			X				X		

Continued

Table 1 Continued

Study procedures	Screening	Baseline	Week	Week	Week	Week	Week	Week	Week	Week	Week
	≤6 weeks	(Day 1)	2*	4*	8*	12*	14*	16*	20*	24*/ ET†	Week 28*/FU‡
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11
Haematology ⁱ	X	X	X	X	X	X	X	X	X	X	
CRP		X		X		X		X		X	
Serum pregnancy test¶¶¶	X										
Serum or urine pregnancy test ¶¶¶											X
HIV, hepatitis B and hepatitis C serology	X										
Biomarker blood samples		X				X				X	
Stool samples		X				X				X	
MRI of sacroiliac joints, spine	X					X				X	
QuantiFERON-TB or T.SPOT TB***	X										
Chest X-ray***	X										
X-ray of the sacroiliac joint		X									
HLA-B27		X									
Adverse events		X	X	X	X	X	X	X	X	X	X

*Weeks after the first intake of the study drug, visits have a time window of ± 7 days.

†ET=early termination visit for subjects who prematurely discontinue the study for any reason.

‡FU=follow-up, a collection of the safety information; to be performed 4 weeks ($+2$ weeks) after week 24/ET visit.

§Interim history to check for exclusion criteria.

¶¶Body temperature, heart rate, blood pressure.

**Height will be measured at screening only.

††Former and actual smoking state at baseline, actual smoking status at subsequent visits.

‡‡Complete blood count, Total bilirubin, ALT, AST, GGT, AP, creatinine.

§§Total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides.

¶¶¶Female patients of childbearing potential only.

***QuantiFERON-TB or T.Spot TB test and Chest X-ray performed within 3 months prior to screening will be accepted.

ALT, alanine aminotransferase; AP, alkaline phosphatase; ASAS, Ankylosing Spondyloarthritis International Society; ASDAS, Ankylosing Spondylitis Disease Activity Score; AST, aspartate aminotransferase; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; BASMI, Bath Ankylosing Spondylitis Metrology Index; BSA, body surface area; CRP, C reactive protein; DAPSA, Disease Activity in Psoriatic Arthritis; ET, early termination; FU, follow-up; GGT, Gamma-Glutamyl Transferase; HAQ-DI, Health Assessment Questionnaire—Disability Index; HDL, high-density lipoprotein, HIV, Human Immunodeficiency Virus; HLA, Human Leucocyte Antigen; i, Complete blood count, Total bilirubin, ALT, AST, GGT, AP, creatinine; LDL, low-density lipoprotein, MASES, Maastricht Ankylosing Spondylitis Enthesitis Score; MDA, minimal disease activity; PASI, Psoriasis Area and Severity Index; PASS, Patient Acceptable Symptom State; PASTOR, Psoriatic Arthritis present with axial involvement; PGA, Patient Global Assessment; PhASS, Physician Acceptable Symptom State; PhGA, Physician Global Assessment.

An external monitor who will visit all participating study sites by regular intervals will provide quality control and quality assurance. The sponsor, any person authorised by the sponsor, the Independent Ethics Committee (IEC)/ Institutional Review Board (IRB) or the competent health authority in order to determine the accuracy, the authenticity of the recorded data and compliance with the study protocol, may audit this study.

The information derived from this clinical study will be used by the sponsor and, therefore, may be disclosed by

the sponsor as required to other clinical investigators or other government agencies. In order to allow for the use of the information derived from this clinical study, it is understood by the investigator that there is an obligation to provide the sponsor with complete test results and all data from this clinical study.

According to the standards of the data protection law, all data obtained in the course of the study must be treated with discretion in order to guarantee the rights of the patient's privacy. Protocol modifications to on-going

Table 2 Main inclusion/exclusion criteria of the PASTOR study.

