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Abstract

Introduction Psoriatic arthritis (PsA) is a complex, immune-mediated disease associated with skin psoriasis that, if left untreated, can lead to joint destruction. Up to 30% of patients with psoriasis progress to PsA. In most cases, psoriasis precedes synovio-entheseal inflammation by an average of 5-7 years, providing a unique opportunity for early and potentially preventive intervention in a susceptible and identifiable population. Guselkumab is an effective IL-23p19 inhibitor FDA-approved for treatment of moderate-severe psoriasis and PsA. The Preventing Arthritis in a Multicenter Psoriasis At Risk cohort (PAMPA) study aims to evaluate the efficacy of guselkumab in preventing PsA and decreasing musculoskeletal power Doppler ultrasound (PDUS) abnormalities in a population of patients with psoriasis who are at-increased risk for PsA progression.

Methods and Analysis The PAMPA study is a multi-center, randomized, double-blind, placebo-controlled, wait-list, interventional, preventive trial comparing PDUS involvement and conversion to PsA in patients with psoriasis at-increased risk for progression treated with guselkumab compared to non-biologic standard of care. The study includes a screening period, a double-blind treatment period (24 weeks), and an open-label follow-up period (72 weeks). At baseline, 200 subjects will be randomized (1:1) to receive either guselkumab 100 mg (Arm 1) or placebo switching to guselkumab 100mg starting at Week 24 (Arm 2). Arm 3 will follow 150 at-risk psoriasis patients who decline biologic therapy and randomization. Changes from baseline in the PDUS score at week 24 and the difference in proportion of patients transitioning to PsA at 2 years will be examined as the co-primary endpoints.

Ethics and dissemination Ethics approval for this study was granted by the coordinating center's (NYU School of Medicine) Institutional Review Board (IRB). Each participating site received approval through their own IRBs. The findings will be shared in peer-reviewed articles and scientific conference presentations.

Trial registration number Registered at ClinicalTrials.gov (NCT05004727).

Strength and Limitations

- This study represents the first approach for the prevention, rather than treatment, of psoriatic arthritis (PsA) and therefore influencing long-term outcomes in psoriatic disease.
- This is the first prospective, randomized controlled trial to investigate any mechanism of action in prevention of PsA development from PsO patients. This study will specifically evaluate the efficacy of an interleukin-23p19 inhibitor, guselkumab, in preventing the development of PsA in population of patients with increased-risk psoriasis.
- Clinical data will be combined with molecular and immunologic analysis to elucidate biological determinants of the transition from psoriasis to PsA.
- A potential limitation is the short course of active drug vs. placebo (6 months) and a relatively short follow up period (2 years) to be able to fully assess conversion from skin to joint involvement.

Introduction

Psoriatic arthritis (PsA) is an immune-mediated inflammatory arthritis associated with skin psoriasis, affecting two million patients in the United States[1]. PsA is characterized by musculoskeletal inflammation that can take various forms, including synovitis, enthesitis, dactylitis, and axial involvement[2]. Up to 30% of patients with psoriasis will develop inflammatory arthritis at a rate of up to 3% per year[1 3], with skin psoriasis preceding synovio-entheseal involvement by an average of 5 to 7 years[2] . Untreated, PsA can lead to erosive and deforming disease associated with significant morbidity and disability[4] . Beyond the skin and joints, PsA is associated with decreased quality of life, high rates of psychosocial stress, and increased rates of unemployment, absenteeism, and productivity loss[5-7] . Despite this burden, and the knowledge that a delay in diagnosis and treatment of as little as 6 months is associated with significantly more radiographic progression and worse function[8], PsA remains underdiagnosed and undertreated[9].

While the last decade has witnessed a therapeutic revolution in treatment options for both psoriasis and PsA[10], joint outcomes have lagged behind skin. The advent of anti-tumor necrosis factor (TNF) agents, followed by antibodies that target molecules in the interleukin (IL)-23/IL-17 axis, have dramatically improved psoriasis response. Remarkably, a significant number of patients can now achieve total clearance of skin disease[11]. However, the magnitude of responses observed in psoriasis has not been achieved in PsA, where up to half the patients do not experience clinically meaningful synovio-entheseal improvement with blockade of TNF or IL-23/IL-17 pathways[12-14]. Therefore, highly effective treatment strategies for PsA remain a significant unmet need and new approaches are warranted, including novel therapeutic targets, combination therapy, and early intervention and prevention[15 16].

Recent efforts in rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) emphasize the concept of treating disease in the pre-clinical stages to possibly delay or even prevent disease onset and lessen severity[17 18]. To formally address this strategy, SLE and RA investigators pioneered trials in subjects with serologic, but no clinical, evidence of disease, and noted improved outcomes and even disease prevention in some cases[19 20]. Additional NIH-supported prevention trials are underway including the SMILE[21] and Stop-RA[22] studies and more are in progress in Europe[23]. These strategies may even be more relevant in PsA given that there is a readily apparent pre-clinical marker (skin psoriasis) that generally precedes joint involvement, creating a unique prospect for early intervention, and possibly even prevention, in a susceptible and identifiable population[24]. Here, we present Preventing Arthritis in a Multicenter Psoriasis At Risk cohort study (PAMPA), the first randomized controlled, interventional trial using a specific target (i.e., guselkumab) to look at prevention of PsA development in a psoriasis population.

The first step in prevention is to identify populations who are at increased risk for PsA[25]. Cross-sectional studies identified several risk factors associated with progression, including obesity[26 27], psoriasis involvement (i.e., increased psoriasis severity or the presence of nail, inverse, or scalp involvement)[28-30], having a first degree relative with PsA[31], and genetic polymorphisms[32]. Additionally, the presence of structural entheseal lesions on high-resolution peripheral quantitative computed tomography (HR-pQCT) or magnetic resonance imaging (MRI) in patients with psoriasis were associated with higher risk of progression[33 34], which is of particular interest as a large percentage of patients with psoriasis have subclinical focal bone loss, enthesitis and new bone formation[35]. Taken together, the accumulated body of evidence further supports the PAMPA study strategy of targeting psoriasis patients who are at the highest risk for, but do not yet fulfill the classification criteria for, overt synovio-entheseal inflammation.

Given the role of IL-23 in psoriatic disease pathogenesis, we propose that prolonged, unresolved skin inflammation driven by IL-23 increases the risk for transition into PsA and that an intervention that targets one of these pivotal molecules (i.e., guselkumab) will significantly reduce or prevent the emergence of the synovio-entheseal phenotype. To achieve this goal, first, we defined a singular target population, one in which clinical, demographic and musculoskeletal imaging factors are present with sufficient strength to suggest that progression to arthritis is likely and which justifies intervention with a systemic medication. Second, we deliberatively chose a therapy that offers practical and biological advantages, including a clinical indication for psoriasis, a proven safety profile, convenience of administration and its acceptability to both patients and physicians. Guselkumab has all these advantages based on its ability to inhibit IL-23p19, and is FDA-approved for the treatment of both moderate-severe plaque psoriasis[36] (our patient population) and active PsA.

The overarching aim of this study is to determine whether guselkumab use can: (1) improve subclinical musculoskeletal inflammation as visualized on specialized ultrasound imaging, and (2) decrease the rate of progression to clinically evident PsA. Concomitantly, PAMPA will focus on better understanding the underlying imaging, immunologic, and environmental features that promote the synovio-entheseal transition from psoriasis to PsA. To this end, a unique array of biologic samples will be collected to help reveal mechanistic pathways associated with progression (or resistance) to PsA transition and severity.

Methods and Analysis

Study design

This is a phase IV, multicenter, double-blind, randomized, placebo-controlled study of the efficacy of guselkumab (compared to standard of care) in preventing abnormalities on musculoskeletal power Doppler ultrasound (PDUS) and conversion to PsA in high-risk psoriatic populations. The study includes a screening period, a 24-week double-blind treatment period (Arm 1 receiving drug and Arm 2 receiving placebo), and a 72-week open-label follow-up period (Figure 1). A third arm (Arm 3) will consist of patients who do not receive any study drug followed prospectively as the natural history control arm.

Study population and randomization

A total of 350 participants with a diagnosis of psoriasis (as determined by a dermatologist) for at least 2 years (in at least 30% of participants) and features of increased risk, defined here as percent psoriasis body surface area (BSA) greater than 3%, and positive imaging findings on musculoskeletal PDUS (Rochester modification of PsASon[37] [RM-PsASon] score greater than 3.36) (Table 1) will be included. Participants that already fulfill CASPAR criteria for PsA will be excluded[38]. Participants will be screened and enrolled from five study sites (community and academic) across North America. Additionally, institutional electronic medical record systems will be utilized, and outreach pursued via research and advocacy groups (e.g., National Psoriasis Foundation, PPACMAN, GRAPPA) and social media.

Table 1. Inclusion/Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
At least 18 years old	Evidence of inflammatory joint pain, enthesitis and/or dactylitis

Willing and able to provide informed consent	Current systemic immunosuppressive medication use (i.e., methotrexate, apremilast) at time of enrollment or biologic use ever
Psoriasis diagnosis (per dermatologist) for at least 2 years (in at least 30% of participants)	Mid-high positive rheumatoid factor and/or anti-citrullinated protein antibodies
Psoriasis body surface area greater than or equal to 3%	Current active malignancy
Positive imaging findings on ultrasound defined as Rochester Modified-PsASon score > 3.36	History of symptomatic polyarticular OA or other joint conditions (such as rheumatoid arthritis, gout) that may impair the ability to assess for psoriatic arthritis development
	Conditions where initiation of guselkumab is prohibited in the prescribing information, including clinically important active infections and untreated latent tuberculosis
	Known hypersensitivity to the study agent

Participants who agree to be actively treated with drug (n=200) will be allocated in a 1:1 randomization to receive either guselkumab 100 mg (Arm 1) or placebo switching to guselkumab at Week 24 (Arm 2). An unblinded statistician has generated the randomization list using blockrand library (V.4.1.0) within the statistical computing language R[39]. Randomization is stratified by site and gender. An independent study team member, outside of the project, will randomize participants via REDCap[40] and convey the drug kit assignments to the pharmacy, allowing for all team members (pharmacy staff included) to remain blinded. Patients who decline to be randomized to biologic therapy will be followed in Arm 3, but will not receive any study intervention (standard of care, control group).

Intervention, Assessments and Endpoints

During the screening period, participants will undergo PDUS and clinical assessments (Table 2) to determine study eligibility. Patients who fulfill criteria will be randomized 1:1 to receive either guselkumab 100 mg (Arm 1) or placebo (Arm 2). Repeat PDUS will be performed at week 24 to assess for any changes. At week 24, participants in Arm 2 will then switch to guselkumab 100 mg; both Arm 1 and 2 participants will continue on guselkumab (open label), being assessed in person every 6 months until the conclusion of the study. Guselkumab is given at its FDA-approved dose for psoriasis: 100 mg at weeks 0 and 4, and then every 8 weeks thereafter. To account for the loading dose and ensure continued blinding at the 6-month timepoint, Arm 1 participants will receive one placebo dose at week 24. A complete drug schedule is detailed in Supplementary Figure 1.

Table 2. Assessment Schedule of PAMPA Study

Study procedures	Screening	Week 0	Week 12#	Week 24	Week 48	Week 72	Week 96
Informed Consent	X						
Inclusion/exclusion	X						
Demographics	X						
Medical history	X						
Psoriatic disease history	X						
Medications	X	X	X	X	X	X	X
Ultrasound	X			X			
Adverse Events			X	X	X	X	X

Skin assessments (BSA, IGA)	X	X		X	X	X	X
MSK assessments (TJC, SJC, SPARCC)	X	X		X	X	X	X
PEST*	X	X	X	X	X	X	X
EQ-5D		X		X			X
FACIT-F	X	X	X	X	X	X	X
Patient pain score	X	X	X	X	X	X	X
Global health score	X	X	X	X	X	X	X
IDEOM MSK 8	X	X	X	X	X	X	X
Safety Labs (CBC, CMP, TB test, serum pregnancy)	X						
RF/ACPA	X						
Urine pregnancy^		X					
Biosampling (plasma, PBMCs, skin swabs, stool)		X					

* PEST will also be performed by telephone or electronically every 3 months if there is not an in-person visit.
# Arm 3 will not have an in-person visit at week 12. They will also not have to undergo safety labs or record adverse events.
^Urine pregnancy test will be done for females of child bearing age the day of the baseline visit, prior to administering the first dose of drug or placebo.
PAMPA Preventing Arthritis in a Multicenter Psoriasis At Risk cohort study; BSA body surface area; IGA investigators global assessment 2011; TJC tender joint count; SJC swollen joint count, SPARCC spondyloarthritis Research Consortium of Canada enthesitis index; PEST psoriasis epidemiology screen tool; FACIT-F functional assessment of chronic illness therapy- fatigue; IDEOM MSK 8 international dermatology outcomes measures musculoskeletal 8; CBC completed blood count; CMP comprehensive metabolic panel; TB tuberculosis; RA rheumatoid factor; ACPA anticitrullinated peptide antibodies; PBMC peripheral blood mononuclear cell.

The ultrasound assessment will consist of an evaluation of grey scale synovitis, power Doppler (PD) findings at joints, erosions, osteophytes, grey scale and PD peritendonitis, and grey scale and PD tenosynovitis. The pre-specified set of 36 joints and 34 periarticular structures will be scanned at each visit. Ultrasounds will be scored via the RM-PsASon by two independent, blinded, central readers who are experts in PDUS imaging. Based on previous data looking at the difference in ultrasound abnormalities between healthy controls and patients with psoriasis[41], participants require a RM-PsASon score of >3.36 at baseline for inclusion. Change in RM-PsASon score will be assessed at 6 months. Further details can be found in the *online supplementary methods*.

Clinical evaluation will be performed by blinded assessors. In-person assessments include skin assessments (BSA, Investigator's Global Assessment Modified 2011), musculoskeletal assessments (66/68 tender/swollen joint count and Spondyloarthritis Research Consortium of Canada enthesitis score), and patient reported outcomes (EQ-5D, Functional Assessment of Chronic Illness Therapy-Fatigue, patient pain score, global health score, and International Dermatology Outcomes Measures-Musculoskeletal-8). They will also complete a modified Psoriasis Epidemiology Screening Test (PEST) to screen for PsA and will be evaluated for fulfillment of modified CASPAR criteria (dactylitis added to the stem) to determine if they have converted to PsA.

The PEST is a validated screening tool for patients with psoriasis to help identify concomitant inflammatory arthritis and was chosen given its ease of use as well as high quality results (sensitivity of 0.94 and specificity of 0.78)[42]. In addition to being performed during site visits, patients will be contacted electronically or by telephone every 3 months to complete the questionnaire. If a participant has a positive PEST, or contacts the study team at any point with new symptoms consistent with the development of PsA, an unscheduled visit will be pursued to determine if progression to synovio-entheseal disease has occurred. If an individual develops PsA, the trial endpoint is reached and a final study visit will be performed.

The primary endpoint is change from baseline in musculoskeletal PDUS total score at week 24 (Box 1). We hypothesize that there will be improvement of ultrasound-based imaging abnormalities at week 24 (Arm 1 vs. Arm 2). The co-primary end point is the proportion of participants developing PsA by modified CASPAR criteria at year 2. We hypothesize that treatment with guselkumab will lead to a decreased transition rate to PsA at year 2 when comparing combined Arm 1 and 2 with Arm 3. Secondary endpoints are outlined in Box 1. Biospecimens (i.e., plasma, peripheral blood mononuclear cells, skin swabs, and stool) will also be collected for further exploratory aims.

