BMJ Open

Efficacy of guselkumab, a selective IL-23 inhibitor, in Preventing Arthritis in a Multicentre Psoriasis At-Risk cohort (PAMPA): protocol of a randomised, double-blind, placebo controlled multicentre trial

Rebecca H Haberman ,[1] Katrina A MacFarlane,[1] Sydney Catron,[1] Jonathan Samuels,[1] Rebecca B Blank,[1] Michael Toprover,[1] Zakwan Uddin,[1] Jiyuan Hu,[2] Rochelle Castillo,[1] Cinty Gong,[3] Kun Qian,[2] Vincent Piguet,[4,5] Francisco Tausk,[6] Jensen Yeung,[5] Andrea L Neimann,[1] Wayne Gulliver,[7] Ralf G Thiele,[8] Joseph F Merola,[9,10] Alexis Ogdie,[11] Proton Rahman,[12] Soumya D Chakravarty ,[3,13] Lihi Eder,[14] C T Ritchlin ,[8] Jose U Scher[1]

To cite: Haberman RH, MacFarlane KA, Catron S, *et al*. Efficacy of guselkumab, a selective IL-23 inhibitor, in Preventing Arthritis in a Multicentre Psoriasis At-Risk cohort (PAMPA): protocol of a randomised, double-blind, placebo controlled multicentre trial. *BMJ Open* 2022;**12**:e063650. doi:10.1136/bmjopen-2022-063650

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2022-063650).

RHH and KAM contributed equally.
CTR and JUS contributed equally.

Received 06 April 2022
Accepted 14 December 2022

For numbered affiliations see end of article.

Correspondence to
Dr Jose U Scher;
jose.scher@nyulangone.org

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 Food and Drug Administration (FDA)-approved for treatment of moderate-to-severe psoriasis and PsA. The Preventing Arthritis in a Multicentre 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 multicentre, randomised, 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 with non-biological 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 randomised (1:1) to receive either guselkumab 100 mg (arm 1) or placebo switching to guselkumab 100 mg starting at week 24 (arm 2). Arm 3 will follow 150 at-risk psoriasis patients who decline biological therapy and randomisation. 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 coprimary endpoints.

Ethics and dissemination Ethics approval for this study was granted by the coordinating centre'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 NCT05004727.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This is a prospective, randomised controlled trial to investigate the efficacy of an interleukin-23p19 inhibitor, guselkumab, in preventing the development of psoriatic arthritis (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 immunological analysis to elucidate biological determinants of the transition from psoriasis to PsA.
⇒ A potential limitation is the short course of active drug versus 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 USA.[1] PsA is characterised 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 5–7 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 antitumour 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) emphasise the concept of treating disease in the preclinical 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 National Institutes of Health (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 preclinical 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 Multicentre Psoriasis At-Risk cohort study (PAMPA), the first randomised controlled, interventional trial using a specific target (ie, 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 (ie, 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 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 fulfil 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 (ie, 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 visualised on specialised ultrasound imaging and (2) decrease the rate of progression to clinically evident PsA. Concomitantly, PAMPA will focus on better understanding the underlying imaging, immunological and environmental features that promote the synovio-entheseal transition from psoriasis to PsA. To this end, a unique array of biological 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, multicentre, double-blind, randomised, placebo-controlled study of the efficacy of guselkumab (compared with 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 enrolment in February 2022 and is planned to conclude enrolment 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