Inclusion criteria	Exclusion criteria
Clinical diagnosis of axial PsA	Any significant acute or chronic infection (at the discretion of the investigator).
Age ≥ 18 and < 65 years from either sex	Patients with any contraindications for the treatment with tofacitinib or for the MRI
Definite diagnosis of PsA according to the CASPAR criteria	Female subjects who are breastfeeding, pregnant, or plan to become pregnant during the study or within 4 weeks following the last dose of study drug.
Evidence of axial involvement (eg, active inflammation, structural changes), that have been demonstrated by previous imaging techniques (eg, X-ray, MRI, CT) based on local assessment	History of recurrent (more than one episode) herpes zoster or disseminated / multi-dermatomal (a single episode) herpes zoster or disseminated (a single episode) herpes simplex.
Presence of chronic (duration ≥ 3 months) back pain	Current malignancies or history of malignancies except adequately treated or excised basal cell or squamous cell carcinoma or cervical carcinoma in situ.
Active disease as defined by a BASDAI value of ≥ 4 and back pain score (BASDAI Question 2) of ≥ 4 (on a 0–10 numerical rating scale)	Patients of 50 years and older, if they ≥ 1 cardiovascular risk factors.
Presence of active inflammation (bone marrow oedema) on MRI of the sacroiliac joints and/or spine according to the definition of ASAS MRI working group – evaluated by central reading of the screening MRI. ^{30–33}	Any subject who has been vaccinated with live or attenuated vaccines within the 4 weeks prior to the first dose of study medication or is to be vaccinated with these vaccines at any time during treatment or within 4 weeks after the last dose of study drug.

ASAS, Assessment of Spondyloarthritis International Society; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; JAK, Janus kinase; ; PASTOR, Psoriatic Arthritis presentIng with axial involvement; PsA, psoriatic arthritis.

studies must be made via a protocol amendment. The sponsor is responsible to obtain independent approval for the amendment from the federal regulatory authority and a positive opinion from the competent ethics committees if required.

Sample size calculation

The sample size is calculated based on results from phase II study with tofacitinib in patients with radiographic axial SpA.²⁷ Treatment with tofacitinib 5 mg two times per day was associated with a mean (SD) absolute reduction of the Berlin MRI osteitis score for the spine (range 0–69) of 2.2 (0.4) points as compared with a reduction of 0.4 in the placebo group after 12 weeks. We assume that in patients axial PsA who treated with tofacitinib, a mean reduction of at least 2.5 points of the total MRI osteitis score including spine and SIJs (range 0–93) at week 12 as compared with baseline will be achieved, while a mean 0.5 points reduction is anticipated in placebo-treated patients. In order to demonstrate a significant difference between tofacitinib and placebo groups using the two-sample t test for the mean difference with the power of 80% and $\alpha=0.05$ (anticipated SD=3.0), at least 74 patients (37 per arm) should be included in the analysis set. Considering some uncertainty in the effect estimation in the given patient population, and some expected dropout and protocol violations, we planned to include a total of 80 patients ($n=40$ per group) to demonstrate the expected treatment effect.

Statistical analyses

The main statistical analysis will be performed on the data collected up to week 24; the safety analysis will include all data collected up to week 28. The primary efficacy endpoint for the overall study will be the improvement of the total Berlin MRI score for active inflammation in SIJs and spine at week 12 as compared with baseline (range for osteitis 0–69 for the spine, 0–24 for the SIJs, 0–93 for the total score). The mean bone marrow oedema change scores (baseline to week 12—the primary endpoint, baseline to week 24 and week 12 to week 24—secondary endpoints) with corresponding 95% CIs will be calculated. Baseline and week 12 measurements will be treated as part of the double-blind portion of the study, and week 24 measurements will be treated as part of the open-label portion of the study.

The primary analysis will be performed in the modified intent-to-treat (ITT) population that will be defined as all patients randomised in the study who receive at least one dose of tofacitinib or placebo. Missing values will be replaced by a non-responder imputation (NRI) method for binary outcomes or by the last observation carried forward method for continuous variables in the primary analysis. The secondary analysis will be performed in the per-protocol population that will be defined as a subset of the ITT population who completed the study without any major protocol violations and received at least two MRI examinations performed according to the protocol.

Box 1 Main outcome parameters of the PASTOR study

Efficacy

Primary endpoint

- ▶ improvement of the total Berlin MRI score for SIJs and spine as compared with baseline after 12 weeks of therapy.