Box 1. PAMPA Study Endpoints

Co-primary outcomes

- **Improvement of musculoskeletal power doppler ultrasound imaging abnormalities at week 24 (Arm 1 vs. Arm 2)**
- **Decrease in transition rate to PsA at year 2 (Arm 1 + 2 vs. Arm 3)**

Secondary outcomes

- Transition to PsA at year 1 *(Arm 1 vs Arm 2)*
- Severity of PsA at the time of synovio-entheseal development at year 2 *(Arms 1+2 vs Arm 3)*: severity will be categorized as mild, moderate, or severe and additionally by continuous variables (e.g., joint and enthesis counts)
- Change from baseline in the ultrasound composite score of synovitis at week 24 *(Arm 1 vs Arm 2)*
- Change from baseline in the ultrasound composite score of enthesitis at week 24 *(Arm 1 vs Arm 2)*
- Change from baseline in BSA at week 24 *(Arm 1 vs Arm 2)*
- Achieved IGA score of 0 or 1 (yes, no) at week 24 *(Arm 1 vs Arm 2)*
- Change from baseline IDEOM-MSK-8 score at 24 weeks *(Arm 1 vs Arm 2)*
- Changes in baseline ultrasound, total score at Week 24 *(Arm 1 vs. Arm 2+3)*
- Changes in baseline FACIT-F score at weeks 24 (*Arm 1 vs. Arm 2)*
- Change in baseline EQ5D at week 24 (*Arm 1 vs Arm 2)*
- Change in baseline EQ5D at year 2 (*Arm 1 + Arm 2 vs Arm 3)*

Exploratory outcomes

- Musculoskeletal domain affected at PsA presentation (enthesitis, axial disease, peripheral arthritis) among those developing clinical PsA
- Presence and number of risk factors for PsA development at baseline (psoriasis phenotype; psoriasis severity; genetic predisposition; co-morbidities such as obesity)
- Association between risk factors and development of PsA at year 2
- Genetic, immune cell phenotype, and microbiome changes and their interactions with treatment assignment

PAMPA Preventing Arthritis in a Multicenter Psoriasis At Risk cohort study; PsA psoriatic arthritis; BSA body surface area; IGA investigators global assessment 2011; FACIT-F functional assessment of chronic illness therapy- fatigue; IDEOM MSK 8 international dermatology outcomes measures musculoskeletal 8.

Data management, quality control, and safety

Each participant will receive an individual study ID number upon enrollment, which will be used to link all data to the participant and help protect confidentiality. All clinical data will be entered directly into a central REDCap database housed at the data coordinating center (NYU Langone Health). Periodic audits will be performed to provide quality control and quality assurance.

Additionally, although guselkumab is an FDA-approved treatment for psoriasis, adverse events will be monitored and reported. Safety oversight will be under the direction of a Data and Safety Monitoring Board, which is composed of experienced dermatology and rheumatology trialists who are not affiliated with any participating site to ensure independence. They will also ensure data integrity and confidentiality; advise on any difficulties with study conduct or enrollment, sample size, and/or data collection; and review and evaluate requests for protocol modifications after the trial begins.

Sample size calculation

Sample size was calculated based on the primary outcome of conversion to PsA at year 2. Based on our previous work and available literature[1], we anticipate the conversion rate to PsA in this high-risk psoriasis group to be at least 5-6% per year in Arm 3 (standard of care) compared to 1.5-2% in the drug arms (Arm 1 and Arm 2). Time to conversion will be measured from time of randomization, and the two randomized arms will be compared using a two-sided chi-squared test with a Type I error rate of 0.05. Utilizing these conservative assumptions at a power of 80% and incorporating an expected attrition rate of approximately 10%, we aim to enroll 100 patients each in Arms 1 and 2 and, to increase the robustness of our sample size, at least 150 for Arm 3. Of note, sample size calculation for the co-primary endpoint of PDUS is less than that needed for PsA conversion and therefore, we will use the higher estimate to ensure both endpoints can be achieved.

Statistical analysis

The main statistical analysis will be performed at week 24 and year 2. The primary efficacy outcomes will be analyzed for the intention-to-treat population, and the two-sided alternative hypotheses will be tested against the null of no difference at significance level of 0.05. Descriptive statistics will be summarized as counts and proportions for categorical data; mean, standard deviation, median, interquartile range, minimum, and maximum for continuous data as appropriate. The primary endpoint of change from baseline in PDUS score at week 24 will be analyzed using a mixed-effects model for repeated measures (MMRM), with treatment group (Arm 1 vs. Arm 2) and baseline variables as fixed effects, and study sites as the random effects. Least-squares mean and 95% confidence interval of the difference in treatment effect will be reported based on the fitted MMRM. The co-primary endpoint of PsA transition rate at year 2 will be analyzed by Chi-squared test of proportions comparing the combined Arm 1 and 2 vs. Arm 3. We will further fit generalized linear mixed-effect model (GLMM) with logit link to evaluate the treatment effect on the transition status with treatment group (Arm 1+2 vs. Arm 3) and baseline variables as fixed effects, and study sites as random effects. The raw and adjusted odds ratio of PsA transition and corresponding 95% confidence interval will be reported. Similarly, secondary endpoints will be assessed using MMRM and GLMM for continuous and binary outcomes, respectively. Transformation of the outcome variables will be considered if the distribution deviates from normality.

Ethics and dissemination

The study will be performed according to the ethical principles of the Declaration of Helsinki, the International Conference of Harmonization Good Clinical Practice guidelines, and local regulations. The study is approved by the coordinating center's (NYU) Institutional Review Board (IRB; s20-01158) and each participating site has also received ethics approval through their own IRB/Research Ethics Board. All patients will be required to provide written informed consent to participate.

Study information is publicly available at www.clinicaltrials.gov. The results of this trial will be published in peer-reviewed journals and presented at academic conferences nationally and internationally.

Patient and public involvement
Patients and the public were not involved in the development of this study.

Discussion
PsA is a chronic inflammatory disease that, despite significant progress in therapeutic options, continues to offer clinically meaningful outcomes in less than 50% of patients. One strategy for improving these outcomes has focused on early and aggressive intervention. The TICOPA study, an open label randomized control trial, showed significant improvement in joint outcomes in the tight control group compared to standard of care, with almost twice the odds of achieving an ACR 20 response[43]. However, despite this finding, within the tight control group, only 62% achieved an ACR20 response by week 48, and only 51% and 38% met criteria for the ACR50 or the ACR70 response.

Therefore, preventive interventional strategies are now of great interest since psoriatic plaques effectively demarcate a pre-clinical disease state from which up to 30% of patients will transition to clinically evident PsA. Who among those patients will ultimately go on to develop synovio-entheseal inflammation, and how to delay or alter the course of that journey, are questions being actively investigated. Two small, nonrandomized studies have looked at the effect of anti-cytokine therapy on patients with psoriasis and imaging abnormalities. As part of the prospective IVEPSA study, 20 psoriasis patients with evidence of very early PsA (based on inflammatory or erosive changes on HR-pQCT or MRI) were given an IL-17 blocking agent[44]. After 24 weeks, patients demonstrated improvement in pain and imaging scores. Savage *et al* followed 23 patients with psoriasis and PDUS abnormalities treated with ustekinumab, and found reduced inflammatory scores by week 12 that were maintained through week 52[45]. While these findings are encouraging, neither study had a control group to better understand possible inherent disease fluctuations in imaging findings. Furthermore, the sample sizes and follow up periods did not allow for any estimates of progression to true PsA by CASPAR criteria.

Recent retrospective observational studies have sought to address the question of whether treatment with biologic agents in psoriasis has an impact on PsA development. However, these studies reported disparate results and reached different conclusions [46-50]. These discrepancies may relate to the populations studied. Gisondi *et al*, Rosenthal *et al*, and Acosta Felquer *et al* looked at dermatology-based psoriasis populations and found decreased risk of PsA progression with the use of biologics. In contrast, Ogdie *et al* and *Merola et* al, using population-based cohorts, found an increased risk of PsA progression for those on biologics, possibly related to confounding by indication and delayed timing of receiving a diagnosis of PsA. The only prospective cohort study of psoriasis and the risk of PsA found that anti-TNF agents did not impact the risk of PsA development[28]. Even the studies that are congruent with the PAMPA study hypothesis that aggressive treatment of psoriasis reduces the risk of PsA, need to be viewed with caution and cannot be interpreted causally[51]. In particular, the groups of patients being compared are not equivalent and the potential for confounding by indication and prognosis is considerable. There are likely unmeasured variables contributing to the choice of medication by providers. These studies are also susceptible to protopathic bias, where a certain therapy (like biologics) may be prescribed because patients have symptoms of, or undiagnosed, PsA which are not captured. Survival bias may also play a role as patients must “survive” without synovio-entheseal involvement to receive a biologic, which leads to differences between groups, especially in terms of disease duration. To address these concerns and discrepancies,

we propose the first randomized controlled trial looking at the effect of highly effective targeted therapy on the progression from skin psoriasis to PsA.

We also aim to better understand the role of imaging in psoriatic disease, which has increased in use dramatically over the last decade. Ultrasound imaging modalities, in particular, have the potential to improve the definition of meaningful subclinical inflammation. Therefore, the proposed study will also employ the use of musculoskeletal PDUS as a co-primary outcome to assess for subclinical evidence of inflammation. Psoriasis patients with imaging abnormalities have an increased risk of progression to PsA[33 34]. However, the specific threshold of abnormalities that correlate with future synovio-entheseal disease and the targeted treatments that ameliorate these findings and/or halt transition to PsA remain to be elucidated. The inclusion of PDUS in the PAMPA study is manifestly intended to address these gaps in knowledge.

Additionally, participants will be biosampled to characterize yet unidentified genetic, immunologic, and microbiome factors that influence progression[24]. The most significant advances in our understanding of the pathogenesis of the psoriasis to PsA continuum is the pivotal role played by a pro-inflammatory subset of CD4+ T helper (Th) cells known as Th17 cells[52]. Th17 and other Type-17 cells are activated by IL-23 to secrete IL-17A, IL-17F and IL-22 which act on resident, epithelial and endothelial cells to, in turn, elicit the production of multiple cytokines and chemokines, often leading to the recruitment of other inflammatory cells and the activation of innate defense mechanisms[53]. In particular, elevation of Type-17 cell subsets have been observed in peripheral blood, skin and joints of patients with psoriasis and PsA [54 55]. Studies of synovial fluid cells and psoriatic plaques also revealed a major role for IL-23 receptor high, CD8+ cells that release IL-17 in disease pathogenesis[56 57]. Another well-established long-term outcome of joint inflammation in PsA is the development of both bony erosions and pathologic new bone formation as a consequence of dysfunctional osteoblast and osteoclast activity. Murine studies showed that both IL-17 and TNF are important in driving abnormal bone resorption, while IL-22 may contribute to osteoproliferation[58 59]. We and others have demonstrated that patients with PsA have an increase in the osteoclast precursor population in their peripheral blood. A better characterization of this population could ultimately serve as a distinctive biomarker for early detection of PsA and as a potential target for arthritis prevention. Similarly, there is increasing evidence that the microbiome, the collection of microorganisms harbored by humans, is another potential triggering factor in the progression. Perturbations of microbial homeostasis (dysbiosis) has been associated with an inflammatory process characteristic of most immune-mediated diseases[60]. In fact, several studies have established a link between microbial dysbiosis and psoriatic disease, both in the skin and in the gut[61-65]. Despite this knowledge, critical gaps in our understanding of PsA etiology and the triggers behind IL-23-driven Type-17 cell expansion and downstream pro-inflammatory cytokine production in the skin and joints greatly hinder our ability to identify pre-clinical arthritis in psoriasis patients. The prospective nature of the current study, which includes biosampling of participants, will also allow us to make contributions to our understanding the underlying gene-microbial-host immune interactions in the psoriasis to PsA continuum.

While the PAMPA study has the potential to greatly expand our comprehension of pre-clinical PsA and possibly revolutionize care, we acknowledge a number of limitations. First, the follow-up period for capturing progression to synovio-entheseal disease is confined to a relatively short period of time, especially given that the average time to progression is 5-7 years. To mitigate this, the protocol pre-specifies that at least 30% of the included population have psoriasis for at least 2 years, ensuring that a robust portion of participants will fit into this time period during the trial.

Second, is the chosen therapeutic approach. We have chosen a selective IL-23 inhibitor, guselkumab, for this interventional trial given its known role in psoriatic disease pathogenesis, its high efficacy and reassuring safety profile[66-68], its status as FDA-approved treatment for psoriasis and PsA, and the prior evidence of improvement in subclinical imaging findings. However, valid arguments may exist for utilizing targeted medications with other mechanisms of action (such as TNF inhibitors, IL-17 inhibitors, Janus kinase inhibitors or phosphodiesterase 4 inhibitors). Further trials targeting different (known or yet to be discovered) cytokines/molecules will be needed to characterize the preventive potential of various pathway-specific therapeutics.

Importantly, the proposed study's population (i.e., patients with psoriasis at-increased risk of progression) represents both a strength and a limitation of this trial. Enrolling enough participants to address progression in a non-enriched psoriasis population would be prohibitive for this study, and many of its kind, given the annual transition rate of up to 3%. We have addressed this by selecting an enriched cohort of patients with psoriasis at-increased risk of progression based on prior data regarding risk factors. These include psoriasis duration, skin inflammatory burden, and evidence of subclinical inflammation on imaging. Overall, it is expected that PAMPA study participants will have a higher annual rate of progression, which will allow for the enrollment of less patients and still assess our primary outcome. Furthermore, by virtue of the pre-specified inclusion criteria, participants will already qualify for the use of biologic therapy (based on advanced psoriasis) which would offer a clear and significant benefit. Conversely, though, by pre-defining the study population and confining to those with previously identified risk factors, the study results may prevent us from assessing the impact and/or relative weight of these features for PsA progression outside of the pre-defined population. Additionally, the obtained outcomes may only be partially generalizable to the broader psoriasis patient population.

The PAMPA study will provide a first-in-kind, unique framework through which the field can better understand the clinical, genetic, immunologic, and environmental factors that may influence and determine progression to PsA. If successful, the study will also provide a novel approach to improve outcomes in psoriatic arthritis.

