The Leeds Teaching Hospitals NHS Trust

NIHR Leeds Biomedical Research Centre &

Leeds Institute of Rheumatic and Musculoskeletal Medicine

GOLMePsA study

Study Full Title: An investigator-initiated double-blind, parallel-group randomised controlled trial of GOLimumab and Methotrexate versus Methotrexate in very early PsA using clinical and whole body MRI outcomes: the GOLMePsA study.

Sponsor Name:	The Leeds Teaching Hospitals NHS Trust
Sponsor Number:	RR13/10782
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INVESTIGATOR DECLARATION AND SIGNATURE(S)

GOLMePsA Protocol v8.0, 9th March 2022

DECLARATION OF PROTOCOL ACCEPTANCE

I confirm that I am fully informed and aware of the requirements of the protocol and agree to conduct the study as set out in this protocol.

Signed:
Dr Helena Marzo-Ortega *Chief Investigator* *Date*

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ABBREVIATIONS

Abbreviation	Term
ACR	American College of Rheumatology
AE	Adverse Event
BSA	Body Surface Area
CI	Chief Investigator
eCRF	[electronic] Case Report Form
DLQI	Dermatology Life Quality Index
DMEC	Data Monitoring and Ethics Committee
DRMD	Division Of Rheumatic And Musculoskeletal Disease
DSUR	Developmental Safety Update Report
ECG	Electrocardiogram
EQ-5D	EuroQol 5 Dimension
ESR	Erythrocyte Sedimentation Rate
GCP	Good Clinical Practice
GOL	Golimumab
GP	General Practitioner
IA	Intra-articular
HAQ-DI	Health Assessment Questionnaire-Disability Index
ICH	International Conference On Harmonisation
IM	Intra-muscular
IMP	Investigational Medicinal Product
IV	Intravenous
LDI	Leeds Dactylitis Index
LEI	Leeds Enthesitis Index
MDA	Minimal Disease Activity
MHRA	Medicines And Healthcare Products Regulatory Agency
mNAPSI	Modified Nail Psoriasis Severity Index
MRI	Magnetic Resonance Imaging
MTX	Methotrexate
NIMP	Non-Investigational Medicinal Product
PASDAS	Psoriatic arthritis Disease Activity Score

Abbreviation	Term
PASI	Psoriasis Area and Severity Index
PsA	Psoriatic Arthritis
PBMC	Peripheral Blood Mononuclear Cells
PIS/ICF	Patient Information Sheet / Informed Consent Form
PO	Oral Route [Per Os]
PsA	Psoriatic arthritis
PsAQoL	Psoriatic Arthritis Quality of Life index
PsARC	Psoriasis Arthritis Response Criteria
Pso	Psoriasis
QA	Quality Assurance
RA	Rheumatoid arthritis
RDMS	Research Data Management System
REC	Research Ethics Committee
RSI	Reference Safety Information
SAE	Serious Adverse Event
SC	Subcutaneous
SD	Standard Deviation
SF-36	Short Form Health Index
SmPC	Summary Of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
TNF	Tumour necrosis factor
ULN	Upper limit of normal
US	Ultrasound
VAS	Visual analogue scale
WB-MRI	Whole-Body Magnetic Resonance Imaging