Secondary endpoints

- ▶ Improvement of the total Berlin MRI score for SIJs and spine at week 24 as compared with baseline and week 12 in patients treated continuously with tofacitinib versus switchers from placebo.
- ▶ Improvement of disease activity, function, axial mobility, clinical, laboratory, imaging and quality of life measures at weeks 12 and 24. (week 12 vs baseline, week 24 vs baseline, week 24 vs week 12).
 - Percentage of patients who achieve an ASAS 20, 40, 5/6 responses and ASAS PR.
 - Percentage of patients who achieve BASDAI 20%, 50% and 70% improvement.
 - Improvement in the ASDAS-CRP.
 - Percentage of patients reaching the ASDAS-CII (≥ 1.1) and ASDAS-MI (≥ 2.0).
 - Percentage of patients achieving ASDAS inactive disease (ASDAS-CRP < 1.3) and ASDAS low disease activity (ASDAS-CRP < 2.1).
 - Improvement in the BASDAI.
 - Improvement in the BASFI.
 - Improvement in the BASMI and chest expansion.
 - Improvement in the ASAS Health Index.
 - Improvement in the HAQ-DI.
 - Improvement in the PGA on NRS.
 - Improvement in the PhGA on NRS.
 - Achievement of the PASS.
 - Achievement of the PhASS.
 - Improvement in the CRP.
 - Achievement of the MDA.
 - Improvement in the DAPSA.
 - Improvement in the SJC and TJC.
 - Improvement in the MASES.
 - Improvement of dactylitis (number of dactylitic phalanges).
 - PASI 75, 90 and 100 responses in the subgroup of subjects with psoriasis involving at least 3% body surface area at baseline.

Safety

AEs, SAEs, and AESI until week 28

ASAS, Ankylosing Spondyloarthritis International Society; ASDAS, Ankylosing Spondylitis Disease Activity Score; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; BASMI, Bath Ankylosing Spondylitis Metrology Index; CII, Clinically Important Improvement; CRP, C reactive protein; DAPSA, Disease Activity in Psoriatic Arthritis; HAQ-DI, Health Assessment Questionnaire—Disability Index; MASES, Maastricht Ankylosing Spondylitis Enthesitis Score; MDA, minimal disease activity; MI, major improvement; NRS, Numerical Rating Scale; PASI, Psoriasis Area and Severity Index; PASS, Patient Acceptable Symptom State; PGA, Patient Global Assessment; PhASS, Physician Acceptable Symptom State; PhGA, Physician Global Assessment, PR, partial remission; SIJs, sacroiliac joints; SJC, swollen joint count; TJC, tender joint count.

To compare the treatment groups, the two-sided t test or Mann-Whitney U-test for continuous variables and Fisher's exact test for the categorical variable will be applied. To compare changes between baseline and after treatment values, we will use the non-parametric Wilcoxon signed rank test for continuous variables and McNemar

test for categorical outcomes. Descriptive statistics will be used to evaluate the demographic, disease and imaging characteristics between groups at baseline and to summarise observed scores and changes from baseline scores for MRI and disease activity over time. For binary endpoints, frequencies and percentages will be reported, and for continuous endpoints, the mean and SD or median and IQR, which is appropriate, will be calculated. The secondary endpoints at week 24 will be investigated by means of descriptive statistics in the whole sample, between baseline and after treatment values. Two-sided p values < 0.05 will be considered statistically significant. The safety analyses will include all patients who get at least one dose of the study drug. Descriptive statistics will be used to assess safety data analysis that will be described as adverse events (AEs), serious AEs (SAEs) and AE of interest.

Study discontinuation

A patient can stop to continue the study at any time for any reason. Nevertheless, these patients will not be excluded from the study if they do not withdraw their consent. If these patients do not return for planned evaluations for unknown reasons, they can be reached by phone, e-mail or letter to hold the patient in the study. After the withdrawal of consent, no additional data will be collected, but earlier collected data may be used in the analysis. The investigator can also remove patients from the study to protect their safety. The sponsor can terminate the study at any time for any reason. In case of premature discontinuation of the study, procedures outlined in the assessment schedule for the 'Early Termination Visit' should be performed within 4 weeks after the last dose of the study drug. The reason for the discontinuation should be documented. After study discontinuation, the patients will be treated according to available standards of care.