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Competing interests

KAM, SC, ZU, RBB, JS, JH, RC, KQ, FT have nothing to disclose. RHH has served as a consultant for Janssen. MT has served as a consultant for Horizon. VP has received honoraria for speaker and/or advisory board member roles from AbbVie, Almirall, Celgene, Janssen, Kyowa Kirin Co. Ltd, LEO Pharma, Novartis, Pfizer, Sanofi, UCB, and Union Therapeutics. In his role as Department Division Director of Dermatology at the University of Toronto, Dr. Piguet has received departmental support in the form of unrestricted educational grants from AbbVie, Bausch Health, Celgene, Janssen, LEO Pharma, Lilly, L'Oréal, NAOS, Novartis, Pfizer, Pierre-Fabre, Sandoz and Sanofi in the past 36 months. JY has served as a speaker, consultant, honoraria, and/or trialist for Abbvie, Amgen, Anacor, Astellas, Bausche, Baxalta, Boehringer Ingelheim, Celgene, Centocor, Coherus, Dermira, Eli Lilly, Forward, Galderma, Janssen, Leo, Medimmune, Merck, Novartis, Pfizer, Regeneron, Roche, Sanofi Genzyme, Sun Pharma, Takeda, UCB, Xenon. ALN declares that she has served as a consultant for Janssen, UCB, AbbVie, BMS and her immediate family member owns shares of stock in J&J, Eli Lilly, AbbVie, and Pfizer. WPG has received grants and research support from AbbVie, Amgen, Eli Lilly, Novartis, Pfizer and honorari for ad boards, invited talks, or consultation from AbbVie, Actelion, Amgen, Arylide, Bausch Health, Boehringer, Celgene, Cipher, Eli Lilly, Galderma, Janssen, LEO Pharma, Merck, Novartis, PeerVoice, Pfizer, Sanofi-Genzyme, Tribute, UCB, Valeant.
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References

1. Ogdie A, Weiss P. The Epidemiology of Psoriatic Arthritis. *Rheum Dis Clin North Am* 2015;41(4):545-68. doi: 10.1016/j.rdc.2015.07.001
2. Ritchlin CT, Colbert RA, Gladman DD. Psoriatic Arthritis. *N Engl J Med* 2017;376(10):957-70. doi: 10.1056/NEJMra1505557
3. Eder L, Chandran V, Shen H, et al. Incidence of arthritis in a prospective cohort of psoriasis patients. *Arthritis care & research* 2011;63(4):619-22. doi: 10.1002/acr.20401
4. Lee S, Mendelsohn A, Sarnes E. The Burden of Psoriatic Arthritis: A Literature Review from a Global Health Systems Perspective. *P T* 2010;35(12):680-89.
5. Husted JA, Gladman DD, Farewell VT, et al. Health-related quality of life of patients with psoriatic arthritis: a comparison with patients with rheumatoid arthritis. *Arthritis Rheum* 2001;45(2):151-8. doi: 10.1002/1529-0131(200104)45:2<151::AID-ANR168>3.0.CO;2-T

6. Kimball AB, Jacobson C, Weiss S, et al. The psychosocial burden of psoriasis. *Am J Clin Dermatol* 2005;6(6):383-92. doi: 10.2165/00128071-200506060-00005
7. Tillett W, Shaddick G, Askari A, et al. Factors influencing work disability in psoriatic arthritis: first results from a large UK multicentre study. *Rheumatology (Oxford)* 2015;54(1):157-62. doi: 10.1093/rheumatology/keu264
8. Haroon M, Gallagher P, FitzGerald O. Diagnostic delay of more than 6 months contributes to poor radiographic and functional outcome in psoriatic arthritis. *Ann Rheum Dis* 2015;74(6):1045-50. doi: 10.1136/annrheumdis-2013-204858
9. Armstrong AW, Robertson AD, Wu J, et al. Undertreatment, treatment trends, and treatment dissatisfaction among patients with psoriasis and psoriatic arthritis in the United States: findings from the National Psoriasis Foundation surveys, 2003-2011. *JAMA Dermatol* 2013;149(10):1180-5. doi: 10.1001/jamadermatol.2013.5264 [published Online First: 2013/08/16]
10. Scher JU. The 2018 landscape of RA, PsA, and SpA pathogenesis. *Curr Opin Rheumatol* 2017 doi: 10.1097/BOR.0000000000000461
11. Armstrong AW, Siegel MP, Bagel J, et al. From the Medical Board of the National Psoriasis Foundation: Treatment targets for plaque psoriasis. *Journal of the American Academy of Dermatology*;76(2):290-98. doi: 10.1016/j.jaad.2016.10.017
12. McInnes IB, Mease PJ, Kirkham B, et al. Secukinumab, a human anti-interleukin-17A monoclonal antibody, in patients with psoriatic arthritis (FUTURE 2): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet* 2015;386(9999):1137-46. doi: 10.1016/S0140-6736(15)61134-5
13. Mease PJ, van der Heijde D, Ritchlin CT, et al. Ixekizumab, an interleukin-17A specific monoclonal antibody, for the treatment of biologic-naive patients with active psoriatic arthritis: results from the 24-week randomised, double-blind, placebo-controlled and active (adalimumab)-controlled period of the phase III trial SPIRIT-P1. *Ann Rheum Dis* 2016 doi: 10.1136/annrheumdis-2016-209709
14. Mease PJ, Gladman DD, Ritchlin CT, et al. Adalimumab for the treatment of patients with moderately to severely active psoriatic arthritis: results of a double-blind, randomized, placebo-controlled trial. *Arthritis Rheum* 2005;52(10):3279-89. doi: 10.1002/art.21306
15. Ritchlin C, Scher JU. Strategies to Improve Outcomes in Psoriatic Arthritis. *Curr Rheumatol Rep* 2019;21(12):72. doi: 10.1007/s11926-019-0876-z [published Online First: 2019/12/10]
16. Haberman RH, Castillo R, Scher JU. Induction of remission in biologic-naive, severe psoriasis and PsA with dual anti-cytokine combination. *Rheumatology (Oxford)* 2021;60(7):e225-e26. doi: 10.1093/rheumatology/keaa880 [published Online First: 2020/12/29]
17. Deane KD, El-Gabalawy H. Pathogenesis and prevention of rheumatic disease: focus on preclinical RA and SLE. *Nat Rev Rheumatol* 2014;10(4):212-28. doi: 10.1038/nrrheum.2014.6
18. Olsen NJ, Karp DR. Autoantibodies and SLE: the threshold for disease. *Nat Rev Rheumatol* 2014;10(3):181-6. doi: 10.1038/nrrheum.2013.184
19. Burmester GR, Pope JE. Novel treatment strategies in rheumatoid arthritis. *The Lancet* 2017;389(10086):2338-48. doi: https://doi.org/10.1016/S0140-6736(17)31491-5
20. Gerlag DM, Safy M, Maijer KI, et al. Effects of B-cell directed therapy on the preclinical stage of rheumatoid arthritis: the PRAIRI study. *Ann Rheum Dis* 2019;78(2):179-85. doi: 10.1136/annrheumdis-2017-212763 [published Online First: 2018/12/07]
21. Study of Anti-Malarials in Incomplete Lupus Erythematosus (SMILE) [Available from: https://clinicaltrials.gov/show/NCT03030118.
22. Strategy to Prevent the Onset of Clinically-Apparent Rheumatoid Arthritis (StopRA) [Available from: https://clinicaltrials.gov/ct2/show/study/NCT02603146.

23. Al-Laith M, Jasenecova M, Abraham S, et al. Arthritis prevention in the pre-clinical phase of RA with abatacept (the APIPPRA study): a multi-centre, randomised, double-blind, parallel-group, placebo-controlled clinical trial protocol. *Trials* 2019;20(1):429. doi: 10.1186/s13063-019-3403-7 [published Online First: 2019/07/17]
24. Scher JU, Ogdie A, Merola JF, et al. Preventing psoriatic arthritis: focusing on patients with psoriasis at increased risk of transition. *Nat Rev Rheumatol* 2019;15(3):153-66. doi: 10.1038/s41584-019-0175-0 [published Online First: 2019/02/12]
25. Perez-Chada LM, Haberman RH, Chandran V, et al. Consensus terminology for preclinical phases of psoriatic arthritis for use in research studies: results from a Delphi consensus study. *Nat Rev Rheumatol* 2021;17(4):238-43. doi: 10.1038/s41584-021-00578-2 [published Online First: 2021/02/17]
26. Eder L, Polachek A, Rosen CF, et al. The Development of Psoriatic Arthritis in Patients With Psoriasis Is Preceded by a Period of Nonspecific Musculoskeletal Symptoms: A Prospective Cohort Study. *Arthritis Rheumatol* 2017;69(3):622-29. doi: 10.1002/art.39973 [published Online First: 2016/10/30]
27. Li W, Han J, Qureshi AA. Obesity and risk of incident psoriatic arthritis in US women. *Ann Rheum Dis* 2012;71(8):1267-72. doi: 10.1136/annrheumdis-2011-201273 [published Online First: 2012/05/09]
28. Eder L, Haddad A, Rosen CF, et al. The Incidence and Risk Factors for Psoriatic Arthritis in Patients With Psoriasis: A Prospective Cohort Study. *Arthritis Rheumatol* 2016;68(4):915-23. doi: 10.1002/art.39494 [published Online First: 2015/11/12]
29. Wilson FC, Icen M, Crowson CS, et al. Incidence and clinical predictors of psoriatic arthritis in patients with psoriasis: a population-based study. *Arthritis Rheum* 2009;61(2):233-9. doi: 10.1002/art.24172 [published Online First: 2009/01/30]
30. Soltani-Arabshahi R, Wong B, Feng BJ, et al. Obesity in early adulthood as a risk factor for psoriatic arthritis. *Arch Dermatol* 2010;146(7):721-6. doi: 10.1001/archdermatol.2010.141 [published Online First: 2010/07/21]
31. Chandran V, Schentag CT, Brockbank JE, et al. Familial aggregation of psoriatic arthritis. *Ann Rheum Dis* 2009;68(5):664-7. doi: 10.1136/ard.2008.089367 [published Online First: 2008/06/06]
32. Patrick MT, Stuart PE, Raja K, et al. Genetic signature to provide robust risk assessment of psoriatic arthritis development in psoriasis patients. *Nat Commun* 2018;9(1):4178. doi: 10.1038/s41467-018-06672-6 [published Online First: 2018/10/12]
33. Simon D, Tascilar K, Kleyer A, et al. Structural entheseal lesions in patients with psoriasis are associated with an increased risk of progression to psoriatic arthritis. *Arthritis Rheumatol* 2020 doi: 10.1002/art.41239 [published Online First: 2020/02/28]
34. Faustini F, Simon D, Oliveira I, et al. Subclinical joint inflammation in patients with psoriasis without concomitant psoriatic arthritis: a cross-sectional and longitudinal analysis. *Annals of the Rheumatic Diseases* 2016;75(12):2068-74. doi: 10.1136/annrheumdis-2015-208821
35. Kocijan R, Englbrecht M, Haschka J, et al. Quantitative and Qualitative Changes of Bone in Psoriasis and Psoriatic Arthritis Patients. *Journal of Bone and Mineral Research* 2015;30(10):1775-83. doi: 10.1002/jbmr.2521
36. Blauvelt A, Papp KA, Griffiths CEM, et al. Efficacy and safety of guselkumab, an anti-interleukin-23 monoclonal antibody, compared with adalimumab for the continuous treatment of patients with moderate to severe psoriasis: Results from the phase III, double-blinded, placebo- and active comparator–controlled VOYAGE 1 trial. *Journal of the American Academy of Dermatology* 2017;76(3):405-17. doi: https://doi.org/10.1016/j.jaad.2016.11.041

37. Anja Ficjan, Rusmir Husic, Judith Gretler, et al. Ultrasound composite scores for the assessment of inflammatory and structural pathologies in Psoriatic Arthritis (PsASon-Score). *Arthritis research & therapy* 2014;16(5):476. doi: 10.1186/s13075-014-0476-2
38. Taylor W, Gladman D, Helliwell P ea. Classification criteria for psoriatic arthritis: development of new criteria from a large international study. *Arthritis Rheum* 2006;54:2665-73.
39. R Core Team. R: A language and environment for statistical computing. . *R Foundation for Statistical Computing, Vienna, Austria*
40. PA Harris, R Taylor, R Thielke, et al. Research electronic data capture (REDCap) – A metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform* 2009;42(2):377-81.
41. Thiele R, Chiu Y, Huertas N, et al. Serum, Cellular and Imaging Markers of Arthritis in Psoriasis Patients and Healthy Controls [abstract]. *Arthritis Rheumatol* 2018;70
42. Helliwell PS. Psoriasis epidemiology screening tool (PEST): A report from the GRAPPA 2009 annual meeting. *J Rheumatol* 38:551-52.
43. Coates LC, Moverley AR, McParland L, et al. Effect of tight control of inflammation in early psoriatic arthritis (TICOPA): a UK multicentre, open-label, randomised controlled trial. *Lancet* 2015;386(10012):2489-98. doi: 10.1016/S0140-6736(15)00347-5 [published Online First: 2015/10/05]
44. Kampylafka E, Simon D, d'Oliveira I, et al. Disease interception with interleukin-17 inhibition in high-risk psoriasis patients with subclinical joint inflammation—data from the prospective IVEPSA study. *Arthritis Research & Therapy* 2019;21(1):178. doi: 10.1186/s13075-019-1957-0
45. Savage L, Goodfield M, Horton L, et al. Regression of Peripheral Subclinical Enthesopathy in Therapy-Naive Patients Treated With Ustekinumab for Moderate-to-Severe Chronic Plaque Psoriasis: A Fifty-Two-Week, Prospective, Open-Label Feasibility Study. *Arthritis Rheumatol* 2019;71(4):626-31. doi: 10.1002/art.40778 [published Online First: 2018/11/24]
46. Meer E, Merola JF, Fitzsimmons R, et al. Does biologic therapy impact the development of PsA among patients with psoriasis? *Ann Rheum Dis* 2021 doi: 10.1136/annrheumdis-2021-220761 [published Online First: 2021/10/08]
47. Acosta Felquer ML, LoGiudice L, Galimberti ML, et al. Treating the skin with biologics in patients with psoriasis decreases the incidence of psoriatic arthritis. *Annals of the Rheumatic Diseases* 2021:annrheumdis-2021-220865. doi: 10.1136/annrheumdis-2021-220865
48. Gisondi P, Bellinato F, Targher G, et al. Biological disease-modifying antirheumatic drugs may mitigate the risk of psoriatic arthritis in patients with chronic plaque psoriasis. *Annals of the Rheumatic Diseases* 2021:annrheumdis-2021-219961. doi: 10.1136/annrheumdis-2021-219961
49. Rosenthal YS, Schwartz N, Sagy I, et al. Incidence of Psoriatic Arthritis Among Patients Receiving Biologic Treatments for Psoriasis: A Nested Case–Control Study. *Arthritis & Rheumatology*;n/a(n/a) doi: https://doi.org/10.1002/art.41946
50. Merola JF, Tian H, Patil D, et al. Incidence and prevalence of psoriatic arthritis in patients with psoriasis stratified by psoriasis disease severity: Retrospective analysis of an electronic health records database in the United States. *J Am Acad Dermatol* 2021 doi: 10.1016/j.jaad.2021.09.019 [published Online First: 2021/09/22]
51. Merola JF, Ogdie A. Does psoriasis treatment affect PsA development? *Nat Rev Rheumatol* 2021;17(12):708-09. doi: 10.1038/s41584-021-00706-y [published Online First: 2021/10/13]