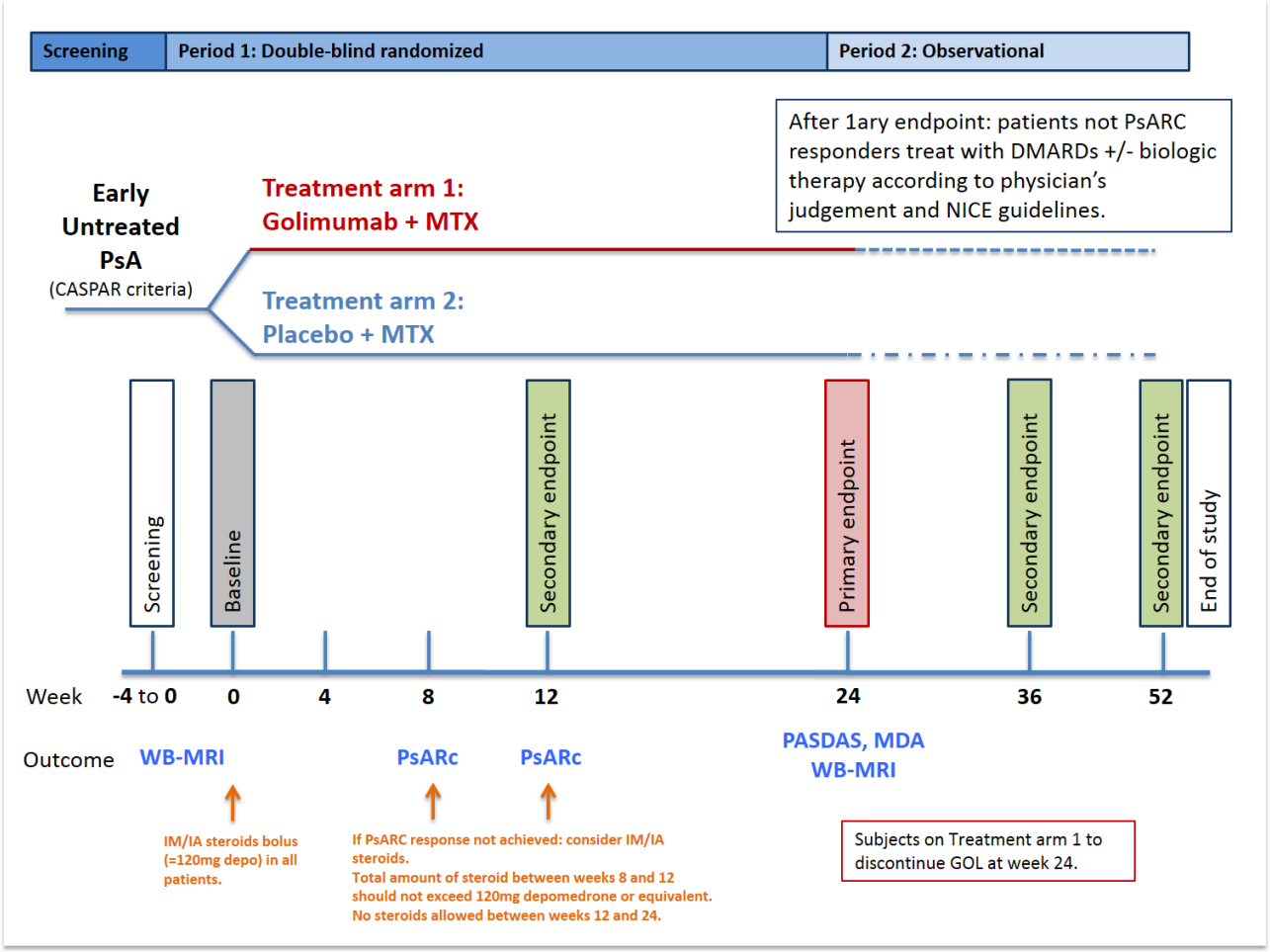
PROTOCOL SYNOPSIS

GENERAL INFORMATION	
Short Title	GOLMePsA
Full Title	An investigator-initiated double-blind, parallel-group randomised controlled trial of GOLimumab and Methotrexate versus Methotrexate in very early PsA using clinical and whole body MRI outcomes: the GOLMePsA study
Sponsor	The Leeds Teaching Hospitals NHS Trust
Sponsor ID	RR13/10782
EudraCT No.	2013-004122-28
MREC No.	14/EM/0124
Chief Investigator	Dr Helena Marzo-Ortega
Co-ordinating Centre	Chapel Allerton Hospital, Leeds
National / International	National
TRIAL INFORMATION	
Phase	Phase IIIb
Indication	Early Psoriatic Arthritis
Design	Investigator initiated, double-blind, randomized, placebo-controlled, two-armed, parallel-group, single centre trial
Number of sites	1
Primary Objective	To assess whether the combination of golimumab with methotrexate and steroids is superior to standard care (MTX monotherapy plus steroids) in reducing clinical disease activity in patients with early, treatment naïve PsA
Secondary Objective(s)	• To assess superiority of combination therapy over standard care in improving US imaging disease activity • To assess superiority of combination therapy over standard care in improving patient-reported quality of life and health status • To assess whether responses on US imaging outcomes are associated with steroid therapy • To assess the extent of association between clinical and US imaging joint assessments at baseline • To assess the extent of association between clinical and US imaging responses to therapy • To identify baseline variables which may be modifiers of clinical or imaging response (e.g. symptom duration, immunological parameters)

	• To assess the test-retest reliability of the PASDAS composite index
Exploratory Objective(s)	• To assess the extent of association between clinical and WB-MRI imaging joint assessments at baseline • To assess the extent of association between clinical and WB-MRI imaging responses to therapy • To quantify the potential treatment effect with respect to WB-MRI disease activity
Primary Endpoint	Clinical disease activity (PASDAS) at 24 weeks
Secondary Endpoint(s)	• Clinical measures of disease activity and achievement of acceptable state or response at 12, 24, 36 and 52 weeks. • US Imaging measures of disease activity and achievement of acceptable state at 12, 24 and 36 weeks. • Patient-reported outcomes at 24 and 52 weeks.
Exploratory Endpoint(s)	• WB-MRI measures of disease activity and achievement of acceptable state at 24 and 36 weeks
TRIAL TIMELINES	
Expected start date	October 2015
Patient enrolment phase	October 2015 - February 2022
Follow-up duration	52 weeks
End of Trial Definition	Last Patient Last Data Item
Expected completion date	December 2023
TRIAL PATIENT INFORMATION	
Number of trial patients	84
Age group of trial patients	≥18
Inclusion criteria	1. Adult patients with a diagnosis of PsA (CASPAR criteria) of up to 24-month duration. 2. Active joint disease as defined by at least 3 swollen and 3 tender joints or 2 swollen and 2 tender joints plus one affected entheseal site (Achilles tendon and/or plantar fascia). 3. Treatment naïve to DMARDs including biologics
Exclusion criteria	1. Age <18 2. Previous treatment with a DMARD or biological therapy for PsA.

INVESTIGATIONAL MEDICINAL PRODUCT	
IMP name(s)	Golimumab (Simponi®)
IMP mode of administration	Subcutaneous injections
Duration of IMP Treatment	24 weeks
IMP Supplier(s)	Janssen Biologics BV
Non IMP name(s)	Methotrexate, corticosteroids

SCHEMATIC DIAGRAM OF RECRUITMENT, RANDOMISATION & TREATMENT



INTRODUCTION

1.1 Background

Psoriatic arthritis (PsA) is a chronic, systemic, inflammatory arthritis, which may be associated to skin psoriasis (Pso). PsA is one of the commonest inflammatory arthritis occurring in up to 0.1% of the general population and in 6%-42% of patients with Pso. In the majority of cases Pso precedes the onset of arthritis by several years. The course of PsA is heterogenous and variable, with some patients having mild disease whilst others evolve into a severe, erosive arthropathy that is often refractory to conventional treatments and may be associated with functional disability and accelerated morbidity (1, 2). Traditionally there has been a delay on patients presenting to outpatient clinics of over 9 years by which time the majority (67%) will have an established, erosive arthropathy with a substantial degree of functional impairment (3-5).

Psoriatic arthritis has many clinical manifestations including arthritis, enthesitis, dactylitis, axial disease, and skin/nail involvement. Traditionally the primary outcome measure used in interventional studies has been the American College of Rheumatology 20% improvement (ACR20) criteria(6), a measure originally developed for rheumatoid arthritis (RA) and which focuses on peripheral joint activity. In addition, a number of studies have used another rheumatoid arthritis measure, the Disease Activity Score for 28 joints (DAS28). However, in PsA, the number of joints assessed should optimally include a 68-tender, 66-swollen joint count, which includes the distal interphalangeal (DIP) joints of the fingers. The Psoriatic Arthritis Response Criteria (PsARC) (7, 8) were developed for a specific Veterans Administration study of sulfasalazine in PsA but are also primarily articular response criteria. Several other candidate composite measures have been proposed, some of which capture aspects of PsA other than the peripheral arthritis. These include the Psoriatic Arthritis Disease Activity Score (PASDAS) and the Composite Psoriatic Disease Activity Index (CPDAI). The newer measures are more responsive in clinical trials and are better able to distinguish different doses of trial medication (9, 10). The PASDAS is a weighted index comprising assessments of joints, function, acute phase response, quality of life (QOL), and patient and physician global by VAS. The score range of the PASDAS is 0–10, with worse disease activity represented by higher scores. Cut-offs for disease activity and response have now been developed and validated using interventional trial data (11).

The use of imaging techniques such as ultrasound (US) and magnetic resonance (MRI) in particular has transformed the understanding of PsA and also provided a useful technique for therapy evaluation. MRI is a sensitive imaging modality that allows for the comprehensive assessment of joints and soft tissues. Whole body MRI (WB-MRI) uses multiple phased arrays coils to allow for multi-joint assessment in one session, which includes both axial and peripheral joints. A recent study has shown that WB-MRI is a feasible technique that confirms sites of active disease but is also sensitive for detection of subclinical disease in patients with PsA particularly with enthesitis and bone marrow oedema (12). Evidence from the RA literature suggests that subclinical bone marrow oedema is one of the main predictors for on-going radiographic progression even in the presence of clinical remission (13). In SpA, there is evidence that bone oedema may be a predictor of future spinal fusion. Therefore, the ability to delineate the total disease burden in PsA, particularly on those joints and/or enthesis not obviously inflamed on clinical examination, may have important implications for understanding the basis for true disease remission following therapy. No study with anti-TNF agents has explored this to date.