Ethics and dissemination

The study will be performed according to the ethical principles of the Declaration of Helsinki, International Conference of Harmonisation Good Clinical Practice guidelines. Besides, the IEC/IRB of each centre obtained and approved the ethical, scientific and medical appropriateness of the study before it was conducted.

The PASTOR study began recruitment in August 2020 by completing the first patient initial visit on 4 August 2020. In December 2020, 19 sites in Germany have been initiated in this study. The first results are estimated to be available in 2022. It is intended that the results of the whole study after the week of 28 will be published approximately 1 year later in a peer-reviewed journal and will be communicated at international meetings.

The study is recorded in the European Union Clinical Trials Register and ClinicalTrials.gov. Study information is publicly available at www.clinicaltrials.gov, and the results of this trial will be published accordingly. Six months after the main publication of the current study, participants' anonymised row data set and anonymised individual

data of patients will be accessible for researchers from centres that contributed to this study. Furthermore, other researchers can submit scientific proposals to use the data set. These proposals will then be assessed and approved by the steering committee of the study.

Patient and public involvement

Patients and/or the public were not involved in the development of this study.

DISCUSSION

This study aims to explore the efficacy of the JAK inhibitor tofacitinib in patients with PsA presenting with axial involvement. Both objective (improvement of the Berlin MRI scores for SIJs and the spine) and patient reported endpoints will be evaluated. Currently, there are only a few studies have been conducted in patients with PsA and axial involvement and mainly data from studies in axial SpA are extrapolated for patients with axial PsA; therefore, it is still unclear which treatment option should be selected for this patient group. If this study confirms our hypothesis that tofacitinib has efficacy for the treatment of patients with PsA with axial involvement, then this may help to support an optimal treatment choice for this patient population.

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Contributors FP and MT wrote the first draft of the manuscript based on protocol Version 2.1 (March 2020). FP, MT, BM and VRR wrote the study protocol. MV was involved in statistical planning and drafting the study protocol. DP developed the idea for this trial, was involved in drafting and revising the study protocol, and was the principal investigator of this trial. All authors provided critical feedback, helped to shape the analysis and approved the final manuscript.

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Competing interests FP: research grants from Novartis; speaker and consulting fees from AbbVie, Amgen, Bristol-Myers Squibb, MSD, Novartis, Pfizer, Roche and UCB Pharma. MT: has nothing to disclose. BM: travel cost, speaker and/or consulting fees from Amgen, Bristol-Myers Squibb, Gilead, Sandoz Hexal and Stadapharm. VR-R: has nothing to disclose. MV: has nothing to disclose. DP: research grants from AbbVie, MSD, Novartis, and Pfizer; speaker and/or consulting fees from AbbVie, Biocad, Bristol-Myers Squibb, Eli Lilly and Company, GlaxoSmithKlein, MSD, Novartis, Pfizer, Roche, Samsung Bioepis, and UCB Pharma.