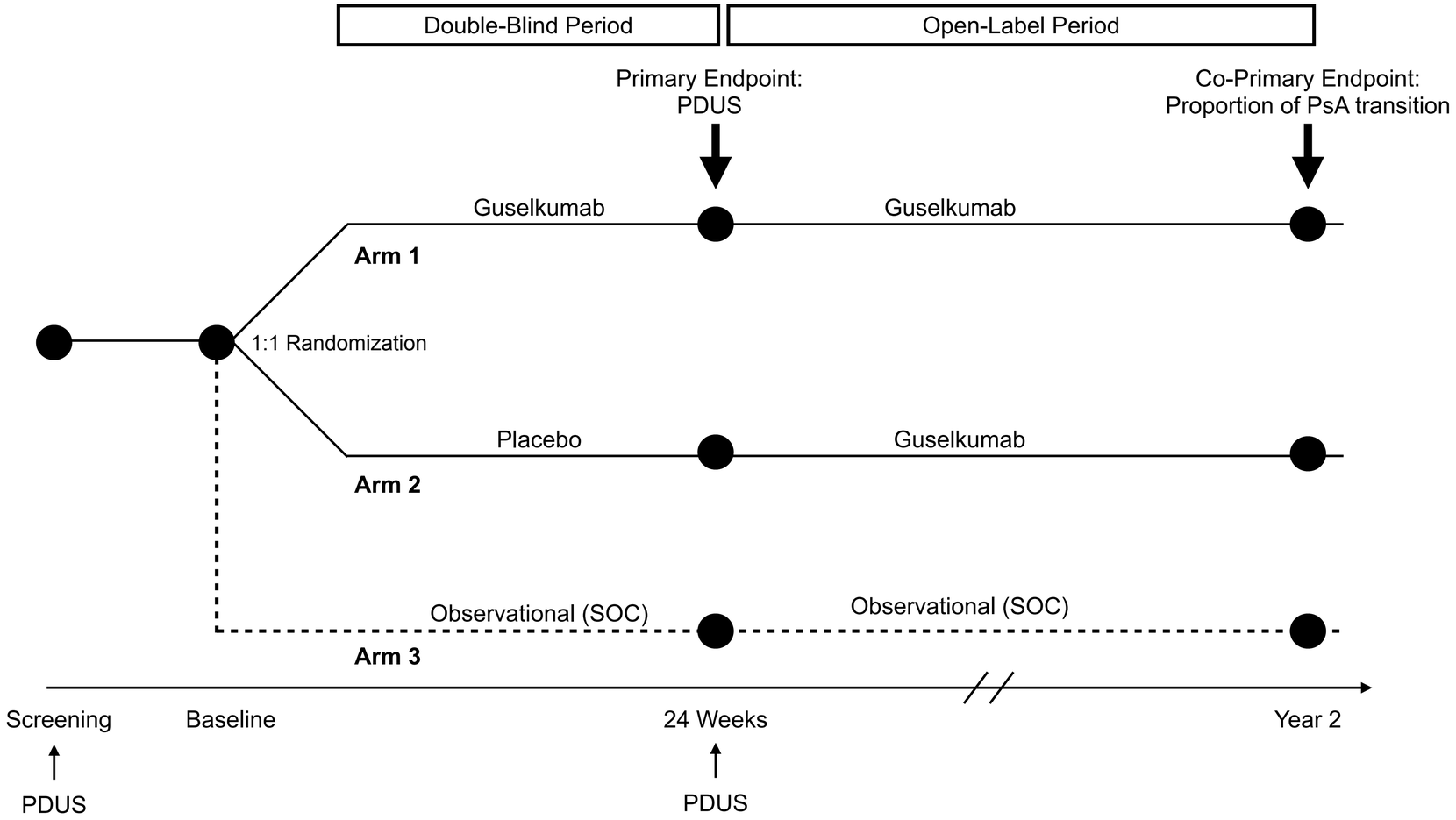
52. Annunziato F, Cosmi L, Santarlasci V, et al. Phenotypic and functional features of human Th17 cells. *The Journal of experimental medicine* 2007;204(8):1849-61. doi: 10.1084/jem.20070663 [published Online First: 2007/07/20]
53. Korn T, Bettelli E, Oukka M, et al. IL-17 and Th17 Cells. *Annual review of immunology* 2009;27:485-517. doi: 10.1146/annurev.immunol.021908.132710 [published Online First: 2009/01/10]
54. Leipe J, Grunke M, Dechant C, et al. Role of Th17 cells in human autoimmune arthritis. *Arthritis Rheum* 2010;62(10):2876-85. doi: 10.1002/art.27622
55. Cauli A, Mathieu A. Th17 and interleukin 23 in the pathogenesis of psoriatic arthritis and spondyloarthritis. *The Journal of rheumatology Supplement* 2012;89:15-8. doi: 10.3899/jrheum.120234
56. Menon B, Gullick NJ, Walter GJ, et al. Interleukin-17+CD8+ T cells are enriched in the joints of patients with psoriatic arthritis and correlate with disease activity and joint damage progression. *Arthritis & rheumatology* 2014;66(5):1272-81. doi: 10.1002/art.38376 [published Online First: 2014/01/29]
57. Clark RA. Resident memory T cells in human health and disease. *Sci Transl Med* 2015;7(269):269rv1. doi: 10.1126/scitranslmed.3010641 [published Online First: 2015/01/09]
58. Mitra A, Raychaudhuri SK, Raychaudhuri SP. Functional role of IL-22 in psoriatic arthritis. *Arthritis research & therapy* 2012;14(2):R65. doi: 10.1186/ar3781 [published Online First: 2012/03/16]
59. Sherlock JP, Joyce-Shaikh B, Turner SP, et al. IL-23 induces spondyloarthropathy by acting on ROR-gammat+ CD3+CD4-CD8- entheseal resident T cells. *Nature medicine* 2012;18(7):1069-76. doi: 10.1038/nm.2817
60. Clemente JC, Manasson J, Scher JU. The role of the gut microbiome in systemic inflammatory disease. *BMJ* 2018;360:j5145. doi: 10.1136/bmj.j5145 [published Online First: 2018/01/10]
61. Dei-Cas I, Giliberto F, Luce L, et al. Metagenomic analysis of gut microbiota in non-treated plaque psoriasis patients stratified by disease severity: development of a new Psoriasis-Microbiome Index. *Sci Rep* 2020;10(1):12754. doi: 10.1038/s41598-020-69537-3 [published Online First: 2020/07/31]
62. Chen D, He J, Li J, et al. Microbiome and Metabolome Analyses Reveal Novel Interplay Between the Skin Microbiota and Plasma Metabolites in Psoriasis. *Front Microbiol* 2021;12:643449. doi: 10.3389/fmicb.2021.643449 [published Online First: 2021/04/03]
63. Olejniczak-Staruch I, Ciazynska M, Sobolewska-Sztychny D, et al. Alterations of the Skin and Gut Microbiome in Psoriasis and Psoriatic Arthritis. *Int J Mol Sci* 2021;22(8) doi: 10.3390/ijms22083998 [published Online First: 2021/05/01]
64. Scher JU, Ubeda C, Artacho A, et al. Decreased bacterial diversity characterizes the altered gut microbiota in patients with psoriatic arthritis, resembling dysbiosis in inflammatory bowel disease. *Arthritis Rheumatol* 2015;67(1):128-39. doi: 10.1002/art.38892 [published Online First: 2014/10/17]
65. Manasson J, Wallach DS, Guggino G, et al. Interleukin-17 Inhibition in Spondyloarthritis Is Associated With Subclinical Gut Microbiome Perturbations and a Distinctive Interleukin-25-Driven Intestinal Inflammation. *Arthritis Rheumatol* 2020;72(4):645-57. doi: 10.1002/art.41169 [published Online First: 2019/11/16]
66. Reich K, Armstrong AW, Langley RG, et al. Guselkumab versus secukinumab for the treatment of moderate-to-severe psoriasis (ECLIPSE): results from a phase 3, randomised controlled trial. *Lancet* 2019;394(10201):831-39. doi: 10.1016/S0140-6736(19)31773-8 [published Online First: 2019/08/14]
67. Blauvelt A, Papp KA, Griffiths CE, et al. Efficacy and safety of guselkumab, an anti-interleukin-23 monoclonal antibody, compared with adalimumab for the continuous

treatment of patients with moderate to severe psoriasis: Results from the phase III, double-blinded, placebo- and active comparator-controlled VOYAGE 1 trial. *J Am Acad Dermatol* 2017;76(3):405-17. doi: 10.1016/j.jaad.2016.11.041 [published Online First: 2017/01/07]

68. Rahman P, Ritchlin CT, Helliwell PS, et al. Pooled Safety Results Through 1 Year of 2 Phase III Trials of Guselkumab in Patients With Psoriatic Arthritis. *J Rheumatol* 2021;48(12):1815-23. doi: 10.3899/jrheum.201532 [published Online First: 2021/05/03]

FIGURE LENGEND

Figure 1. Study Design of the PAMPA Study. PAMPA Preventing Arthritis in a Multicenter Psoriasis At Risk cohort study; PDUS power doppler ultrasound; PsA psoriatic arthritis; SOC standard of care.


Double-Blind Period
Open-Label Period
Primary Endpoint:
PDUS
Co-Primary Endpoint:
Proportion of PsA transition
Guselkumab
Guselkumab
Arm 1
1:1 Randomization
Placebo
Guselkumab
Arm 2
Observational (SOC)
Observational (SOC)
Arm 3
Screening
Baseline
24 Weeks
Year 2
PDUS
PDUS

Supplement to

Efficacy of Guselkumab, a selective IL-23 inhibitor, in Preventing Arthritis in a Multi-center Psoriasis At-Risk cohort (PAMPA): protocol of a randomized, double-blind, placebo controlled multicenter trial

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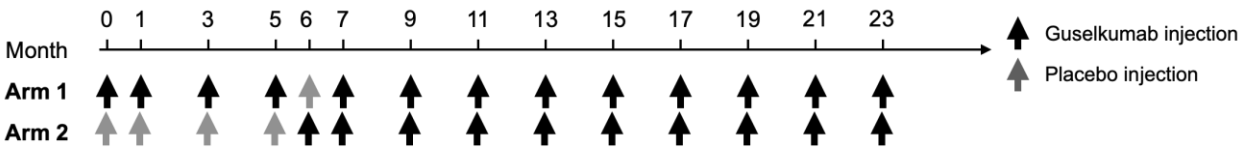

Supplementary Figure 1. Drug and placebo schedule. Black arrows indicate guselkumab injection, gray arrows indicate placebo injection.

Supplementary Methods

Participating Sites

New York University Langone Health and Langone Orthopedic Hospital (coordinating center)
University of Toronto and Women's College Hospital
University of Rochester Medical Center
Memorial University of Newfoundland
Brigham and Women's Hospital, Harvard Medical School
Perelman School of Medicine at the University of Pennsylvania (alternate site)

Ultrasound Protocol

All sites will be scanned longitudinally and any pathology detected in the longitudinal plane will be confirmed in the transverse plane. The following sites will be scanned bilaterally:

Entheseal sites:

1. Quadriceps insertion at the superior pole of patella
2. Patellar ligament origin at the distal pole of patella
3. Patellar ligament insertion at the tibial tuberosity
4. Achilles tendon insertion into the calcaneus
5. Plantar fascia insertion into the calcaneus
6. Common extensor tendon insertion into the lateral epicondyle

Joints:

1. Wrist (radio-carpal, mid-carpal)
2. Metacarpophalangeal, proximal interphalangeal, distal interphalangeal joints (digits 1-5)

Tendon sheaths and tendons:

1. In the dorsal wrist: Compartment 4 (extensor digitorum) and 6 (extensor carpi ulnaris)
2. In the dorsal hand: Extensor digitorum 1-5 at the level of the MCP joint
3. In the palmar hand: Flexor digitorum 1-5

Rochester-Modified PsASon Scoring System

The lowest RM-PsASon score a participant may have at baseline is 0. The highest RM-PsASon score a participant may have at baseline is 614.

1) **Synovitis and power Doppler signal/joint[1]:** Graded from 0-3 as absent, mild, moderate or severe according to images of a reference atlas.
PD signal: 0=no PD-signal, 1=up to three single or two confluent signals, 2=less than half of the visible intracapsular area and 3=half or more of the visible intracapsular area covered by PD-signals.

2) **Bone erosions/joint[2]**: Score is based on maximal diameter of cortical break.
Grade 0: no erosion, grade 1: erosion of <2 mm, grade 2: erosion of >2 mm, grade 3: large destruction of the joint

3) **Osteophytes/joint[2]**:Score is based on maximal distance between the 'original' and new cortical lining (=maximal height)
Grade 0: no osteophyte, grade 1: osteophyte of <1 mm, grade 2: osteophyte of >1 mm, grade 3: large and diffuse osteophytes

4) **Peritendinitis/fingers**[3]: The presence of peritendinitis is assessed at dorsal scans of MCP 2-5 and is characterized by hypoechoic swelling of the soft tissue surrounding the extensor digitorum tendon, with or without peri-tendinous PD-signals. B-mode (B-perisyn) as well as PD-findings in perisynovial tissue (PD-perisyn) and is graded with 0=absent or 1=present.

5) **Enthesitis**[4]: Enthesitis is graded according to Madrid Sonographic Enthesis Index (MASEI): Structure is considered pathological (score=1) if there is a loss of fibrillar pattern, hypoechoic aspect, or fusiform thickening of the entheses. Erosions are defined as a cortical breakage with a step-down contour defect at the attachment of entheses at bone and graded with 0=absent or 3=present. Fascia and tendon thickness are measured at the point of maximal thickness on the bony insertion and graded with 0=normal or 1=thickened according to the reference values of the MASEI index. Enthesophytes are defined as calcifications at the entheses insertions into bone and graded with 0=absent, 1=small calcification, 2=clear presence of enthesophyte/calcification, 3= large calcifications or ossifications. PD-signals within entheses are scored with 0=absent or 3=present. Bursitis is investigated at the level of distal patellar tendon (infrapatellar bursitis) and the level of Achilles tendon insertion (retrocalcaneal bursitis) and graded with 0=absent and 1=present.