Ultrasound allows visualization of different joint areas such as enthesis, bone, bursa and tendons and other soft tissue structures. It is non-invasive, providing easier joint access than MRI at the bedside and can scan multiple joints in one sitting.

Mounting evidence over the past two decades in rheumatoid arthritis (RA) has shown that early and aggressive treatment of RA with DMARDs and biologics reduces the effects of the disease in terms of joint damage and disability (14). This has indeed led to clinical remission being an achievable goal in many patients receiving biologics, chiefly TNF blockers received early in the disease course (15) (16). Although the optimal treatment strategy in RA is still being debated, strategies utilizing combination therapy with biologics and corticosteroids have proven extremely effective particularly when used early in the disease course (15, 17). In fact, it has been suggested that this favourable outcome is attributable mainly to a treat-to-target strategy rather than the superiority of any specific drug (18, 19). Data in PsA sparse, with only limited evidence on the efficacy of conventional DMARDs such as methotrexate or leflunomide (20). To date, TNF inhibitors have been the only drugs shown to be efficacious in the treatment of the heterogenous clinical manifestations of the disease including joints, spine, skin and nails (21-24). Similar to RA, TNF inhibitors have also been shown to halt the progression of structural damage in peripheral joints in PsA (25). Recently, treatment agents that act through the inhibition of TNF, such as golimumab, have shown good efficacy for joint and skin manifestations of PsA in advanced disease resistant to conventional DMARDs (26).

1.2 Golimumab background

Golimumab (SIMPONI®) is a human IgG1κ monoclonal antibody against tumor necrosis factor-α (TNF-α). Golimumab (alone or in combination with methotrexate (MTX) is indicated for the treatment of active and progressive psoriatic arthritis in adult patients when the response to previous disease-modifying anti-rheumatic drug (DMARD) therapy has been inadequate. The safety and efficacy of subcutaneous (SC) golimumab used for reducing signs and symptoms of active PsA, associated skin and nail disease, and inhibition of structural damage was evaluated in the GO-REVEAL trial (21). At Week 14, treatment with golimumab 50 mg resulted in a significantly greater proportion of patients who achieved an ACR 20 response, compared to placebo (51% vs 9%; $p<0.001$). Further, golimumab also demonstrated inhibition of structural damage at 24 and 52 Weeks with significant improvements in joints, skin, and radiographic benefits have been observed through Week 104. From the point of patients' reported outcomes, golimumab significantly improved physical function and health-related quality of life through Week 52.

It is therefore postulated that aggressive intervention in PsA with golimumab together with a step-up methotrexate protocol immediately after diagnosis combined with intra-articular or intramuscular corticosteroid use could lead to a state of minimal disease activity (MDA) (27) or near clinical remission and complete ablation of inflammation as shown by WB-MRI and US at 24 weeks.

1.3 Rationale for the proposed study

Psoriatic arthritis can cause a considerable amount of disability in affected patients, which is equivalent to that of RA and can be present from earlier on in the disease process. To date TNF blockers are shown to be the more efficacious agents in the treatment of PsA, however a subset of patients will not achieve a significant response to single therapy. Further the use of biologics on treatment naïve patients has not been studied in PsA. Experience from RA shows that early implementation of a treat-to-target strategy in early disease leads to prompt control of inflammation which is sustained over 5 years and reflected in persistent halting of radiographic progression. Radiographic involvement in the early disease stages in PsA is not widespread and does not represent

a sensitive measurable outcome. Some factors contributing to this may be the heterogeneity of the disease affecting different joint groups or restrictions on the study designs. We therefore aim to address these issues by using a recently-developed clinical efficacy outcome, PASDAS, which has been shown to have good sensitivity to change, and by including WB-MRI as an exploratory endpoint.

WB-MRI is a safe and sensitive imaging technique with the capability to perform multi-joint imaging. The advantage of WB-MRI is that it can give information on subclinical inflammation, which is particularly relevant in oligo-articular joint patterns.

It is hypothesized that:

Early prompt intervention in PsA with a treatment strategy using a combination of golimumab and methotrexate plus corticosteroids will lead to improvement in a new clinical disease activity measure at week 24, which will be superior to that shown by the combination of methotrexate plus placebo plus corticosteroids, by at least 1 unit on the scale.

A subset of PsA patients at presentation have a substantial amount of subclinical joint/entheseal inflammation that can be identified by WB-MRI and US. Using WB-MRI and US will permit identification of patients whose response to therapy has been successful even at the subclinical level.

STUDY AIM AND OBJECTIVES

2.1 Study aim

The aim of the study is to assess the clinical efficacy of a treatment strategy in early, treatment naïve PsA patients, using a combination of early TNFi therapy (golimumab) plus methotrexate plus steroids versus standard care (MTX monotherapy plus steroids) at 24 weeks.

2.2 Primary objective

The primary objective of this study is to assess whether the combination of golimumab with methotrexate and steroids is superior to standard care (MTX monotherapy plus steroids) in reducing disease activity in patients with early, treatment naïve PsA.

2.3 Secondary objective(s)

- To assess superiority of combination therapy over standard care in improving US-detected joint and entheseal pathology
- To assess superiority of combination therapy over standard care in improving patient-reported quality of life and health status
- To assess whether responses on US imaging outcomes are associated with steroid therapy
- To assess the extent of association between clinical and US imaging joint assessments at baseline
- To assess the extent of association between clinical and US imaging responses to therapy
- To identify baseline variables which may be modifiers of clinical or imaging response (e.g. symptom duration, immunological parameters)
- To assess the test-retest reliability of the PASDAS composite index.

2.4 Exploratory objective(s)

- To assess the extent of association between clinical and WB-MRI joint assessments at baseline
- To assess the extent of association between clinical and WB-MRI responses to therapy
- To quantify the potential treatment effect with respect to WB-MRI disease activity

STUDY ENDPOINTS

3.1 Primary endpoint

Disease activity

- Disease activity (PASDAS score) at 24 weeks.

3.2 Secondary endpoint(s)

The following endpoints will be assessed:

Efficacy measures

- **Clinical measures of disease activity**
  - Disease activity measures:
    - PASDAS at 12, 36 and 52 weeks
    - Enthesitis score at 12, 24, 36 and 52 weeks
    - Dactylitis score at 12, 24, 36 and 52 weeks
    - PASI score (28) at 12, 24, 36 and 52 weeks
    - mNAPSI score (29) at 12, 24, 36 and 52 weeks
    - CPDAI score (30) at 24 and 52 weeks
  - Acceptable state or response:
    - Proportion achieving MDA at 12, 24, 36 and 52 weeks
    - Proportion achieving PsARC response at 8, 12, 24, 36 and 52 weeks
    - Proportions achieving ACR20/50/70 responses at 12, 24, 36 and 52 weeks
    - Proportion achieving at least PASI75 at 12, 24, 36 and 52 weeks in the subset of patients in whom at least 3% of the BSA was affected by psoriasis at baseline
  - Composite index test-retest reliability
    - PASDAS score at screening and at baseline visit.