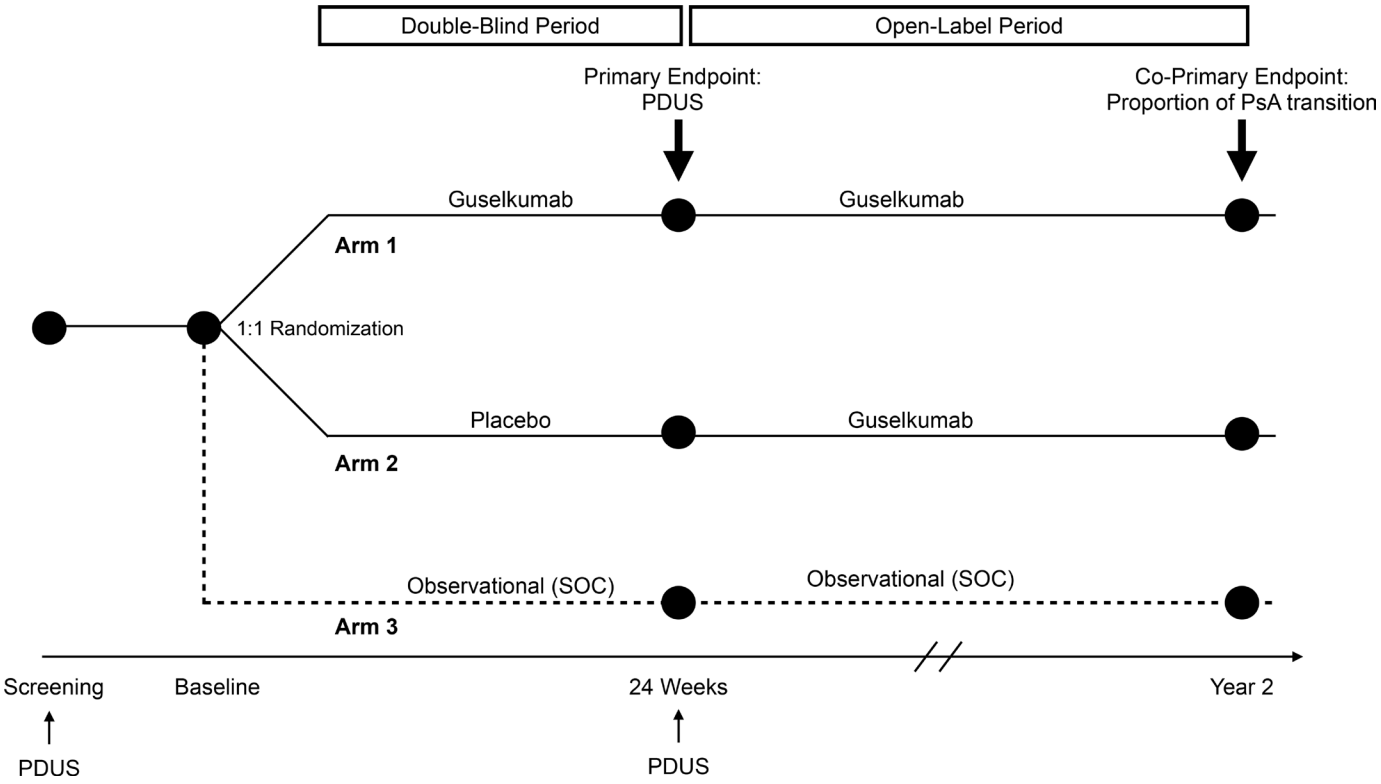

Figure 1 Study design of the PAMPA study. PAMPA, Preventing Arthritis in a Multicentre Psoriasis At-Risk cohort study; PDUS, power doppler ultrasound; PsA, psoriatic arthritis; SOC, standard of care.

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 biological therapy. No participants will be randomised 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 randomisation

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 per cent 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 fulfil 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 online supplemental file 1). Additionally, institutional electronic medical record systems will be used, and outreach pursued via research and advocacy groups (eg, National Psoriasis Foundation, PPACMAN, GRAPPA) and social media.

Participants who agree to be actively treated with drug (n=200) will be allocated in a 1:1 randomisation to receive either guselkumab 100 mg (arm 1) or placebo switching to guselkumab at week 24 (arm 2). An unblinded statistician has generated the randomisation list using blockrand library (V.4.1.0) within the statistical computing language R.[39] Randomisation is stratified by site and gender. An

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 (ie, methotrexate, apremilast) at time of enrolment or biological use ever
Psoriasis diagnosis (per dermatologist) for at least 2 years (in at least 30% of participants)	Mid-to-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 osteoarthritis (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

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
EuroQoL-5D (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					

*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.
†PEST will also be performed by telephone or electronically every 3 months if there is not an in-person visit.
‡Urine pregnancy test will be done for females of childbearing age the day of the baseline visit, prior to administering the first dose of drug or placebo.
ACPA, anticitrullinated peptide antibodies; BSA, body surface area; CBC, completed blood count; CMP, comprehensive metabolic panel; FACIT-F, functional assessment of chronic illness therapy-fatigue; IDEMO MSK-Q, International Dermatology Outcomes Measures Musculoskeletal-Questionnaire; IGA, investigators global assessment 2011; PAMPA, Preventing Arthritis in a Multicentre Psoriasis At-Risk cohort study; PBMC, peripheral blood mononuclear cell; PEST, psoriasis epidemiology screen tool; RF, rheumatoid factor; SJC, swollen joint count; SPARCC, Spondyloarthritis Research Consortium of Canada Enthesitis Index; TB, tuberculosis; TJC, tender joint count.

independent study team member, outside of the project, will randomise 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 randomised to biological 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 fulfil criteria will be randomised 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 time point, arm 1 participants will receive one placebo dose at week 24. A complete drug schedule is detailed in online supplemental figure 1. Participants may continue to use topical treatments or phototherapy throughout the duration of the study.