References

1. Hammer HB, Bolton-King P, Bakkeheim V, et al. Examination of intra and interrater reliability with a new ultrasonographic reference atlas for scoring of synovitis in patients with rheumatoid arthritis. *Ann Rheum Dis* 2011;70(11):1995-8. doi: 10.1136/ard.2011.152926 [published Online First: 2011/07/26]
2. Finzel S, Ohrndorf S, Englbrecht M, et al. A detailed comparative study of high-resolution ultrasound and micro-computed tomography for detection of arthritic bone erosions. *Arthritis Rheum* 2011;63(5):1231-6. doi: 10.1002/art.30285 [published Online First: 2011/05/04]
3. Gutierrez M, Filippucci E, De Angelis R, et al. Subclinical entheseal involvement in patients with psoriasis: an ultrasound study. *Semin Arthritis Rheum* 2011;40(5):407-12. doi: 10.1016/j.semarthrit.2010.05.009 [published Online First: 2010/08/07]
4. de Miguel E, Cobo T, Munoz-Fernandez S, et al. Validity of enthesis ultrasound assessment in spondyloarthropathy. *Ann Rheum Dis* 2009;68(2):169-74. doi: 10.1136/ard.2007.084251 [published Online First: 2008/04/09]

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	3
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	5
	2b	Specific objectives or hypotheses	6
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	6
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	NA- protocol
Participants	4a	Eligibility criteria for participants	6
	4b	Settings and locations where the data were collected	6
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	7
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	7
	6b	Any changes to trial outcomes after the trial commenced, with reasons	NA-protocol
Sample size	7a	How sample size was determined	8
	7b	When applicable, explanation of any interim analyses and stopping guidelines	8
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	6
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	6
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	6
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	6
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	6-7

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	7
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	8
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	8
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	NA
	13b	For each group, losses and exclusions after randomisation, together with reasons	NA
Recruitment	14a	Dates defining the periods of recruitment and follow-up	NA
	14b	Why the trial ended or was stopped	NA
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	NA
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	NA
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	NA
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	NA
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	NA
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	NA
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	9-11
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	9-11
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	9-11
Other information			
Registration	23	Registration number and name of trial registry	3
Protocol	24	Where the full trial protocol can be accessed, if available	Protocol paper
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	12

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

BMJ Open

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Primary Subject Heading:	Dermatology
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Title: Efficacy of Guselkumab, a selective IL-23 inhibitor, in Preventing Arthritis in a Multi-center Psoriasis At-Risk cohort (PAMPA): protocol of a randomized, double-blind, placebo controlled multicenter trial

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Abstract

Introduction Psoriatic arthritis (PsA) is a complex, immune-mediated disease associated with skin psoriasis that, if left untreated, can lead to joint destruction. Up to 30% of patients with psoriasis progress to PsA. In most cases, psoriasis precedes synovio-entheseal inflammation by an average of 5-7 years, providing a unique opportunity for early and potentially preventive intervention in a susceptible and identifiable population. Guselkumab is an effective IL-23p19 inhibitor FDA-approved for treatment of moderate-severe psoriasis and PsA. The Preventing Arthritis in a Multicenter Psoriasis At Risk cohort (PAMPA) study aims to evaluate the efficacy of guselkumab in preventing PsA and decreasing musculoskeletal power Doppler ultrasound (PDUS) abnormalities in a population of patients with psoriasis who are at-increased risk for PsA progression.

Methods and Analysis The PAMPA study is a multi-center, randomized, double-blind, placebo-controlled, interventional, preventive trial comparing PDUS involvement and conversion to PsA in patients with psoriasis at-increased risk for progression treated with guselkumab compared to non-biologic standard of care. The study includes a screening period, a double-blind treatment period (24 weeks), and an open-label follow-up period (72 weeks). At baseline, 200 subjects will be randomized (1:1) to receive either guselkumab 100 mg (Arm 1) or placebo switching to guselkumab 100mg starting at Week 24 (Arm 2). Arm 3 will follow 150 at-risk psoriasis patients who decline biologic therapy and randomization. Changes from baseline in the PDUS score at week 24 and the difference in proportion of patients transitioning to PsA at 96 weeks will be examined as the co-primary endpoints.

Ethics and dissemination Ethics approval for this study was granted by the coordinating center's (NYU School of Medicine) Institutional Review Board (IRB). Each participating site received approval through their own IRBs. The findings will be shared in peer-reviewed articles and scientific conference presentations.

Trial registration number Registered at ClinicalTrials.gov (NCT05004727).

Strength and Limitations

- This is a prospective, randomized controlled trial to investigate the efficacy of an interleukin-23p19 inhibitor, guselkumab, in preventing the development of PsA in population of patients with increased-risk psoriasis.
- Power Doppler Musculoskeletal ultrasound will be used to assess subclinical baseline articular and periarticular abnormalities and identify the impact of guselkumab on these abnormalities.
- Clinical data will be combined with molecular and immunologic analysis to elucidate biological determinants of the transition from psoriasis to PsA.
- A potential limitation is the short course of active drug vs. placebo (6 months) and a relatively short follow up period (2 years) to be able to fully assess conversion from skin to joint involvement.

Introduction

Psoriatic arthritis (PsA) is an immune-mediated inflammatory arthritis associated with skin psoriasis, affecting two million patients in the United States[1]. PsA is characterized by musculoskeletal inflammation that can take various forms, including synovitis, enthesitis, dactylitis, and axial involvement[2]. Up to 30% of patients with psoriasis have inflammatory arthritis and the rate of progression from psoriasis to PsA occurs at up to 3% per year[1, 3], with skin psoriasis preceding synovio-entheseal involvement by an average of 5 to 7 years[2] . Untreated, PsA can lead to erosive and deforming disease associated with significant morbidity and disability[4] . Beyond the skin and joints, PsA is associated with decreased quality of life, high rates of psychosocial stress, and increased rates of unemployment, absenteeism, and productivity loss[5-7] . Despite this burden, and the knowledge that a delay in diagnosis and treatment of as little as 6 months is associated with significantly more radiographic progression and worse function[8], PsA remains underdiagnosed and undertreated[9].

While the last decade has witnessed a therapeutic revolution in treatment options for both psoriasis and PsA[10], joint outcomes have lagged behind skin. The advent of anti-tumor necrosis factor (TNF) agents, followed by antibodies that target molecules in the interleukin (IL)-23/IL-17 axis, have dramatically improved psoriasis response. Remarkably, a significant number of patients can now achieve total clearance of skin disease[11]. However, the magnitude of responses observed in psoriasis has not been achieved in PsA, where up to half the patients do not experience clinically meaningful synovio-entheseal improvement with blockade of TNF or IL-23/IL-17 pathways[12-14]. Therefore, highly effective treatment strategies for PsA remain a significant unmet need and new approaches are warranted, including novel therapeutic targets, combination therapy, and early intervention and prevention[15, 16].

Recent efforts in rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) emphasize the concept of treating disease in the pre-clinical stages to possibly delay or even prevent disease onset and lessen severity[17, 18]. To formally address this strategy, SLE and RA investigators pioneered trials in subjects with serologic, but no clinical, evidence of disease, and noted improved outcomes and even disease prevention in some cases[19, 20]. Additional NIH-supported prevention trials are underway including the SMILE[21] and Stop-RA[22] studies and more are in progress in Europe[23]. These strategies may even be more relevant in PsA given that there is a readily apparent pre-clinical marker (skin psoriasis) that generally precedes joint involvement, creating a unique prospect for early intervention, and possibly even prevention, in a susceptible and identifiable population[24]. Here, we present Preventing Arthritis in a Multicenter Psoriasis At Risk cohort study (PAMPA), the first randomized controlled, interventional trial using a specific target (i.e., guselkumab) to look at prevention of PsA development in a psoriasis population.

The first step in prevention is to identify populations who are at increased risk for PsA[25]. Cross-sectional studies identified several risk factors associated with progression, including obesity[26, 27], psoriasis involvement (i.e., increased psoriasis severity or the presence of nail, inverse, or scalp involvement)[28-30], having a first degree relative with PsA[31], and genetic polymorphisms[32]. Additionally, the presence of structural entheseal lesions on high-resolution peripheral quantitative computed tomography (HR-pQCT) or magnetic resonance imaging (MRI) in patients with psoriasis were associated with higher risk of progression[33, 34], which is of particular interest as a large percentage of patients with psoriasis have subclinical focal bone loss, enthesitis and new bone formation[35]. Taken together, the accumulated body of evidence further supports the PAMPA study strategy of targeting psoriasis patients who are at the highest risk for, but do not yet fulfill the classification criteria for, overt synovio-entheseal inflammation.

Given the role of IL-23 in psoriatic disease pathogenesis, we propose that prolonged, unresolved skin inflammation driven by IL-23 increases the risk for transition into PsA and that an intervention that targets one of these pivotal molecules (i.e., guselkumab) will significantly reduce or prevent the emergence of the synovio-entheseal phenotype. To achieve this goal, first, we defined a singular target population, one in which clinical, demographic and musculoskeletal imaging factors are present with sufficient strength to suggest that progression to arthritis is likely and which justifies intervention with a systemic medication. Second, we deliberatively chose a therapy that offers practical and biological advantages, including a clinical indication for psoriasis, a proven safety profile, convenience of administration and its acceptability to both patients and physicians. Guselkumab has all these advantages based on its ability to inhibit IL-23p19, and is FDA-approved for the treatment of both moderate-severe plaque psoriasis[36] (our patient population) and active PsA.

The overarching aim of this study is to determine whether guselkumab use can: (1) improve subclinical musculoskeletal inflammation as visualized on specialized ultrasound imaging, and (2) decrease the rate of progression to clinically evident PsA. Concomitantly, PAMPA will focus on better understanding the underlying imaging, immunologic, and environmental features that promote the synovio-entheseal transition from psoriasis to PsA. To this end, a unique array of biologic samples will be collected to help reveal mechanistic pathways associated with progression (or resistance) to PsA transition and severity.

Methods and Analysis

Study design

This is a phase IV, multicenter, double-blind, randomized, placebo-controlled study of the efficacy of guselkumab (compared to standard of care) in preventing abnormalities on musculoskeletal power Doppler ultrasound (PDUS) and conversion to PsA in high-risk psoriatic populations. The study opened for enrollment in February 2022 and is planned to conclude enrollment in September 2024. The study includes a screening period, a 24-week double-blind treatment period (Arm 1 receiving drug and Arm 2 receiving placebo), and a 72-week open-label follow-up period (Figure 1). A third arm (Arm 3) will consist of participants who do not receive any study drug followed prospectively as the natural history comparator arm based on their personal preference to avoid biologic therapy. No participants will be randomized into Arm 3 as it was deemed neither feasible nor ethical to withhold systemic treatment for 96 weeks, and assuming many of them may want to initiate immunomodulatory therapy during that time period.

Study population and randomization

A total of 350 participants with a diagnosis of psoriasis (as determined by a dermatologist) for at least 2 years (in at least 30% of participants) and features of increased risk, defined here as percent psoriasis body surface area (BSA) greater than 3%, and positive imaging findings on musculoskeletal PDUS (Rochester modification of PsASon[37] [RM-PsASon] score greater than 3.36) (Table 1) will be included. Participants that already fulfill CASPAR criteria for PsA will be excluded[38]. Participants in all arms will be screened and enrolled from five study sites (community and academic) across North America (full list available in the Supplement). Additionally, institutional electronic medical record systems will be utilized, and outreach pursued via research and advocacy groups (e.g., National Psoriasis Foundation, PPACMAN, GRAPPA) and social media.

Table 1. Inclusion/Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
At least 18 years old	Evidence of inflammatory joint pain, enthesitis and/or dactylitis
Willing and able to provide informed consent	Current systemic immunosuppressive medication use (i.e., methotrexate, apremilast) at time of enrollment or biologic use ever
Psoriasis diagnosis (per dermatologist) for at least 2 years (in at least 30% of participants)	Mid-high positive rheumatoid factor and/or anti-citrullinated protein antibodies (greater than 2 times the upper limit of normal)
Psoriasis body surface area greater than or equal to 3%	Current active malignancy
Positive imaging findings on ultrasound defined as Rochester Modified-PsASon score > 3.36	History of symptomatic polyarticular OA or other joint conditions (such as rheumatoid arthritis, gout) that may impair the ability to assess for psoriatic arthritis development
	Conditions where initiation of guselkumab is prohibited in the prescribing information, including clinically important active infections and untreated latent tuberculosis
	Known hypersensitivity to the study agent

Participants who agree to be actively treated with drug (n=200) will be allocated in a 1:1 randomization to receive either guselkumab 100 mg (Arm 1) or placebo switching to guselkumab at Week 24 (Arm 2). An unblinded statistician has generated the randomization list using blockrand library (V.4.1.0) within the statistical computing language R[39]. Randomization is stratified by site and gender. An independent study team member, outside of the project, will randomize participants via REDCap[40] and convey the drug kit assignments to the pharmacy, allowing for all team members (pharmacy staff included) to remain blinded. Patients who decline to be randomized to biologic therapy will be followed in Arm 3, but will not receive any study intervention (standard of care, control group).

Intervention, Assessments and Endpoints

During the screening period, participants will undergo PDUS and clinical assessments (Table 2) to determine study eligibility. Patients who fulfill criteria will be randomized 1:1 to receive either guselkumab 100 mg (Arm 1) or placebo (Arm 2). Repeat PDUS will be performed at week 24 to assess for any changes. At week 24, participants in Arm 2 will then switch to guselkumab 100 mg; both Arm 1 and 2 participants will continue on guselkumab (open label), being assessed in person every 24 weeks until the conclusion of the study. Guselkumab is given at its FDA-approved dose for psoriasis: 100 mg at weeks 0 and 4, and then every 8 weeks thereafter. To account for the loading dose and ensure continued blinding at the 24-week timepoint, Arm 1 participants will receive one placebo dose at week 24. A complete drug schedule is detailed in Supplementary Figure 1. Participants may continue to use topical treatments or phototherapy throughout the duration of the study.

Table 2. Assessment Schedule of PAMPA Study

Study procedures	Screening	Week 0	Week 12#	Week 24	Week 48	Week 72	Week 96
Informed Consent	X						
Inclusion/exclusion	X						
Demographics	X						
Medical history	X						
Psoriatic disease history	X						
Medications	X	X	X	X	X	X	X
Ultrasound	X			X			
Adverse Events			X	X	X	X	X
Skin assessments (BSA, IGA)	X	X		X	X	X	X
MSK assessments (TJC, SJC, SPARCC enthesitis index, dactylitis count)	X	X		X	X	X	X
PEST*	X	X	X	X	X	X	X
EQ-5D		X		X			X
FACIT-F	X	X	X	X	X	X	X
Patient pain score	X	X	X	X	X	X	X
Global health score	X	X	X	X	X	X	X
IDEOM MSK-Q	X	X	X	X	X	X	X
Safety Labs (CBC, CMP, TB test, serum pregnancy)	X						
RF/ACPA	X						
Urine pregnancy^		X					
Biosampling (plasma, PBMCs, skin swabs, stool)		X					

* PEST will also be performed by telephone or electronically every 3 months if there is not an in-person visit.
# Arm 3 will not have an in-person visit at week 12. They will also not have to undergo safety labs or record adverse events.
^Urine pregnancy test will be done for females of child bearing age the day of the baseline visit, prior to administering the first dose of drug or placebo.
PAMPA Preventing Arthritis in a Multicenter Psoriasis At Risk cohort study; BSA body surface area; IGA investigators global assessment 2011; TJC tender joint count; SJC swollen joint count, SPARCC spondyloarthritis Research Consortium of Canada enthesitis index; PEST psoriasis epidemiology screen tool; FACIT-F functional assessment of chronic illness therapy- fatigue; IDEOM MSK international dermatology outcomes measures musculoskeletal; CBC completed blood count; CMP comprehensive metabolic panel; TB tuberculosis; RF rheumatoid factor; ACPA anticitrullinated peptide antibodies; PBMC peripheral blood mononuclear cell.

The ultrasound assessment will consist of an evaluation of grey scale synovitis, power Doppler (PD) findings at joints, erosions, osteophytes, grey scale and PD peritendonitis, and grey scale and PD tenosynovitis. The pre-specified set of 36 joints and 34 periarticular structures will be scanned at each visit. Ultrasounds will be scored via the RM-PsASon by two independent, blinded, central readers who are experts in PDUS imaging. Based on previous data looking at the difference in ultrasound abnormalities between healthy controls and patients with psoriasis[41], participants require a RM-PsASon score of >3.36 at baseline for inclusion. Change in RM-PsASon score will be assessed at 24 weeks. Further details can be found in the *online supplementary methods*.