- **Imaging measures of disease activity**
  - Measures of joint/enthesis pathology
    - Total scores for synovitis/enthesitis identified by US at 12, 24 and 36 weeks
  - Acceptable state
    - Proportion achieving US remission at 12, 24 and 36 weeks

- **Patient-reported outcomes**
  - Patient VAS global disease Activity at 24 and 52 weeks
  - DLQI at 24 and 52 weeks (31)
  - SF-36 Mental Component Summary and Physical Component Summary at 24 and 52 weeks (32)

Other secondary endpoints

- **Treatment-related endpoints**
  - Proportion of patients requiring additional steroid therapy up to week 12
  - Cumulative steroid dose received up to week 12

3.3 Exploratory endpoints

- Established scores for inflammatory lesions (bone marrow oedema or osteitis and synovitis) identified by WB-MRI at 24 and 36 weeks (see section 8.5.1) (in a subset of patients)
- Imaging measures of disease activity in expanded set of sites (the expanded ultrasound variables will only be available for a subset of patients)
  - Measures of joint/enthesis pathology
    - Total scores for synovitis/enthesitis identified by US at 12, 24 and 36 weeks (using OMERACT joint/enthesis sets; using OMERACT scoring)
  - Acceptable state
    - Proportion achieving US remission at 12, 24 and 36 weeks (using OMERACT joint/enthesis sets)
- **Immunological parameters**
  - T and B cell frequencies at 24 and 52 weeks in a subset of patients who agree to take part in the biomarker sub-study.

STUDY VARIABLES

4.1 Standard variables

- Age
- Sex
- Ethnicity
- Height
- Weight
- Medical / surgical / family history
- Concomitant medication

4.2 Efficacy variables

- PASDAS (0-10)
- Leeds Enthesitis Index (0-6)
- Physician assessment of arthritis, Likert scale (1-5; used in composite outcomes)
- Physician global assessment of psoriatic disease VAS (mm; used in composite outcomes)
- Leeds Dactylitis Index (0-~40)
- Psoriasis Area Severity Index (0-72)
- Modified Nail Psoriasis Severity Index (0-140)
- Tender joint count (out of 68; used in composite outcomes)
- Swollen joint count (out of 66; used in composite outcomes)
- Composite Psoriatic Disease Activity Index (range 0-15)
- Minimal disease activity (yes/no)
- PsARC response (yes/no)
- ACR response (yes/no)
- Percentage of Body Surface Area (%)

- C-reactive protein level (mg/L; used in composite outcomes)
- US grey scale score (total 0-72; 0-144 for OMERACT definition subset)
- US power Doppler score (total 0-72; 0-144 for OMERACT definition subset)
- US Global OMERACT-EULAR Score System (GLOESS) score (total 0-72; 0-144 for OMERACT definition subset)
- US number of entheses with grey scale abnormalities (0-10; 0-12 for OMERACT definition subset)
- US enthesis power Doppler score (total 0-30; 0-36 for OMERACT definition subset)
- US total enthesis thickness score (0-30; 0-36 for OMERACT definition subset)
- US total enthesis erosion score (0-30; 0-36 for OMERACT definition subset)
- US number of entheses with calcification (0-10)US number of entheses with enthesophytes (0-10)
- US enthesis inflammation score (0-70)
- US enthesis chronicity score (0-50)
- US remission (yes/no)
- Patient assessment of arthritis, Likert scale (1-5; used in composite outcomes)
- Patient global assessment of psoriatic disease activity VAS (mm)
- Patient articular pain assessment VAS (mm; used in composite outcomes)
- ASQoL (0-18; used in composite outcomes)
- Health Assessment Questionnaire Disability Index (0-3; used in composite outcomes)
- Dermatology Life Quality Index (0-30)
- SF-36 mental and physical component scores (0-100)
- Cumulative dose of steroid (mg)
- SPARCC spinal inflammation score (0-108)
- SPARCC sacro-iliac joint inflammation score (0-72)
- HIMRISS BML score (0-100)
- HIMRISS effusion & synovitis score (0-30)
- KIMRISS score (0-763)
- CANDEN spine inflammation score (0-614)
- CANDEN spine fat score (0-510)
- CANDEN spine bone erosion score (0-208)
- CANDEN new bone formation score (0-460)
- HEMRIS score (inflammation sum score 0-24; structural sum score 0-18)
- MRI-WIPE score (0-738)
- T-cell subset frequencies (IRC, naïve, Treg)
- B-cells

4.3 Safety variables

- Number of patients experiencing SAEs and AEs.
- Any clinically significant worsening of a pre-existing condition.
- An AE occurring from overdose of an IMP, whether accidental or intentional.
- An AE occurring from abuse (e.g. use for nonclinical reasons) of an IMP.
- An AE that has been associated with the discontinuation of the use of an IMP.

STUDY DESIGN

5.1 Study description

GOLMEPsA is an investigator initiated, randomised, double-blind, placebo-controlled, two-armed, parallel-group, single-centre imaging study. Patients with the following criteria will be recruited:

- Treatment-naïve PsA patients classified according to CASPAR criteria (33)
- Up to 24 month diagnosis
- At least ≥3 swollen and 3 tender joints or 2 swollen and 2 tender joints and one tender enthesis.

The trial will start with a four-week screening phase, and informed consent will be obtained at the screening visit. A (revised) total of 84 patients will be randomised on a 1:1 basis to receive one of the following:

Treatment Arm 1 (Group A): Immediate golimumab (50 mg SC four weekly) and MTX (starting at 15 mg weekly with rapid escalation up to 25 mg over 4 weeks) combination therapy administered for a total duration of 24 weeks.

Treatment Arm 2 (Group B): MTX monotherapy (starting at 15 mg weekly with rapid escalation up to 25 mg over 4 weeks) plus placebo SC injections four weekly for 24 weeks.

Both treatment arms will receive a "bolus" dose of methylprednisolone (120mg IM or equivalent amount intra-articularly in case of oligoarticular, ≤4 swollen joints, presentation) with the aim to achieve rapid ablation of inflammation at baseline. In addition, both treatment arms will adopt a "treat-to-target" (TT) algorithm (see Schematic Diagram) involving further corticosteroid injections (intra-muscular or intra-articular) if not achieving a PsARC response at weeks 8 and 12 (secondary endpoint). Steroid amount given between both visits will not exceed a maximum amount of 120mg methylprednisolone per patient.

No further steroids will be allowed beyond week 12. Any patients showing an unacceptable degree of disease activity (as judged by the study clinician by clinical assessment in conjunction with PsARC) beyond this point and before the week 24 assessment will cease to follow the study treatment protocol (withdrawal) and will be treated as deemed necessary by the study physician according to clinical protocols and NICE guidelines. In these cases, subjects in the subset in whom WB-MRI was to be collected will undergo WB-MRI as per exploratory objective (see Week X 'withdrawal visit', summary schedule of study assessments section 8.6) and will continue to be observed for the rest of the study duration.