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

prespecified 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 online supplemental 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 (EuroQol-5D (EQ-5D), Functional Assessment of Chronic Illness Therapy-Fatigue, patient pain score, global health score and International Dermatology Outcomes Measures Musculoskeletal-Questionnaire (IDEOM 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 online supplemental file 1). They will also complete a modified Psoriasis Epidemiology Screening Test (PEST) to screen for PsA and will be evaluated for fulfilment 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 hypothesise that there will be improvement of ultrasound-based imaging abnormalities at week 24 (arm 1 vs arm 2). The coprimary end point is the proportion of participants developing PsA by modified CASPAR criteria at week 96. We hypothesise that treatment with guselkumab will lead to a decreased transition rate to PsA at year 2 when comparing combined arms 1 and 2 with arm 3. Secondary endpoints are outlined in box 1. Biospecimens (ie, plasma, peripheral blood mononuclear cells, skin swabs and stool) will also be collected for further exploratory aims.

Box 1 PAMPA study endpoints

Coprimary outcomes

⇒ Change in musculoskeletal power Doppler ultrasound imaging abnormalities at week 24 (arm 1 vs arm 2).

⇒ Percent of patients transitioning 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 synovioentheseal development at week 96 (arms 1+2 vs arm 3): severity will be categorised as mild, moderate or severe and additionally by continuous variables (eg, 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).

⇒ Change from baseline in IDEOM-MSKQ score at week 24 (arm 1 vs arm 2).

⇒ Change from baseline in ultrasound total score at week 24 (arm 1 vs arm 2+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; comorbidities 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.

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

Data management, quality control and safety

Each participant will receive an individual study ID number on enrolment, 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 centre (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 enrolment, 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 with 1.5%–2% in the drug arms (arm 1 and arm 2). Time to conversion will be measured from time of randomisation, and the two randomised arms will be compared by using a two-sided χ^2 test with a type I error rate of 0.05. Using these conservative assumptions at a power of 80% and incorporating an expected attrition rate of approximately 10%, we aim to enrol 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 coprimary 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 analysed 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 summarised as counts and proportions for categorical data; mean, SD, median, IQR, minimum and maximum for continuous data as appropriate. The primary endpoint of change from baseline in PDUS score at week 24 will be analysed 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% CI of the difference in treatment effect will be reported based on the fitted MMRM. The coprimary endpoint of PsA transition rate at week 96 will be analysed by χ^2 test of proportions comparing the combined arm 1 and 2 versus arm 3. We will further fit generalised 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 OR of PsA transition and corresponding 95% CI 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 Harmonisation Good Clinical Practice guidelines and local regulations. The study is approved by the coordinating centre'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 randomised control trial using methotrexate, showed significant improvement in joint outcomes in the tight control group compared with standard of care, with almost twice the odds of achieving an American College of Rheumatology (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 preclinical 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, non-randomised 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 biological 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 (ie, biologics) may be prescribed because patients have symptoms of, or undiagnosed, disease (ie, 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 randomised 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 CT 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 coprimary 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 characterise yet unidentified genetic, immunological 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 proinflammatory 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 defence 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 pathological 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 characterisation 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 an increasing evidence that the microbiome, the collection of microorganisms harboured 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 aetiology 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 preclinical 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 preclinical PsA and possibly revolutionise 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 prespecifies 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 using 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 characterise the preventive potential of various pathway-specific therapeutics.

Importantly, the proposed study's population (ie, 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 enrolment of less patients and still assess our primary outcome. Furthermore, by virtue of the prespecified inclusion criteria, participants will already qualify for the use of biological therapy (based on moderate to severe psoriasis involvement), which would offer a clear and significant benefit. Conversely, though, by predefining 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 predefined population. Additionally, the obtained outcomes may only be partially generalisable 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, immunological 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 PsA.