Clinical evaluation will be performed by blinded assessors. In-person assessments include skin assessments (BSA, Investigator's Global Assessment Modified 2011), musculoskeletal assessments (66/68 tender/swollen joint count and Spondyloarthritis Research Consortium of Canada enthesitis index, dactylitis count), and patient reported outcomes (EQ-5D, Functional Assessment of Chronic Illness Therapy-Fatigue, patient pain score, global health score, and International Dermatology Outcomes Measures Musculoskeletal-Questionnaire [IDEMO MSK-Q]). The IDEOM MSK-Q is a PRO aimed at identifying musculoskeletal symptoms and measuring their intensity and impact on health-related quality of life in patients with psoriatic

disease (further details can be found in the Supplement). They will also complete a modified Psoriasis Epidemiology Screening Test (PEST) to screen for PsA and will be evaluated for fulfillment of modified CASPAR criteria (dactylitis added to the stem) to determine if they have converted to PsA.

The PEST is a validated screening tool for patients with psoriasis to help identify concomitant inflammatory arthritis and was chosen given its ease of use as well as high quality results (sensitivity of 0.94 and specificity of 0.78)[42]. In addition to being performed during site visits, patients will be contacted electronically or by telephone every 12 weeks to complete the questionnaire. If a participant has a positive PEST, or contacts the study team at any point with new symptoms consistent with the development of PsA, an unscheduled visit will be pursued to determine if progression to synovio-entheseal disease has occurred. If an individual develops PsA, the trial endpoint is reached and a final study visit will be performed.

The primary endpoint is change from baseline in musculoskeletal PDUS total score at week 24 (Box 1). We hypothesize that there will be improvement of ultrasound-based imaging abnormalities at week 24 (Arm 1 vs. Arm 2). The co-primary end point is the proportion of participants developing PsA by modified CASPAR criteria at week 96. We hypothesize that treatment with guselkumab will lead to a decreased transition rate to PsA at year 2 when comparing combined Arm 1 and 2 with Arm 3. Secondary endpoints are outlined in Box 1. Biospecimens (i.e., plasma, peripheral blood mononuclear cells, skin swabs, and stool) will also be collected for further exploratory aims.

Box 1. PAMPA Study Endpoints

Co-primary outcomes

- **Improvement of musculoskeletal power doppler ultrasound imaging abnormalities at week 24 (Arm 1 vs. Arm 2)**
- **Decrease in transition rate to PsA at week 96 (Arm 1 + 2 vs. Arm 3)**

Secondary outcomes

- Transition to PsA at week 48 *(Arm 1 vs Arm 2)*
- Severity of PsA at the time of synovio-entheseal development at week 96 *(Arms 1+2 vs Arm 3)*: severity will be categorized as mild, moderate, or severe and additionally by continuous variables (e.g., joint and enthesis counts)
- Change from baseline in the ultrasound composite score of synovitis at week 24 *(Arm 1 vs Arm 2)*
- Change from baseline in the ultrasound composite score of enthesitis at week 24 *(Arm 1 vs Arm 2)*
- Change from baseline in BSA at week 24 *(Arm 1 vs Arm 2)*
- Achieved IGA score of 0 or 1 (yes, no) at week 24 *(Arm 1 vs Arm 2)*
- Changes in baseline FACIT-F score at weeks 24 (*Arm 1 vs. Arm 2)*
- Change in baseline EQ5D at week 24 (*Arm 1 vs Arm 2)*
- Change in baseline EQ5D at week 96 (*Arm 1 + Arm 2 vs Arm 3)*

Exploratory outcomes

- Musculoskeletal domain affected at PsA presentation (enthesitis, axial disease, peripheral arthritis) among those developing clinical PsA
- Presence and number of risk factors for PsA development at baseline (psoriasis phenotype; psoriasis severity; genetic predisposition; co-morbidities such as obesity)
- Association between risk factors and development of PsA at year 2

- Genetic, immune cell phenotype, and microbiome changes (cutaneous and intestinal) and their interactions with treatment assignment

PAMPA Preventing Arthritis in a Multicenter Psoriasis At Risk cohort study; PsA psoriatic arthritis; BSA body surface area; IGA investigators global assessment 2011; FACIT-F functional assessment of chronic illness therapy- fatigue; IDEOM MSK 8 international dermatology outcomes measures musculoskeletal 8.

Data management, quality control, and safety

Each participant will receive an individual study ID number upon enrollment, which will be used to link all data to the participant and help protect confidentiality. All clinical data will be entered directly into a central REDCap database housed at the data coordinating center (NYU Langone Health). Periodic audits will be performed to provide quality control and quality assurance.

Additionally, although guselkumab is an FDA-approved treatment for psoriasis, adverse events will be monitored and reported. Safety oversight will be under the direction of a Data and Safety Monitoring Board, which is composed of experienced dermatology and rheumatology trialists who are not affiliated with any participating site to ensure independence. They will also ensure data integrity and confidentiality; advise on any difficulties with study conduct or enrollment, sample size, and/or data collection; and review and evaluate requests for protocol modifications after the trial begins.

Sample size calculation

Sample size was calculated based on the primary outcome of conversion to PsA at year 2. Based on our previous work and available literature[1], we anticipate the conversion rate to PsA in this high-risk psoriasis group to be at least 5-6% per year in Arm 3 (standard of care) compared to 1.5-2% in the drug arms (Arm 1 and Arm 2). Time to conversion will be measured from time of randomization, and the two randomized arms will be compared using a two-sided chi-squared test with a Type I error rate of 0.05. Utilizing these conservative assumptions at a power of 80% and incorporating an expected attrition rate of approximately 10%, we aim to enroll 100 patients each in Arms 1 and 2 and, to increase the robustness of our sample size, at least 150 for Arm 3. Of note, sample size calculation for the co-primary endpoint of PDUS is less than that needed for PsA conversion and therefore, we will use the higher estimate to ensure both endpoints can be achieved.

Statistical analysis

The main statistical analysis will be performed at week 24 and week 96. The primary efficacy outcomes will be analyzed for the intention-to-treat population, and the two-sided alternative hypotheses will be tested against the null of no difference at significance level of 0.05. Descriptive statistics will be summarized as counts and proportions for categorical data; mean, standard deviation, median, interquartile range, minimum, and maximum for continuous data as appropriate. The primary endpoint of change from baseline in PDUS score at week 24 will be analyzed using a mixed-effects model for repeated measures (MMRM), with treatment group (Arm 1 vs. Arm 2) and baseline variables as fixed effects, and study sites as the random effects. Least-squares mean and 95% confidence interval of the difference in treatment effect will be reported based on the fitted MMRM. The co-primary endpoint of PsA transition rate at week 96 will be analyzed by Chi-squared test of proportions comparing the combined Arm 1 and 2 vs. Arm 3. We will further fit generalized linear mixed-effect model (GLMM) with logit link to evaluate the treatment effect on the transition status with treatment group (Arm 1+2 vs. Arm 3) and baseline variables as fixed effects, and study sites as random effects. The raw and adjusted odds ratio of PsA transition and corresponding 95% confidence interval will be reported. Similarly, secondary endpoints will be assessed using MMRM and GLMM for continuous and

binary outcomes, respectively. Transformation of the outcome variables will be considered if the distribution deviates from normality.

Ethics and dissemination
The study will be performed according to the ethical principles of the Declaration of Helsinki, the International Conference of Harmonization Good Clinical Practice guidelines, and local regulations. The study is approved by the coordinating center's (NYU) Institutional Review Board (IRB; s20-01158) and each participating site has also received ethics approval through their own IRB/Research Ethics Board. All patients will be required to provide written informed consent to participate.

Study information is publicly available at www.clinicaltrials.gov. The results of this trial will be published in peer-reviewed journals and presented at academic conferences nationally and internationally.

Patient and public involvement
Patients and the public were not involved in the development of this study.

Discussion
PsA is a chronic inflammatory disease that, despite significant progress in therapeutic options, continues to offer clinically meaningful outcomes in less than 50% of patients. One strategy for improving these outcomes has focused on early and aggressive intervention. The TICOPA study, an open label randomized control trial using methotrexate, showed significant improvement in joint outcomes in the tight control group compared to standard of care, with almost twice the odds of achieving an ACR 20 response[43]. However, despite this finding, within the tight control group, only 62% achieved an ACR20 response by week 48, and only 51% and 38% met criteria for the ACR50 or the ACR70 response.

Therefore, preventive interventional strategies are now of great interest since psoriatic plaques effectively demarcate a pre-clinical disease state from which up to 30% of patients will transition to clinically evident PsA. Who among those patients will ultimately go on to develop synovio-entheseal inflammation, and how to delay or alter the course of that journey, are questions being actively investigated. Two small, nonrandomized studies have looked at the effect of anti-cytokine therapy on patients with psoriasis and imaging abnormalities. As part of the prospective IVEPSA study, 20 psoriasis patients with evidence of very early PsA (based on inflammatory or erosive changes on HR-pQCT or MRI) were given an IL-17 blocking agent[44]. After 24 weeks, patients demonstrated improvement in pain and imaging scores. Savage *et al* followed 23 patients with psoriasis and PDUS abnormalities treated with ustekinumab, and found reduced inflammatory scores by week 12 that were maintained through week 52[45]. While these findings are encouraging, neither study had a control group to better understand possible inherent disease fluctuations in imaging findings. Furthermore, the sample sizes and follow up periods did not allow for any estimates of progression to true PsA by CASPAR criteria.

Recent retrospective observational studies have sought to address the question of whether treatment with biologic agents in psoriasis has an impact on PsA development. However, these studies reported disparate results and reached different conclusions [46-50]. These discrepancies may relate to the populations studied. Gisondi *et al*, Rosenthal *et al*, and Acosta Felquer *et al* looked at dermatology-based psoriasis populations and found decreased risk of PsA progression with the use of biologics. In contrast, Ogdie *et al* and Merola *et* al, using population-based cohorts, found an increased risk of PsA progression for those on biologics, possibly related to confounding by indication and delayed timing of receiving a diagnosis of PsA.

The only prospective cohort study of psoriasis and the risk of PsA found that anti-TNF agents did not impact the risk of PsA development[28]. Even the studies that are congruent with the PAMPA study hypothesis that aggressive treatment of psoriasis reduces the risk of PsA, need to be viewed with caution and cannot be interpreted causally[51]. In particular, the groups of patients being compared are not equivalent and the potential for confounding by indication and prognosis is considerable. There are likely unmeasured variables contributing to the choice of medication by providers. These studies are also susceptible to protopathic bias, where a certain therapy (i.e., biologics) may be prescribed because patients have symptoms of, or undiagnosed, disease (i.e., PsA) which are not captured. Survival bias may also play a role as patients must "survive" without synovio-entheseal involvement to receive a biologic, which leads to differences between groups, especially in terms of disease duration. To address these concerns and discrepancies, we propose the first randomized controlled trial looking at the effect of highly effective targeted therapy on the progression from skin psoriasis to PsA.

We also aim to better understand the role of imaging in psoriatic disease, which has increased in use dramatically over the last decade. Ultrasound imaging modalities, in particular, have the potential to improve the definition of meaningful subclinical inflammation. While other imaging modalities, such as high-resolution peripheral quantitative computed tomography or MRI, have been used, ultrasound is easily accessible, has few (if any) contraindications, and is already being applied in clinical settings. Therefore, the proposed study will also employ the use of musculoskeletal PDUS as a co-primary outcome to assess for subclinical evidence of inflammation. Psoriasis patients with imaging abnormalities have an increased risk of progression to PsA[33, 34]. However, the specific threshold of abnormalities that correlate with future synovio-entheseal disease and the targeted treatments that ameliorate these findings and/or halt transition to PsA remain to be elucidated. The inclusion of PDUS in the PAMPA study is manifestly intended to address these gaps in knowledge.

Additionally, participants will be biosampled to characterize yet unidentified genetic, immunologic, and microbiome factors that influence progression[24]. The most significant advances in our understanding of the pathogenesis of the psoriasis to PsA continuum is the pivotal role played by a pro-inflammatory subset of CD4+ T helper (Th) cells known as Th17 cells[52]. Th17 and other Type-17 cells are activated by IL-23 to secrete IL-17A, IL-17F and IL-22 which act on resident, epithelial and endothelial cells to, in turn, elicit the production of multiple cytokines and chemokines, often leading to the recruitment of other inflammatory cells and the activation of innate defense mechanisms[53]. In particular, elevation of Type-17 cell subsets have been observed in peripheral blood, skin and joints of patients with psoriasis and PsA [54, 55]. Studies of synovial fluid cells and psoriatic plaques also revealed a major role for IL-23 receptor high, CD8+ cells that release IL-17 in disease pathogenesis[56, 57]. Another well-established long-term outcome of joint inflammation in PsA is the development of both bony erosions and pathologic new bone formation as a consequence of dysfunctional osteoblast and osteoclast activity. Murine studies showed that both IL-17 and TNF are important in driving abnormal bone resorption, while IL-22 may contribute to osteoproliferation[58, 59]. We and others have demonstrated that patients with PsA have an increase in the osteoclast precursor population in their peripheral blood. A better characterization of this population could ultimately serve as a distinctive biomarker for early detection of PsA and as a potential target for arthritis prevention. Similarly, there is increasing evidence that the microbiome, the collection of microorganisms harbored by humans, is another potential triggering factor in the progression. Perturbations of microbial homeostasis (dysbiosis) has been associated with an inflammatory process characteristic of most immune-mediated diseases[60]. In fact, several studies have established a link between microbial dysbiosis and psoriatic disease, both in the skin and in the gut[61-65]. Despite this knowledge, critical gaps in our understanding of PsA etiology and the

triggers behind IL-23-driven Type-17 cell expansion and downstream pro-inflammatory cytokine production in the skin and joints greatly hinder our ability to identify pre-clinical arthritis in psoriasis patients. The prospective nature of the current study, which includes biosampling of participants, will also allow us to make contributions to our understanding of the underlying pathogenesis and immune endotypes in the psoriasis to PsA continuum.

While the PAMPA study has the potential to greatly expand our comprehension of pre-clinical PsA and possibly revolutionize care, we acknowledge a number of limitations. First, the follow-up period for capturing progression to synovio-entheseal disease is confined to a relatively short period of time, especially given that the average time to progression is 5-7 years. To mitigate this, the protocol pre-specifies that at least 30% of the included population have psoriasis for at least 2 years, ensuring that a robust portion of participants will fit into this time period during the trial.

Second, is the chosen therapeutic approach. We have chosen a selective IL-23 inhibitor, guselkumab, for this interventional trial given its known role in psoriatic disease pathogenesis, its high efficacy and reassuring safety profile[66-68], its status as FDA-approved treatment for psoriasis and PsA, and the prior evidence of improvement in subclinical imaging findings. However, valid arguments may exist for utilizing targeted medications with other mechanisms of action (such as TNF inhibitors, IL-17 inhibitors, Janus kinase inhibitors or phosphodiesterase 4 inhibitors). Further trials targeting different (known or yet to be discovered) cytokines/molecules will be needed to characterize the preventive potential of various pathway-specific therapeutics.