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REFERENCES

- Alinaghi F, Calov M, Kristensen LE, *et al*. Prevalence of psoriatic arthritis in patients with psoriasis: a systematic review and meta-analysis of observational and clinical studies. *J Am Acad Dermatol* 2019;80:e19:251–65.
- Prey S, Paul C, Bronsard V, *et al*. Assessment of risk of psoriatic arthritis in patients with plaque psoriasis: a systematic review of the literature. *J Eur Acad Dermatol Venereol* 2010;24:31–5.
- Taylor W, Gladman D, Helliwell P, *et al*. Classification criteria for psoriatic arthritis: development of new criteria from a large international study. *Arthritis Rheum* 2006;54:2665–73.
- Gladman DD, Shuckett R, Russell ML, *et al*. Psoriatic arthritis (PSA)—an analysis of 220 patients. *Q J Med* 1987;62:127–41.
- Gladman DD. Axial disease in psoriatic arthritis. *Curr Rheumatol Rep* 2007;9:455–60.
- Jadon DR, Sengupta R, Nightingale A, *et al*. Axial disease in psoriatic arthritis study: defining the clinical and radiographic phenotype of psoriatic spondyloarthritis. *Ann Rheum Dis* 2017;76:701–7.
- Chandran V. Psoriatic spondylitis or ankylosing spondylitis with psoriasis: same or different? *Curr Opin Rheumatol* 2019;31:329–34.
- Rudwaleit M, Landewé R, van der Heijde D, *et al*. The development of assessment of spondyloarthritis International Society classification criteria for axial spondyloarthritis (Part I): classification of paper patients by expert opinion including uncertainty appraisal. *Ann Rheum Dis* 2009;68:770–6.
- Rudwaleit M, van der Heijde D, Landewé R, *et al*. The development of assessment of spondyloarthritis International Society classification criteria for axial spondyloarthritis (Part II): validation and final selection. *Ann Rheum Dis* 2009;68:777–83.
- Poggenborg RP, Sørensen IJ, Pedersen SJ, *et al*. Magnetic resonance imaging for diagnosing, monitoring and prognostication in psoriatic arthritis. *Clin Exp Rheumatol* 2015;33:S66–9.
- Helliwell PS. Axial disease in psoriatic arthritis. *Rheumatology* 2020;59:1193–5.
- Feld J, Chandran V, Haroon N, *et al*. Axial disease in psoriatic arthritis and ankylosing spondylitis: a critical comparison. *Nat Rev Rheumatol* 2018;14:363–71.
- Gossec L, Baraliakos X, Kerschbaumer A, *et al*. EULAR recommendations for the management of psoriatic arthritis with pharmacological therapies: 2019 update. *Ann Rheum Dis* 2020;79:700.1–12.
- Coates LC, Kavanaugh A, Mease PJ, *et al*. Group for research and assessment of psoriasis and psoriatic arthritis 2015 treatment recommendations for psoriatic arthritis. *Arthritis Rheumatol* 2016;54:n/a–71.
- Feld J, Ye JY, Chandran V, *et al*. Is axial psoriatic arthritis distinct from ankylosing spondylitis with and without concomitant psoriasis? *Rheumatology* 2020;59:1340–6.
- Goel N, FitzGerald O, Gladman DD, *et al*. Grappa 2018 project report. *J Rheumatol Suppl* 2019;95:54–7.
- Ward MM, Deodhar A, Gensler LS, *et al*. 2019 update of the American College of Rheumatology/Spondylitis association of America/Spondyloarthritis research and treatment network recommendations for the treatment of ankylosing spondylitis and Nonradiographic axial spondyloarthritis. *Arthritis Rheumatol* 2019;71:1599–613.
- van der Heijde D, Ramiro S, Landewé R, *et al*. 2016 update of the ASAS-EULAR management recommendations for axial spondyloarthritis. *Ann Rheum Dis* 2017;76:978–91.
- Baraliakos X, Coates LC, Gossec L. Secukinumab improves axial manifestations in patients with psoriatic arthritis and inadequate response to NSAIDs: primary analysis of the maximise trial. *Ann Rheum Dis* 2019;78:195–6.
- Haroon M, Ahmad M, Baig MN, *et al*. Inflammatory back pain in psoriatic arthritis is significantly more responsive to corticosteroids compared to back pain in ankylosing spondylitis: a prospective, open-labelled, controlled pilot study. *Arthritis Res Ther* 2018;20:73.