All subjects reaching 24 weeks (primary endpoint) will be invited for repeat WB-MRI (if in WB-MRI subset) and US examination of a set core of joints and entheses (as per baseline assessment). Subjects will also be assessed for PASDAS (primary outcome), MDA and PsARC and other relevant clinical outcomes.

Subjects in Treatment arm 1 (GOL+MTX) will have GOL discontinued at week 24, will continue MTX and will be observed thereafter for the duration of the observational phase of the study (until week 52). In case of disease flare during this period (defined as in section 8.18), subjects will be invited to have repeated imaging assessments (US and WB-MRI as per "Extra visit" section 8.6) and will be treated according to existing clinical protocols and NICE guidelines. Observation will not be interrupted and all data from these participants will be collected until the end of the study period.

Subjects in Treatment arm 1 not achieving PsARC improvement by week 24 will have GOL discontinued and will be treated according to existing clinical protocols and NICE guidelines, and will be observed until the end of the study period.

Subjects on Treatment arm 2 (MTX+placebo) achieving PsARC improvement at week 24 will be allowed to continue their MTX treatment and shall be observed for the duration of the observational phase of the study (until week 52). In case of disease flare (defined as in section 8.18) beyond week 24, subjects will be invited to have repeated imaging assessments (WB-MRI if in WB-MRI subset), US as per "Extra visit") and will be treated according to existing clinical protocols and NICE guidance.

Subjects on Treatment arm 2 not achieving PsARC improvement by week 24 will be treated according to existing clinical protocols and NICE guidance and observed until the end of the study Period.

Corticosteroids: Patients on both groups can receive further IM/IA corticosteroids at weeks 8 and 12 if a PsARC response is not achieved at these visits. The maximum amount of corticosteroids given between these 2 visits should not exceed 120mg intramuscular methylprednisolone (or comparable amount intra-articularly; unless contraindicated or not tolerated). No further corticosteroids are allowed between weeks 12 and 24.

At and/or after the primary endpoint (week 24) intramuscular or intra-articular steroids are permitted unless a clinical or imaging assessment is scheduled within the following 6 weeks. The same applies to oral formulation of steroids.

Methotrexate: All patients will receive (from the research team) a prescription for oral MTX (if tolerated, more details in section 7.3) at a starting dose of MTX 15mg weekly. If tolerated, MTX will be increased to 20mg and 25 mg weekly at weeks 2 (patient given prescription at baseline visit by the research team) and 4 respectively. Subcutaneous MTX may be administered if intolerance to oral MTX is observed. All patients will receive oral folic acid at a dose of 5mg daily except the day of MTX, i.e. 6 days per week.

All patients will receive haematology and biochemistry monitoring on DMARD therapy according to local guidelines.

All patients recruited to this study, irrespective of therapy change (as outlined above), will continue to be followed up for the 52 week study duration with imaging and immunological studies as per protocol (unless consent is withdrawn).

Patients will undergo all of the following radiological assessments (eligibility limitation may apply) at baseline and at visits as stated below:

- WB-MRI (if eligible and in WB-MRI subset) at baseline, weeks 24 and 36 and time of withdrawal (Week X) or flare (Week Y) if applicable (section 8.6).
- Ultrasound (US) of a set core of joints and entheses will be performed at baseline, weeks 24 and 36 and/or at time of withdrawal (Week X) and/or at time of flare (Week Y) if applicable.
- Radiographs of hands and feet will be taken at screening to confirm the patient meets CASPAR criteria (section 8.6).

- Patients consenting to the biomarker sub-study will provide samples (PBMC, serum at baseline and weeks 12, 24, 36 and 52 and at the time of flare in the case of an initial responder or study withdrawal (week X) to evaluate for changes in immunological parameters.

This study will take place in the rheumatology department and the associated research facilities at Chapel Allerton Hospital / The Leeds Teaching Hospitals NHS Trust.

The study will also use Patient Identification Centres (PICs) from within the Yorkshire region, patients referred to the study team via PICs will also be seen at the rheumatology outpatient department in Chapel Allerton Hospital, Leeds.

5.2 Study duration

The total duration of the study for patients completing all visits from screening to final assessment will be 52 weeks plus up to 4 weeks.

5.3 Rationale for study design and selection of dose

Based on data from the GO-REVEAL trial (21) golimumab treated patients experienced significant improvements in joint, skin, and nail disease, compared with patients in the placebo group through 24 weeks of therapy. Two different doses of golimumab (50 mg and 100 mg) were tested with no clear evidence of improved ACR responses with golimumab 100 mg compared to golimumab 50 mg. Current product licensing recommends dose of 100 mg to be used on subjects ≥100 kg in weight. This recommendation will also be applied to study subjects whenever applicable. Methotrexate initiation at 15mg and escalation to 25mg is in line with current clinical practice in Leeds. Methylprednisolone 120mg injection IA/IM is the standard dose used in Leeds and represents a pragmatic approach to induce rapid suppression of inflammation.

SELECTION AND WITHDRAWAL OF SUBJECTS

6.1 Target population

Patients with early, treatment-naive PsA, of up to 24-month from diagnosis.

6.2 Estimated number of eligible patients

A (revised) total of 84 patients are planned for enrolment. This number is estimated allowing for a 10% drop-out rate. At present we see approximately 4-6 patients meeting the clinical eligibility criteria per month yielding at least 48 eligible patients per year.

6.3 Eligibility criteria

6.3.1. Inclusion criteria

Patients meeting all of the following criteria will be considered for enrolment into the study:

INCL1.	Male and female patients aged ≥18 years at the time of signing the Informed Consent Form.
INCL2.	Subjects with a diagnosis of psoriatic arthritis as per the Classification for Psoriatic Arthritis (CASPAR) criteria (see appendix 3) confirmed up to 24 months prior to screening.
INCL3.	Subjects with active PsA defined as the presence of at least 3/78 tender and at least 3/76 swollen joints (see section 8.2.3 and section 8.2.4) or 2 swollen and 2 tender joints plus one affected entheseal site (Achilles tendon and/or plantar fascia) at baseline.