Importantly, the proposed study's population (i.e., patients with psoriasis at-increased risk of progression) represents both a strength and a limitation of this trial. Enrolling enough participants to address progression in a non-enriched psoriasis population would be prohibitive for this study, and many of its kind, given the annual transition rate of up to 3%. We have addressed this by selecting an enriched cohort of patients with psoriasis at-increased risk of progression based on prior data regarding risk factors. These include psoriasis duration, skin inflammatory burden, and evidence of subclinical inflammation on imaging. Overall, it is expected that PAMPA study participants will have a higher annual rate of progression, which will allow for the enrollment of less patients and still assess our primary outcome. Furthermore, by virtue of the pre-specified inclusion criteria, participants will already qualify for the use of biologic therapy (based on moderate to severe psoriasis involvement) which would offer a clear and significant benefit. Conversely, though, by pre-defining the study population and confining to those with previously identified risk factors, the study results may prevent us from assessing the impact and/or relative weight of these features for PsA progression outside of the pre-defined population. Additionally, the obtained outcomes may only be partially generalizable to the broader psoriasis patient population. We also acknowledge, in the assessment of progression, Arm 3 is not a direct comparator for Arms 1 and 2 as these participants are choosing not to be exposed to biologics, creating an inherent selection bias. However, this remains the only feasible and ethical comparator group.

The PAMPA study will provide a first-in-kind, unique framework through which the field can better understand the clinical, genetic, immunologic, and environmental factors that may influence and determine progression to PsA. If successful, the study will also provide a novel approach to improve outcomes in psoriatic arthritis.

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Competing interests
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References

1. Ogdie, A. and P. Weiss, *The Epidemiology of Psoriatic Arthritis.* Rheum Dis Clin North Am, 2015. **41**(4): p. 545-68.
2. Ritchlin, C.T., R.A. Colbert, and D.D. Gladman, *Psoriatic Arthritis.* N Engl J Med, 2017. **376**(10): p. 957-970.
3. Eder, L., et al., *Incidence of arthritis in a prospective cohort of psoriasis patients.* Arthritis Care Res (Hoboken), 2011. **63**(4): p. 619-22.
4. Lee, S., A. Mendelsohn, and E. Sarnes, *The Burden of Psoriatic Arthritis: A Literature Review from a Global Health Systems Perspective.* P T, 2010. **35**(12): p. 680-689.
5. Husted, J.A., et al., *Health-related quality of life of patients with psoriatic arthritis: a comparison with patients with rheumatoid arthritis.* Arthritis Rheum, 2001. **45**(2): p. 151-8.
6. Kimball, A.B., et al., *The psychosocial burden of psoriasis.* Am J Clin Dermatol, 2005. **6**(6): p. 383-92.
7. Tillett, W., et al., *Factors influencing work disability in psoriatic arthritis: first results from a large UK multicentre study.* Rheumatology (Oxford), 2015. **54**(1): p. 157-62.
8. Haroon, M., P. Gallagher, and O. FitzGerald, *Diagnostic delay of more than 6 months contributes to poor radiographic and functional outcome in psoriatic arthritis.* Ann Rheum Dis, 2015. **74**(6): p. 1045-50.
9. Armstrong, A.W., et al., *Undertreatment, treatment trends, and treatment dissatisfaction among patients with psoriasis and psoriatic arthritis in the United States: findings from the National Psoriasis Foundation surveys, 2003-2011.* JAMA Dermatol, 2013. **149**(10): p. 1180-5.
10. Scher, J.U., *The 2018 landscape of RA, PsA, and SpA pathogenesis.* Curr Opin Rheumatol, 2017.
11. Armstrong, A.W., et al., *From the Medical Board of the National Psoriasis Foundation: Treatment targets for plaque psoriasis.* Journal of the American Academy of Dermatology. **76**(2): p. 290-298.
12. McInnes, I.B., et al., *Secukinumab, a human anti-interleukin-17A monoclonal antibody, in patients with psoriatic arthritis (FUTURE 2): a randomised, double-blind, placebo-controlled, phase 3 trial.* Lancet, 2015. **386**(9999): p. 1137-46.
13. Mease, P.J., et al., *Ixekizumab, an interleukin-17A specific monoclonal antibody, for the treatment of biologic-naive patients with active psoriatic arthritis: results from the 24-week randomised, double-blind, placebo-controlled and active (adalimumab)-controlled period of the phase III trial SPIRIT-P1.* Ann Rheum Dis, 2016.
14. Mease, P.J., et al., *Adalimumab for the treatment of patients with moderately to severely active psoriatic arthritis: results of a double-blind, randomized, placebo-controlled trial.* Arthritis Rheum, 2005. **52**(10): p. 3279-89.
15. Ritchlin, C. and J.U. Scher, *Strategies to Improve Outcomes in Psoriatic Arthritis.* Curr Rheumatol Rep, 2019. **21**(12): p. 72.

16. Haberman, R.H., R. Castillo, and J.U. Scher, *Induction of remission in biologic-naive, severe psoriasis and PsA with dual anti-cytokine combination.* Rheumatology (Oxford), 2021. **60**(7): p. e225-e226.
17. Deane, K.D. and H. El-Gabalawy, *Pathogenesis and prevention of rheumatic disease: focus on preclinical RA and SLE.* Nat Rev Rheumatol, 2014. **10**(4): p. 212-28.
18. Olsen, N.J. and D.R. Karp, *Autoantibodies and SLE: the threshold for disease.* Nat Rev Rheumatol, 2014. **10**(3): p. 181-6.
19. Burmester, G.R. and J.E. Pope, *Novel treatment strategies in rheumatoid arthritis.* The Lancet, 2017. **389**(10086): p. 2338-2348.
20. Gerlag, D.M., et al., *Effects of B-cell directed therapy on the preclinical stage of rheumatoid arthritis: the PRAIRI study.* Ann Rheum Dis, 2019. **78**(2): p. 179-185.
21. *Study of Anti-Malarials in Incomplete Lupus Erythematosus (SMILE)*. Available from: https://clinicaltrials.gov/show/NCT03030118.
22. *Strategy to Prevent the Onset of Clinically-Apparent Rheumatoid Arthritis (StopRA)*. Available from: https://clinicaltrials.gov/ct2/show/study/NCT02603146.
23. Al-Laith, M., et al., *Arthritis prevention in the pre-clinical phase of RA with abatacept (the APIPPRA study): a multi-centre, randomised, double-blind, parallel-group, placebo-controlled clinical trial protocol.* Trials, 2019. **20**(1): p. 429.
24. Scher, J.U., et al., *Preventing psoriatic arthritis: focusing on patients with psoriasis at increased risk of transition.* Nat Rev Rheumatol, 2019. **15**(3): p. 153-166.
25. Perez-Chada, L.M., et al., *Consensus terminology for preclinical phases of psoriatic arthritis for use in research studies: results from a Delphi consensus study.* Nat Rev Rheumatol, 2021. **17**(4): p. 238-243.
26. Eder, L., et al., *The Development of Psoriatic Arthritis in Patients With Psoriasis Is Preceded by a Period of Nonspecific Musculoskeletal Symptoms: A Prospective Cohort Study.* Arthritis Rheumatol, 2017. **69**(3): p. 622-629.
27. Li, W., J. Han, and A.A. Qureshi, *Obesity and risk of incident psoriatic arthritis in US women.* Ann Rheum Dis, 2012. **71**(8): p. 1267-72.
28. Eder, L., et al., *The Incidence and Risk Factors for Psoriatic Arthritis in Patients With Psoriasis: A Prospective Cohort Study.* Arthritis Rheumatol, 2016. **68**(4): p. 915-23.
29. Wilson, F.C., et al., *Incidence and clinical predictors of psoriatic arthritis in patients with psoriasis: a population-based study.* Arthritis Rheum, 2009. **61**(2): p. 233-9.
30. Soltani-Arabshahi, R., et al., *Obesity in early adulthood as a risk factor for psoriatic arthritis.* Arch Dermatol, 2010. **146**(7): p. 721-6.
31. Chandran, V., et al., *Familial aggregation of psoriatic arthritis.* Ann Rheum Dis, 2009. **68**(5): p. 664-7.
32. Patrick, M.T., et al., *Genetic signature to provide robust risk assessment of psoriatic arthritis development in psoriasis patients.* Nat Commun, 2018. **9**(1): p. 4178.

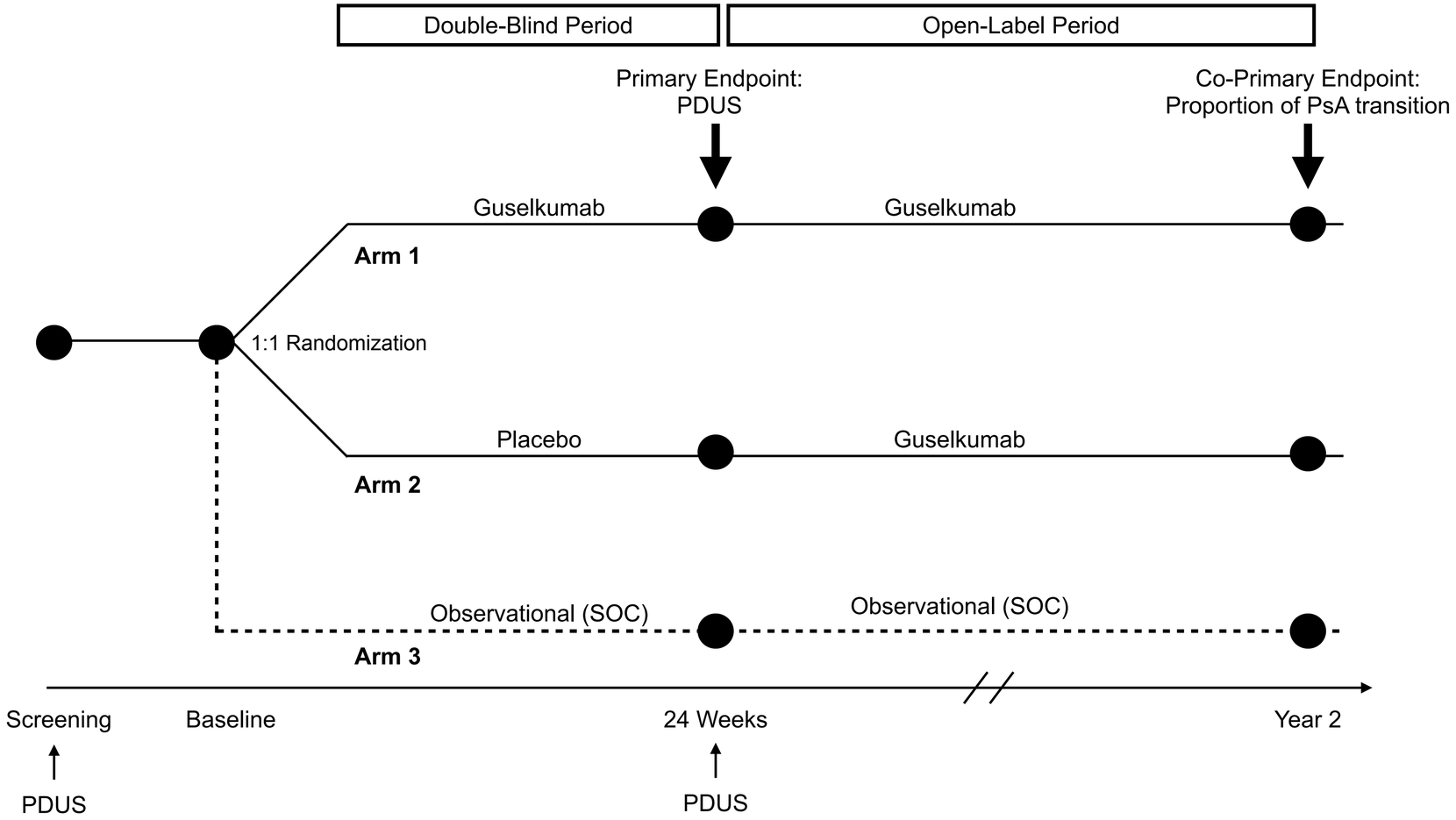
33. Simon, D., et al., *Structural entheseal lesions in patients with psoriasis are associated with an increased risk of progression to psoriatic arthritis.* Arthritis Rheumatol, 2020.
34. Faustini, F., et al., *Subclinical joint inflammation in patients with psoriasis without concomitant psoriatic arthritis: a cross-sectional and longitudinal analysis.* Annals of the Rheumatic Diseases, 2016. **75**(12): p. 2068-2074.
35. Kocijan, R., et al., *Quantitative and Qualitative Changes of Bone in Psoriasis and Psoriatic Arthritis Patients.* Journal of Bone and Mineral Research, 2015. **30**(10): p. 1775-1783.
36. Blauvelt, A., et al., *Efficacy and safety of guselkumab, an anti-interleukin-23 monoclonal antibody, compared with adalimumab for the continuous treatment of patients with moderate to severe psoriasis: Results from the phase III, double-blinded, placebo- and active comparator–controlled VOYAGE 1 trial.* Journal of the American Academy of Dermatology, 2017. **76**(3): p. 405-417.
37. Anja Ficjan, et al., *Ultrasound composite scores for the assessment of inflammatory and structural pathologies in Psoriatic Arthritis (PsASon-Score).* Arthritis Res Ther, 2014. **16**(5): p. 476.
38. Taylor W, Gladman D, and e.a. Helliwell P, *Classification criteria for psoriatic arthritis: development of new criteria from a large international study.* Arthritis Rheum, 2006. **54**: p. 2665-73.
39. R Core Team, *R: A language and environment for statistical computing. .* R Foundation for Statistical Computing, Vienna, Austria.
40. PA Harris, et al., *Research electronic data capture (REDCap) – A metadata-driven methodology and workflow process for providing translational research informatics support.* J Biomed Inform. , 2009. **42**(2): p. 377-81.
41. Thiele, R., et al., *Serum, Cellular and Imaging Markers of Arthritis in Psoriasis Patients and Healthy Controls [abstract].* Arthritis Rheumatol, 2018. **70**.
42. Helliwell, P.S., *Psoriasis epidemiology screening tool (PEST): A report from the GRAPPA 2009 annual meeting.* J. Rheumatol. . **38**: p. 551-552.
43. Coates, L.C., et al., *Effect of tight control of inflammation in early psoriatic arthritis (TICOPA): a UK multicentre, open-label, randomised controlled trial.* Lancet, 2015. **386**(10012): p. 2489-98.
44. Kampylafka, E., et al., *Disease interception with interleukin-17 inhibition in high-risk psoriasis patients with subclinical joint inflammation—data from the prospective IVEPSA study.* Arthritis Research & Therapy, 2019. **21**(1): p. 178.
45. Savage, L., et al., *Regression of Peripheral Subclinical Enthesopathy in Therapy-Naive Patients Treated With Ustekinumab for Moderate-to-Severe Chronic Plaque Psoriasis: A Fifty-Two-Week, Prospective, Open-Label Feasibility Study.* Arthritis Rheumatol, 2019. **71**(4): p. 626-631.
46. Meer, E., et al., *Does biologic therapy impact the development of PsA among patients with psoriasis?* Ann Rheum Dis, 2021.
47. Acosta Felquer, M.L., et al., *Treating the skin with biologics in patients with psoriasis decreases the incidence of psoriatic arthritis.* Annals of the Rheumatic Diseases, 2021: p. annrheumdis-2021-220865.