- 21 Lim CP, Cao X, Structure CX. Structure, function, and regulation of STAT proteins. *Mol Biosyst* 2006;2:536–50.
- 22 Mease P, Hall S, FitzGerald O, *et al.* Tofacitinib or adalimumab versus placebo for psoriatic arthritis. *N Engl J Med* 2017;377:1537–50.
- 23 Gladman D, Rigby W, Azevedo VF, *et al.* Tofacitinib for psoriatic arthritis in patients with an inadequate response to TNF inhibitors. *N Engl J Med* 2017;377:1525–36.
- 24 Mease P, Coates LC, Helliwell PS, *et al.* Efficacy and safety of filgotinib, a selective Janus kinase 1 inhibitor, in patients with active psoriatic arthritis (EQUATOR): results from a randomised, placebo-controlled, phase 2 trial. *Lancet* 2018;392:2367–77.
- 25 McInnes I, Anderson J, Magrey M. Efficacy and safety of upadacitinib versus placebo and adalimumab in patients with active psoriatic arthritis and inadequate response to non-biologic disease-modifying anti-rheumatic drugs (SELECT-PSA-1): a double-blind, randomized controlled phase 3 trial. *Ann Rheum Dis* 2020;79:12–13.
- 26 Genovese MC, Lertratanakul A, Anderson J, *et al.* OP0223 efficacy and safety of upadacitinib in patients with active psoriatic arthritis and inadequate response to biologic disease-modifying anti-rheumatic drugs (SELECT-PSA-2): a double-blind, randomized controlled phase 3 trial. *Ann Rheum Dis* 2020;79:139–39.
- 27 van der Heijde D, Deodhar A, Wei JC, *et al.* Tofacitinib in patients with ankylosing spondylitis: a phase II, 16-week, randomised, placebo-controlled, dose-ranging study. *Ann Rheum Dis* 2017;76:1340–7.
- 28 van der Heijde D, Baraliakos X, Gensler LS, *et al.* Efficacy and safety of filgotinib, a selective Janus kinase 1 inhibitor, in patients with active ankylosing spondylitis (TORTUGA): results from a randomised, placebo-controlled, phase 2 trial. *Lancet* 2018;392:2378–87.
- 29 van der Heijde D, Song I-H, Pangan AL, *et al.* Efficacy and safety of upadacitinib in patients with active ankylosing spondylitis (SELECT-AXIS 1): a multicentre, randomised, double-blind, placebo-controlled, phase 2/3 trial. *Lancet* 2019;394:2108–17.
- 30 Rudwaleit M, Jurik AG, Hermann K-GA, *et al.* Defining active sacroiliitis on magnetic resonance imaging (MRI) for classification of axial spondyloarthritis: a consensual approach by the ASAS/OMERACT MRI group. *Ann Rheum Dis* 2009;68:1520–7.
- 31 Lambert RGW, Bakker PAC, van der Heijde D, *et al.* Defining active sacroiliitis on MRI for classification of axial spondyloarthritis: update by the ASAS MRI Working group. *Ann Rheum Dis* 2016;75:1958–63.
- 32 Maksymowych WP, Lambert RG, Østergaard M, *et al.* MRI lesions in the sacroiliac joints of patients with spondyloarthritis: an update of definitions and validation by the ASAS MRI Working group. *Ann Rheum Dis* 2019;78:1550–8.
- 33 Hermann K-GA, Baraliakos X, van der Heijde DMFM, *et al.* Descriptions of spinal MRI lesions and definition of a positive MRI of the spine in axial spondyloarthritis: a consensual approach by the ASAS/OMERACT MRI study Group. *Ann Rheum Dis* 2012;71:1278–88.
- 34 Chan A-W, Tetzlaff JM, Altman DG, *et al.* Spirit 2013 statement: defining standard protocol items for clinical trials. *Ann Intern Med* 2013;158:200–7.
- 35 Althoff CE, Sieper J, Song I-H, *et al.* Active inflammation and structural change in early active axial spondyloarthritis as detected by whole-body MRI. *Ann Rheum Dis* 2013;72:967–73.
- 36 Song I-H, Hermann K, Haibel H, *et al.* Effects of etanercept versus sulfasalazine in early axial spondyloarthritis on active inflammatory lesions as detected by whole-body MRI (ESTHER): a 48-week randomised controlled trial. *Ann Rheum Dis* 2011;70:590–6.
- 37 Song I-H, Hermann KG, Haibel H, *et al.* Relationship between active inflammatory lesions in the spine and sacroiliac joints and new development of chronic lesions on whole-body MRI in early axial spondyloarthritis: results of the ESTHER trial at week 48. *Ann Rheum Dis* 2011;70:1257–63.
- 38 Pedersen SJ, Poddubnyy D, Sørensen IJ, *et al.* Course of magnetic resonance Imaging-Detected inflammation and structural lesions in the Sacroiliac joints of patients in the randomized, double-blind, placebo-controlled Danish multicenter study of adalimumab in spondyloarthritis, as assessed by the Berlin and spondyloarthritis research Consortium of Canada methods. *Arthritis Rheumatol* 2016;68:418–29.