INCL4.	Are capable of understanding and signing an informed consent form.
INCL5.	Women of childbearing potential or men capable of fathering children must be using adequate birth control measures (e.g.: abstinence, oral contraceptives, intrauterine device, barrier method with spermicide, surgical sterilization) during the study and for 6 months after receiving the last administration of study agent. Female subjects of childbearing potential must test negative for pregnancy. Female subjects must agree to not donate eggs (ova, oocytes) during the study and for 6 months after last dose of study agent. Male subjects must agree to not donate sperm while in the study and for 6 months after last dose of study agent.
INCL6.	Patients fulfilling the following TB criteria:
INCL6.1.	Have no history of latent or active TB prior to screening. An exception is made for subjects with a history of latent TB and documentation of having completed appropriate treatment for latent TB 3 years prior to the first administration of study agent. It is the responsibility of the investigator to verify the adequacy of previous antituberculous treatment and provide appropriate documentation.
INCL6.2.	Have no signs or symptoms suggestive of active TB upon medical history and/or physical examination.
INCL6.3.	Have had no close contact with a person with active TB or, if there has been such a contact, will be referred to a physician specializing in TB to undergo additional evaluation, and if warranted, receive appropriate treatment as if having latent TB prior to or simultaneously with the first administration of study agent.
INCL6.4.	Have confirmed either: ▪ Within 6 weeks prior to the administration of study agent, a negative QuantiFERON-TB Gold test result; **or** ▪ Within 12 weeks from a newly identified positive QuantiFERON-TB Gold test result (in which active TB has been ruled out) and for which appropriate treatment for latent TB has been initiated either prior to, or simultaneously with, the first administration of study agent.
INCL6.5.	In the event of 2 indeterminate QuantiFERON-TB Gold in-tube tests results, the subjects will be treated as if having latent TB prior or simultaneously with the first administration of study agent.
INCL6.6.	Have a chest radiograph (posterior-anterior view), read by a qualified radiologist, whose diagnostic assessment is consistent with no evidence of current active TB or old inactive TB, and taken within 12 months of the study.
INCL6.7.	Have a screening laboratory test result as follows:
	INCL6.7.1. - Hb≥8.5 g/dL or ≥5.3 mmol/L
	INCL6.7.2. - White blood cell (WBC) count ≥3.5x10^3 cells/uL
	INCL6.7.3. - Neutrophils ≥1.5 x10^3 cells/uL
	INCL6.7.4. - Platelets ≥100x10^3 cells/uL
	INCL6.7.5. - Serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels not exceeding 1.5 times the upper limit of normal (ULN) for the central laboratory conducting the test.
	INCL6.7.6. - Serum creatinine not exceeding 1.5 mg/dL

6.3.2. Exclusion criteria

Patients fulfilling any of the following conditions or characteristics will be excluded from study enrolment:

EXCL 1.	Previous treatment with any conventional or biological DMARDs, where "treatment" is defined as a therapeutic dosage according to each product's SmPC. Topical preparations for psoriasis are not considered DMARDs (examples include, but are not limited to, steroids, salicylic acid, tar).
EXCL 2.	Any chronic inflammatory arthritis diagnosed before 16 years old.

6.3.3. Exclusions for general safety

EXCL3.	Patients with significant concurrent medical diseases including uncompensated congestive heart failure, myocardial infarction within 52 weeks from screening, unstable angina pectoris, uncontrolled hypertension (BP>160/95), severe pulmonary disease, or history of human immunodeficiency virus (HIV) infection, immunodeficiency syndromes, central nervous system (CNS) demyelinating events suggestive of multiple sclerosis, renal or gastrointestinal conditions, which in the opinion of the investigator places the patient at an unacceptable risk for participation in the study or would make implementation of the protocol difficult.
EXCL4.	Patients with cancer or a history of cancer (other than resected cutaneous basal cell carcinoma, and in situ cervical cancer) within 5 years of screening.
EXCL5.	Patients with current crystal or infective arthritis.
EXCL6.	Patients with chronic infection of the upper respiratory tract (e.g. Sinusitis), chest (e.g. Bronchiectatic lung disease), urinary tract or skin (e.g. Paronychia, chronic ulcers, open wounds) within 4 weeks of screening.
EXCL7.	Patients who have a chest radiograph within 3 months prior to the first administration of study agent that shows an abnormality suggestive of a malignancy or current active infection, including (but not limited to) TB, histoplasmosis or coccidioidomycosis.
EXCL8.	Patients with any ongoing or active infection or any major episode of infection requiring hospitalization or treatment with IV antibiotics within the preceding 30 days of screening and/or orally administered antibiotics in the preceding 15 days of screening.
EXCL9.	Patients with abnormal liver function including known liver cirrhosis, fibrosis, or known alcoholic steatohepatitis (NASH) at the time of screening or abnormal blood tests as shown by: • Aminotransferase (AST) / alanine aminotransferase (ALT) > 3x ULN, OR • Bilirubin >51umol/L.
EXCL10.	Patients with known severe hypoproteinaemia at the time of screening, e.g.: in nephrotic syndrome; OR impaired renal function, as shown by: Serum Creatinine > 133 μmol/L.
EXCL11.	Patients with known significantly impaired bone marrow function as for example significant anaemia, leukopaenia, neutropaenia or thrombocytopaenia as shown by the following laboratory values at the time of screening: • White blood cells < 3000 x 10^6/L; • Platelets < 125 x 10^9/L; • Haemoglobin < 9.0 g/dL for males and < 8.5 g/dL for females.
EXCL12.	Patients with a history of latent or active TB prior to screening will not be eligible. For exceptions, refer to inclusion criteria (INCL6 group).

EXCL13.	Subjects must undergo screening for hepatitis B and C virus (HBV, HBC). At a minimum, this includes testing for Hepatitis B surface antigen (HBsAg), Hepatitis B core antibody (anti-HBc) and Hepatitis C antibody (Anti-HCV Ab), • Subjects who test positive for surface antigen (HBsAg+) are not eligible for this study, regardless of the results of other hepatitis B tests. • Subjects who test negative for surface antigen (HBsAg-) and test positive for core antibody (anti-HBc+) are eligible for this study provided that the HBV DNA test is done. All subjects who test positive for core antibody (anti-HBc+) must undergo further testing for hepatitis B deoxyribonucleic acid (HBV DNA test). ○ If the HBV DNA test is positive, the subject is not eligible for this study. ○ If the HBV DNA test is negative, the subject is eligible for this study. • In the event the DNA test cannot be performed, the subject is not eligible for the study.
EXCL14.	Primary or secondary immunodeficiency (history of or currently active) unless related to primary disease under investigation.
EXCL15.	Pregnancy, lactation (nursing) or women of child-bearing potential (WCBP) unwilling to use an effective birth control measure (see appendix 1) whilst receiving treatment and after the last dose of protocol treatment as indicated in the relevant SmPC.
EXCL16.	Men whose partners are of child-bearing potential but who are unwilling to use an effective birth control measure whilst receiving treatment and after the last dose of protocol treatment as indicated in the relevant SmPC.
EXCL17.	Patients who have received any systemic/intra-articular corticosteroids within 4 weeks prior to screening. Topical preparations with steroids for cutaneous use, or inhalers for the treatment of asthma are not considered systemic/intra-articular corticosteroids.
EXCL18.	Patients with a history of confirmed blood dyscrasia.
EXCL19.	Patients with a history of mental illness that would interfere with their ability to comply with the study protocol.
EXCL20.	Patients with a history of drug and/or alcohol abuse that would interfere with their ability to comply with the study protocol.
EXCL21.	Patients with a history of any viral hepatitis within 1 year of screening
EXCL22.	Patients who have received or are expected to receive any live virus or bacterial vaccinations or treatments that include live organisms (eg. a therapeutic infectious agent such as BCG that is instilled into the bladder for the treatment of cancer) within 3 months prior to the first administration of study agent, during the trial, or within 6 months after the last administration of the study agent.
EXCL23.	Patients who demonstrate Hypersensitivity to the IMP's active substance, or any of the excipients detailed in the SmPC.