48. Gisondi, P., et al., *Biological disease-modifying antirheumatic drugs may mitigate the risk of psoriatic arthritis in patients with chronic plaque psoriasis.* Annals of the Rheumatic Diseases, 2021: p. annrheumdis-2021-219961.
49. Rosenthal, Y.S., et al., *Incidence of Psoriatic Arthritis Among Patients Receiving Biologic Treatments for Psoriasis: A Nested Case–Control Study.* Arthritis & Rheumatology. **n/a**(n/a).
50. Merola, J.F., et al., *Incidence and prevalence of psoriatic arthritis in patients with psoriasis stratified by psoriasis disease severity: Retrospective analysis of an electronic health records database in the United States.* J Am Acad Dermatol, 2021.
51. Merola, J.F. and A. Ogdie, *Does psoriasis treatment affect PsA development?* Nat Rev Rheumatol, 2021. **17**(12): p. 708-709.
52. Annunziato, F., et al., *Phenotypic and functional features of human Th17 cells.* J Exp Med, 2007. **204**(8): p. 1849-61.
53. Korn, T., et al., *IL-17 and Th17 Cells.* Annu Rev Immunol, 2009. **27**: p. 485-517.
54. Leipe, J., et al., *Role of Th17 cells in human autoimmune arthritis.* Arthritis Rheum, 2010. **62**(10): p. 2876-85.
55. Cauli, A. and A. Mathieu, *Th17 and interleukin 23 in the pathogenesis of psoriatic arthritis and spondyloarthritis.* J Rheumatol Suppl, 2012. **89**: p. 15-8.
56. Menon, B., et al., *Interleukin-17+CD8+ T cells are enriched in the joints of patients with psoriatic arthritis and correlate with disease activity and joint damage progression.* Arthritis Rheumatol, 2014. **66**(5): p. 1272-81.
57. Clark, R.A., *Resident memory T cells in human health and disease.* Sci Transl Med, 2015. **7**(269): p. 269rv1.
58. Mitra, A., S.K. Raychaudhuri, and S.P. Raychaudhuri, *Functional role of IL-22 in psoriatic arthritis.* Arthritis Res Ther, 2012. **14**(2): p. R65.
59. Sherlock, J.P., et al., *IL-23 induces spondyloarthropathy by acting on ROR-gammat+ CD3+CD4-CD8- entheseal resident T cells.* Nat Med, 2012. **18**(7): p. 1069-76.
60. Clemente, J.C., J. Manasson, and J.U. Scher, *The role of the gut microbiome in systemic inflammatory disease.* BMJ, 2018. **360**: p. j5145.
61. Dei-Cas, I., et al., *Metagenomic analysis of gut microbiota in non-treated plaque psoriasis patients stratified by disease severity: development of a new Psoriasis-Microbiome Index.* Sci Rep, 2020. **10**(1): p. 12754.
62. Chen, D., et al., *Microbiome and Metabolome Analyses Reveal Novel Interplay Between the Skin Microbiota and Plasma Metabolites in Psoriasis.* Front Microbiol, 2021. **12**: p. 643449.
63. Olejniczak-Staruch, I., et al., *Alterations of the Skin and Gut Microbiome in Psoriasis and Psoriatic Arthritis.* Int J Mol Sci, 2021. **22**(8).
64. Scher, J.U., et al., *Decreased bacterial diversity characterizes the altered gut microbiota in patients with psoriatic arthritis, resembling dysbiosis in inflammatory bowel disease.* Arthritis Rheumatol, 2015. **67**(1): p. 128-39.
65. Manasson, J., et al., *Interleukin-17 Inhibition in Spondyloarthritis Is Associated With Subclinical Gut Microbiome Perturbations and a Distinctive Interleukin-25-Driven Intestinal Inflammation.* Arthritis Rheumatol, 2020. **72**(4): p. 645-657.

66. Reich, K., et al., *Guselkumab versus secukinumab for the treatment of moderate-to-severe psoriasis (ECLIPSE): results from a phase 3, randomised controlled trial.* Lancet, 2019. **394**(10201): p. 831-839.
67. Blauvelt, A., et al., *Efficacy and safety of guselkumab, an anti-interleukin-23 monoclonal antibody, compared with adalimumab for the continuous treatment of patients with moderate to severe psoriasis: Results from the phase III, double-blinded, placebo- and active comparator-controlled VOYAGE 1 trial.* J Am Acad Dermatol, 2017. **76**(3): p. 405-417.
68. Rahman, P., et al., *Pooled Safety Results Through 1 Year of 2 Phase III Trials of Guselkumab in Patients With Psoriatic Arthritis.* J Rheumatol, 2021. **48**(12): p. 1815-1823.

FIGURE LENGEND

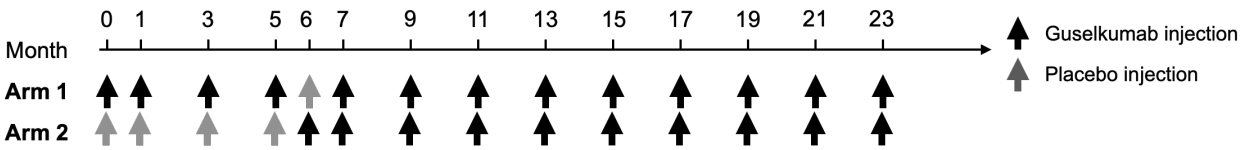
Figure 1. Study Design of the PAMPA Study. PAMPA Preventing Arthritis in a Multicenter Psoriasis At Risk cohort study; PDUS power doppler ultrasound; PsA psoriatic arthritis; SOC standard of care.


Double-Blind Period
Open-Label Period
Primary Endpoint:
PDUS
Co-Primary Endpoint:
Proportion of PsA transition
Guselkumab
Guselkumab
Arm 1
1:1 Randomization
Placebo
Guselkumab
Arm 2
Observational (SOC)
Observational (SOC)
Arm 3
Screening
Baseline
24 Weeks
Year 2
PDUS
PDUS

Supplement to

Efficacy of Guselkumab, a selective IL-23 inhibitor, in Preventing Arthritis in a Multi-center Psoriasis At-Risk cohort (PAMPA): protocol of a randomized, double-blind, placebo controlled multicenter trial

Rebecca H. Haberman, MD, MSCI[1+]; Katrina A. MacFarlane, MSc[1+]; Sydney Catron, BS[1+]; Jonathan Samuels, MD[1]; Rebecca B. Blank, MD, PhD[1]; Michael Toprover, MD[1]; Zakwan Uddin, BA[1]; Jiyuan Hu, PhD[2]; Rochelle L. Castillo, MD, MSCI[1]; Cinty Gong, PhD[3]; Kun Qian, MS[2]; Vincent Piguet, MD[4], PhD; Francisco Tausk, MD[5]; Jensen Yeung, MD[4]; Andrea L. Neimann, MD[6], Wayne P. Gulliver, MD[7]; Ralf G. Thiele, MD[8] Joseph F. Merola, MD, MMSc[9]; Alexis Ogdie, MD, MSCE[10]; Proton Rahman, MD[11]; Soumya D. Chakravarthy, MD, PhD[3,12]; Lihi Eder, MD[13]; Christopher T. Ritchlin MD, MPH[8]*; and Jose U. Scher, MD[1]*



Supplementary Figure 1. Drug and placebo schedule. Black arrows indicate guselkumab injection, gray arrows indicate placebo injection.

Supplementary Methods

Participating Sites

New York University Langone Health and Langone Orthopedic Hospital (coordinating center)
University of Toronto and Women's College Hospital
University of Rochester Medical Center
Memorial University of Newfoundland
Brigham and Women's Hospital, Harvard Medical School
Perelman School of Medicine at the University of Pennsylvania (alternate site)

Ultrasound Protocol

All sites will be scanned longitudinally and any pathology detected in the longitudinal plane will be confirmed in the transverse plane. The following sites will be scanned bilaterally:

Entheseal sites:

1. Quadriceps insertion at the superior pole of patella
2. Patellar ligament origin at the distal pole of patella
3. Patellar ligament insertion at the tibial tuberosity
4. Achilles tendon insertion into the calcaneus
5. Plantar fascia insertion into the calcaneus
6. Common extensor tendon insertion into the lateral epicondyle

Joints:

1. Wrist (radio-carpal, mid-carpal)
2. Metacarpophalangeal, proximal interphalangeal, distal interphalangeal joints (digits 1-5)

Tendon sheaths and tendons:

1. In the dorsal wrist: Compartment 4 (extensor digitorum) and 6 (extensor carpi ulnaris)
2. In the dorsal hand: Extensor digitorum 1-5 at the level of the MCP joint
3. In the palmar hand: Flexor digitorum 1-5

Rochester-Modified PsASon Scoring System

The lowest RM-PsASon score a participant may have at baseline is 0. The highest RM-PsASon score a participant may have at baseline is 614.

1) **Synovitis and power Doppler signal/joint[1]:** Graded from 0-3 as absent, mild, moderate or severe according to images of a reference atlas.
PD signal: 0=no PD-signal, 1=up to three single or two confluent signals, 2=less than half of the visible intracapsular area and 3=half or more of the visible intracapsular area covered by PD-signals.

2) **Bone erosions/joint[2]**: Score is based on maximal diameter of cortical break.
Grade 0: no erosion, grade 1: erosion of <2 mm, grade 2: erosion of >2 mm, grade 3: large destruction of the joint

3) **Osteophytes/joint[2]**:Score is based on maximal distance between the 'original' and new cortical lining (=maximal height)
Grade 0: no osteophyte, grade 1: osteophyte of <1 mm, grade 2: osteophyte of >1 mm, grade 3: large and diffuse osteophytes

4) **Peritendinitis/fingers**[3]: The presence of peritendinitis is assessed at dorsal scans of MCP 2-5 and is characterized by hypoechoic swelling of the soft tissue surrounding the extensor digitorum tendon, with or without peri-tendinous PD-signals. B-mode (B-perisyn) as well as PD-findings in perisynovial tissue (PD-perisyn) and is graded with 0=absent or 1=present.

5) **Enthesitis**[4]: Enthesitis is graded according to Madrid Sonographic Enthesis Index (MASEI): Structure is considered pathological (score=1) if there is a loss of fibrillar pattern, hypoechoic aspect, or fusiform thickening of the entheses. Erosions are defined as a cortical breakage with a step-down contour defect at the attachment of entheses at bone and graded with 0=absent or 3=present. Fascia and tendon thickness are measured at the point of maximal thickness on the bony insertion and graded with 0=normal or 1=thickened according to the reference values of the MASEI index. Enthesophytes are defined as calcifications at the entheses insertions into bone and graded with 0=absent, 1=small calcification, 2=clear presence of enthesophyte/calcification, 3= large calcifications or ossifications. PD-signals within entheses are scored with 0=absent or 3=present. Bursitis is investigated at the level of distal patellar tendon (infrapatellar bursitis) and the level of Achilles tendon insertion (retrocalcaneal bursitis) and graded with 0=absent and 1=present.

IDEOM MSK Questionnaire (IDEOM MSK-Q)

The IDEOM MSK-Q was developed by the International Dermatology Outcomes Measures (IDEOM). The IDEOM MSK-Q is patient-reported outcome measure (PROM) to identify musculoskeletal (MSK) symptoms and measure their intensity and impact on health-related quality of life in patients with psoriatic disease. It was developed to be used in research and clinical practice settings.

- The IDEOM MSK-Q consists of 9 questions evaluating 3 constructs
    - Musculoskeletal symptoms: pain, joint swelling, joint stiffness
    - Impact of musculoskeletal symptoms: work and/or school activities; family, social and/or leisure activities; physical activity, sleep, emotional state)
    - Fatigue.

- The content validity (i.e., relevance, comprehensiveness, and comprehensibility) of the tool was assessed in a multi-phase pilot testing study. This pilot testing study included: (1) an online survey with trained patient-research partners (PRPs) with psoriatic disease, in-person discussions, (2) voting including PRPs, clinicians, researchers, and other relevant stakeholders, and (3) semi-structured interviews with patients with psoriatic disease from a tertiary center using the Three-step test interview technique. Data was analyzed using NVivo Software. During the pilot testing, the instrument was modified, refined, and re-tested until the content validity of the instrument was deemed sufficient and no more changes were suggested by patients.

References

1. Hammer HB, Bolton-King P, Bakkeheim V, et al. Examination of intra and interrater reliability with a new ultrasonographic reference atlas for scoring of synovitis in patients with rheumatoid arthritis. *Ann Rheum Dis* 2011;70(11):1995-8. doi: 10.1136/ard.2011.152926 [published Online First: 2011/07/26]
2. Finzel S, Ohrndorf S, Englbrecht M, et al. A detailed comparative study of high-resolution ultrasound and micro-computed tomography for detection of arthritic bone erosions. *Arthritis Rheum* 2011;63(5):1231-6. doi: 10.1002/art.30285 [published Online First: 2011/05/04]

3. Gutierrez M, Filippucci E, De Angelis R, et al. Subclinical entheseal involvement in patients with psoriasis: an ultrasound study. *Semin Arthritis Rheum* 2011;40(5):407-12. doi: 10.1016/j.semarthrit.2010.05.009 [published Online First: 2010/08/07]
4. de Miguel E, Cobo T, Munoz-Fernandez S, et al. Validity of enthesis ultrasound assessment in spondyloarthropathy. *Ann Rheum Dis* 2009;68(2):169-74. doi: 10.1136/ard.2007.084251 [published Online First: 2008/04/09]

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym *Page 1*
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry *Page 2*
	2b	All items from the World Health Organization Trial Registration Data Set *N/A*
Protocol version	3	Date and version identifier *N/A*
Funding	4	Sources and types of financial, material, and other support *Page 1 and Page 12*
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors *Page 1*
	5b	Name and contact information for the trial sponsor *Page 1*
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities *Page 13*
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) *N/A*
Introduction		
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention *Page 4-5*
	6b	Explanation for choice of comparators *Page 5, paragraph 3*
Objectives	7	Specific objectives or hypotheses *Page 5, paragraph 2*

Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) *Page 5, paragraph 3*
Methods: Participants, interventions, and outcomes		
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained *Page 5, paragraph 4*
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) *Page 5-6, Table 1*
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered *Page 6, paragraph 2, Table 2*
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) *N/A*
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests). *N/A*
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial *Page 6, paragraph 2*
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended *Page 7-8, Box 1*
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) *Table 2, Figure*
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations *Page 8, paragraph 3*
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size *Page 5, paragraph 4*
Methods: Assignment of interventions (for controlled trials)		
Allocation:		

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions *Page 6, paragraph 2*
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned *N/A*
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions *N/A*
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how *Page 7, paragraph 1 and 2*
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial *Supplementary Consent form, page 2*
Methods: Data collection, management, and analysis		
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol *Page 7, paragraph 2*
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols *N/A*
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol *Page 9, paragraph 1*
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol *Page 9, paragraph 4*
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses) *Page 9, paragraph 4*

	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) *Page 9, paragraph 4*
Methods: Monitoring		
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed *Page 9, paragraph 2*
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial *N/A*
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct *Page 9, paragraph 2*
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor *N/A*
Ethics and dissemination		
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval *Page 9, paragraph 5*
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) *N/A*
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) *Page 10, paragraph 1, Sample consent form*
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable *N/A*
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial *page 9, paragraph 1*
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site *Page 13*
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators *N/A*

Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation *N/A*
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions *Page 2*
	31b	Authorship eligibility guidelines and any intended use of professional writers *N/A*
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code *N/A*
Appendices		
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates *Supplement*
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.