Author affiliations
[1]Department of Medicine, Division of Rheumatology, New York University Grossman School of Medicine and Psoriatic Arthritis Center, NYU Langone Health, New York, New York, USA
[2]Department of Population Health, New York University Grossman School of Medicine, New York, NY, USA
[3]Janssen Scientific Affairs LLC, Horsham, Pennsylvania, USA
[4]University of Toronto, Toronto, Ontario, Canada
[5]Division of Dermatology, Department of Medicine, Women's College Hospital, Toronto, Ontario, Canada
[6]Department of Dermatology, University of Rochester Medical Center, Rochester, New York, USA
[7]Department of Dermatology, Memorial University of Newfoundland, St. John's, Newfoundland and Labrador, Canada
[8]Department of Medicine, Division of Allergy, Immunology, and Rheumatology, University of Rochester Medical Center, Rochester, NY, USA
[9]Harvard Medical School, Boston, Massachusetts, USA
[10]Department of Dermatology/Department of Medicine/Division of Rheumatology, Brigham and Women's Hospital, Boston, Massachusetts, USA
[11]University of Pennsylvania Perelman School of Medicine, Philadelphia, Pennsylvania, USA
[12]Department of Medicine, Division of Rheumatology, Memorial University of Newfoundland, St. John's, NL, Canada
[13]Drexel University College of Medicine, Philadelphia, Pennsylvania, USA
[14]Department of Medicine, Division of Rheumatology, University of Toronto and Women's College Hospital, Toronto, ON, Canada

Acknowledgements The authors wish to thank PPACMAN members who contributed to these ideas during annual meetings and workshops.

Contributors CTR and JUS are the trial PIs and conceived the trial hypothesis. CTR, JUS, SDC, CG, WG, RGT, JFM, AO, PR, LE and RHH all contributed to protocol development and refinement. JH and KQ developed the statistical analysis plan. KAM, SC, JS, RBB, MT, ZU, RC, VP, FT, JY and ALN are responsible for implementation of the trail. RHH, JUS, CTR, WG, RGT, JFM, AO, PR and KAM wrote this protocol paper. SC, JS, RBB, MT, ZU, JH, RC, KQ, VP, FT, JY, ALN, SDC and CG contributed with refinement and approved the final draft.

Funding This work was supported by Janssen Scientific Affairs LLC (CNTO1959PSA2002).

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, LEO Pharma, Novartis, Pfizer, Sanofi, UCB and Union Therapeutics. In his role as Department Division Director of Dermatology at the University of Toronto. VP 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. WG 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. Other: Clinical trials (study fees): AbbVie, Asana Biosciences, Astellas, Boerhinger-Ingleheim, Celgene, Corrona/National Psoriasis Foundation, Devonian, Eli Lilly, Galapagos, Galderma, Janssen, LEO Pharma, Novartis, Pfizer, Regeneron, UCB. RGT has served as a consultant for Novartis, Bioclinica. JFM has served as a consultant and/or investigator for Amgen, Bristol-Myers Squibb, AbbVie, Dermavant, Eli Lilly, Novartis, Janssen, UCB, Sanofi, Regeneron, Sun Pharma, Biogen, Pfizer and Leo Pharma. AO has received esearch grants from AbbVie, Novartis, and Pfizer to University of Pennsylvania and Amgen to FORWARD/NDB; has research collaborations with GSK and Harvard Pilgrim; and has received consulting fees from AbbVie, Amgen, Bristol Myers Squibb, Celgene, CorEvitas, Gilead, Happify Health, Janssen, Lilly, Novartis, Pfizer, and UCB; royalties from Novartis (to spouse).PR has received esearch grants from Janssen and Novartis and speaker and consulting fees from Abbott, AbbVie, Amgen, Bristol-Myers Squibb, Celgene, Eli Lilly, Janssen, Novartis, and Pfizer. LE has received grants from Novartis, Eli Lily, UCB, Pfizer, Abbvie, Sandoz, Janssen and consulting fees from Janssen, Abbvie, Pfizer, UCB, Eli Lily, Novartis. CTR has served as a consultant for Abbvie, Amgen, UCB, Novartis, Lilly, Janssen, MoonLake, Pfizer. JUS has served as a consultant for Janssen, Novartis, Pfizer, Sanofi, Amgen, UCB and AbbVie; and has received funding for investigator-initiated studies from Janssen and Pfizer. CG and SDC are employees of Janssen Scientific Affairs, LLC and shareholders in Johnson & Johnson, of which Janssen Scientific Affairs, LLC is a wholly owned subsidiary.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

ORCID iDs
Rebecca H Haberman http://orcid.org/0000-0002-7119-8136
Soumya D Chakravarty http://orcid.org/0000-0001-7957-838X
C T Ritchlin http://orcid.org/0000-0002-2602-1219

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