6.4 Screening failures

Patients who sign an informed consent form and fail to meet the inclusion and/or exclusion criteria are defined as screen failures. For all screen failures, the investigator is to maintain a screen log that documents the screening number, patient initials, and reason(s) for screen failure. A copy of the log should be retained in the trial master file.

6.5 Withdrawal criteria

Subjects will be fully withdrawn from the study (i.e. from any further study medication or study procedure) for the following reasons:

1. At their own request or at the request of their legally authorized representative*. Patients will be reminded during the informed consent process that they remain free to withdraw from the study at any time without giving a reason – their care will not be compromised.
2. If, in the investigator's opinion, continuation in the study would be detrimental to the subject's well-being.
3. At the specific request of the sponsor.

* “Legally authorized representative” means an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject’s participation in the procedure(s) involved in the research.

In all cases, the reason for and date of withdrawal must be recorded in the eCRF and in the subject's medical records. The study team will request the permission of the subject to be followed up to establish whether the reason was an AE, and, if so, this must be reported in accordance with the procedures in section 9.6. Every attempt will be made to follow up the patient, unless the patient decides otherwise, in which case it is accepted this will not be possible. Exact status determined by the subject e.g. withdrawal from treatment but follow-up permitted, withdrawal from study with follow-up not permitted, will be recorded on the eCRF.

6.6 Recruitment, consent and randomisation processes

6.6.1. Eligibility Screening

All participants screened for eligibility for the trial, including those who go on to be randomized, will be included on the trial-specific screening log. Anonymised information will be collected including:

- Age
- Gender
- Ethnicity
- Date screened
- Randomised/Not randomised
- If not randomised, reason for non-randomisation:
    - Not eligible for trial participation and reason for this, or

- Eligible but declined and reason for this, or
- Other reason for non-randomisation

This information will be collected and reviewed throughout the trial.

6.6.2. Recruitment and informed consent

Patients will be approached during routine appointments and will be provided with verbal and written details about the trial. A verbal explanation of the trial together with the Patient Information Sheet (PIS) and Informed Consent Form (ICF) will be provided by the patient's clinical team (medical and nursing). This will include detailed information about the rationale, design and personal implications of the trial.

Following information provision, patients will have as long as they need to consider participation (a minimum of 24 hours is advised) and will be given the opportunity to discuss the trial with their family and other healthcare professionals before they are asked whether they would be willing to participate.

Assenting patients will then be formally assessed for eligibility and invited to provide informed, written consent. The eligibility decision will be recorded by a clinician delegated to do so and will be recorded in the patient's notes and in the eCRF. The Chief Investigator, or any other clinically qualified member of the trial team who has received Good Clinical Practice (GCP) training and is authorised on the trial delegation log, are permitted to receive informed consent. Where the patient is able to provide fully informed consent but is unable to sign or otherwise mark the consent form, provision for completion of the consent form by a witness will be made. This should be a carer, friend/family member, or a local member of the clinical team who is independent of the research team. Where English is not the patient's first language every effort will be made to provide a Trust interpreter according to normal Trust procedures. The right of the patient to refuse consent without giving reasons will be respected. Further, the patient will remain free to withdraw from the study at any time without giving reasons and without prejudicing any further treatment.

A record of the consent process detailing the date of consent will be kept in the patient's notes. The original ICF will be retained in the Trial Master File (TMF), a copy of the ICF will be given to the patient and a second copy filed in the hospital notes (as per local practice).

Where valid, informed consent is obtained from the patient and the patient subsequently becomes unable to give informed consent by virtue of physical or mental incapacity, the consent previously given when capable remains legally valid. Patients who lose capacity after informed consent has been obtained will continue with protocol treatment and follow-up at the discretion of the treating investigator.

6.6.3. Randomisation process

Patients will be randomised on a 1:1 basis to receive combination therapy of golimumab and methotrexate or methotrexate monotherapy and placebo. Randomly-permuted block sizes will be used; randomisation will be stratified by the number of involved joints (oligoarticular: ≤4 joints involved /polyarticular: >4 joints involved).

Informed written consent for entry into the trial must be obtained prior to randomisation. Randomisation is subject to the participant fulfilling all the eligibility criteria. Randomization should take place as soon as possible after consent is provided and must be performed by an authorized member of the clinical team at the site using the LTHT Pharmacy randomisation service.

Note that patients must complete their baseline quality of life questionnaires prior to randomisation (see section 8.8).

The following information is required in order for the patient to be randomized. The delegated member of the research team operating the randomization should have all necessary details to hand:

- Patient initials and date of birth
- Name of person undertaking randomisation
- Name of the treating investigator
- Confirmation of eligibility
- Confirmation of written informed consent and date
- Oligo/polyarthritis status
- Confirmation that baseline quality of life questionnaires have been completed

A unique GOLMePsA trial IMP kit identifier will be assigned at randomization but neither patients nor the clinical team will be informed of their allocated treatment arm.

After randomization the research team will:

- Ensure that patients are notified of their appointment dates.
- Notify the patient's GP of their participation in the trial (using the current REC-approved letter template)

Following patient randomisation, the authorised person performing the randomisation must complete the Patient Randomisation form. The Patient Randomisation will contain the patient's details (initials, date of birth, trial number) and the date of randomisation.

LTHT Pharmacy will also complete a Patient Randomisation form. The Patient Randomisation form completed by LTHT Pharmacy will contain the patient's details (initials, date of birth, trial number), the date of randomisation and treatment allocation.

6.6.4. Study Blinding

6.6.4.1. Type of blinding

The trial will be double-blind.

6.6.4.2. Procedure for production and maintenance of blind

Pre-filled syringes will be available from pharmacy (provided by Janssen Biologics BV) with identical external appearance and no identifiers aside from the patient's study number. The internal fluid will be visible to the naked eye. It will be impossible for either the patient or the study nurse/doctor to identify the product as either golimumab or placebo. The placebo injections will also be provided by Janssen Biologics BV and will consist of an aqueous medium of histidine sorbitol and polysorbate 80 at pH 5.5.

6.6.4.3. Breaking the blind in an emergency

Emergency unblinding (during normal working hours and out of hours) refers to breaking the blind revealing to which arm the patient has been randomized. This should be done only when, in the judgement of the treating physician, emergency unblinding is absolutely necessary for the

management of an individual patient and where stopping the blinded medication is not sufficient. Blinding codes should, if possible, be broken on the instruction of the Chief Investigator. However, where emergency unblinding is deemed necessary, the inability to contact the Chief Investigator will not preclude the act of unblinding. During working hours unblinding can be facilitated by contacting the clinical trials pharmacy team. Out of hours the treating physician should contact the on-call pharmacist. The LTHT pharmacy will follow the emergency unblinding procedures as identified in their Standard Operating Procedure.

6.6.5. Patients who withdraw consent

All patients have the right to withdraw consent at any time without prejudice. At the time of withdrawal of consent, a full efficacy and safety evaluation should be performed if patient consents. Patients who withdraw from study treatment will be encouraged to continue to attend for follow-up after that point but they remain free to entirely withdraw from all trial procedures at any time.

Unless the patient specifically withdraws consent for their data to be stored, all data and samples collected from them will continue to be stored as per the original patient consent.

6.6.6. Managing/replacing patients who withdraw early

Follow-up information will be obtained at the time of withdrawal for patients who discontinue study participation or are withdrawn from the study.

For patients who prematurely withdraw from the study, final procedures will be performed at the time of the withdrawal visit (see section 8.15).

Patients withdrawn from the study will not be replaced, regardless of the reason for withdrawal. An effort must be made to determine why a patient fails to return for the necessary visits or is dropped from the study. This information should be recorded on the patient's eCRF.

6.6.7. Definition for the end of the trial

The end of the trial is defined as the date when the last recruited patient’s last data item is captured in the eCRF.

STUDY TREATMENTS

7.1 General information on the products (trial drugs) to be used

Product	Dosage Form	Dosage Regimen	Duration
Golimumab	50 mg* SC injection	4 weekly	24 weeks
Placebo	SC injection	4 weekly	24 weeks
Methotrexate	2.5 mg or 10 mg tablets (50mg/mL prefilled syringes)	Weekly (maximum 25 mg)	For duration of study (& post study completion)

**100 mg Golimumab will be used if patient ≥100 kg in weight.*

7.2 Investigational medicinal product (IMP)

Within the trial the following are classed as Investigational Medicinal Products (IMPs):

- **Golimumab (Simponi®):**
  - Golimumab (Simponi®) and placebo solution for injection in pre-filled syringe.
  - Composition: One 0.5 ml pre-filled pen or pre-filled syringe contains 50 mg of golimumab, histidine, sorbitol and polysorbate 80 at pH5.5.
  - Golimumab and placebo provided by Janssen Biologics BV

7.2.1. Summary of product characteristics (SmPC)

The SmPC for golimumab (Simponi®), with particular reference to its section 4.8, will be used in this study as the main RSI document (see section 9.4).

7.3 Non-Investigational Medicinal Product (NIMPs)

Within the trial treatment intervention, the following are classed as Non-Investigational Medicinal Product (NIMPs):

- **Methotrexate**

Methotrexate will be administered orally in both treatment arms at a starting dose of 15mg weekly. If tolerated, it will be increased to 20mg and 25mg weekly at weeks 2 and 4 respectively in both treatment arms.

Subcutaneous MTX may be administered if intolerance to oral MTX is observed.

MTX will be prescribed by the research team and supplied by the hospital pharmacy.

- **Corticosteroids: methylprednisolone**

Both groups will receive corticosteroids at baseline up to a dose of 120 mg methylprednisolone (unless contraindicated or not tolerated). This will be performed either as a stat bolus intra-muscular injection (if ≥4 swollen joints) or as intra-articular injections (to a maximum of 4 joints injected per visit; 20-80mg per joint with the remainder, if appropriate, given as an intra-muscular injection). The steroid dose administered per joint will be as follows: 80 mg for shoulders, knees or hips; 40 mg if ankles, wrists or elbows; 20 mg if small joints of hands or feet.

Oral steroids (regardless of the indication) are not allowed until week 24. Failure to comply will result in withdrawal from trial medication (section 7.10). The use of other forms of steroids until week 24 is restricted (as mentioned in exclusion criteria 17, section 6.3.3 of this protocol).

After the completion of trial-related procedures pertaining to week 24, any form of steroid is allowed in accordance to indication and national/local guidance.

7.4 Administration/handling of the trial drugs

7.4.1. Handling, storage and supply

Study drug(s) will be delivered to pharmacy and labelled according to the terms of the trial's MHRA approval.

7.4.2. Administration of the trial drugs

Golimumab (Simponi®) should be injected subcutaneously once every four weeks.

In patients weighing 100 kg or more at baseline, the starting dose of golimumab will be 100 mg four weekly to be continued for the duration of the interventional period (week 0 to 24), even in cases of subsequent intentional weight loss.

In these cases, the investigators, taking into account the increased risk of certain serious adverse drug reactions with the 100 mg dose compared with the 50 mg dose (see section 7.7 and section 7.8) will perform regular monitoring as specified in the summary schedule of study assessments (section 8.6).

The IMP will be administered by a suitably qualified and authorised member of the research team (i.e. study doctor or nurse) in an outpatient clinic setting within The Leeds Teaching Hospitals NHS Trust.

7.5 Prior and concomitant illnesses

Any concomitant diseases not included in the exclusion criteria are to be controlled using appropriate medication before the patient enters the study and if medically appropriate, the medication is to be continued during the entire study period. Concomitant medical conditions, any relevant medications, and any changes to both of these will be documented appropriately in the eCRF. Any new illness or worsening of a previous medical condition is to be recorded as an AE.

7.6 Prior and concomitant medications

7.6.1. Prohibited prior medications

Prohibited prior medications are listed on the exclusion criteria.

7.6.2. Permitted concomitant medications

All concomitant medication taken during the study must be recorded on the source data worksheets. Treatment with concomitant PsA and coexisting Pso therapies during the study is permitted only as outlined in the exclusion criteria (section 6.3.2 and section-6.3.3) and described in the paragraphs below. Patients taking permitted medication should be on chronic stable doses at the baseline visit (week 0).

The following medications will be permitted during the interventional period (week 0 to 24):

1. Folic Acid

All patients will receive folic acid prophylaxis with generic 5mg tablets 6 days/week given orally (except day of methotrexate). Folic acid will be supplied locally by the Trust's pharmacy.

2. Corticosteroids

Period 1 (Double blind randomised phase): Both groups will receive corticosteroids at baseline up to a dose of 120 mg methylprednisolone (unless contraindicated or not tolerated). This will be performed

either as a stat bolus intra-muscular injection (if ≥4 swollen joints) or as intra-articular injections (to a maximum of 4 joints injected per visit; 20-80mg per joint with the remainder, if appropriate, given as an intra-muscular injection). In addition, any swollen joint observed at subsequent visits (only at either week 8 or at week 12) may be injected with methylprednisolone (20-80 mg per joint) to a maximum dose of 120 mg methylprednisolone into a maximum of four joints between both visits. In case of ≥4 swollen joints at either week 8 or at week 12, a dose of methylprednisolone 120 mg IM could be administered instead of intra-articular injections. Any injections at baseline will ONLY be done after the baseline US and WB-MRI scan has been performed. No corticosteroid injections will be allowed between weeks 12 and 24. Other limitations apply as outlined in section 7.3.

Use of oral corticosteroid will not be permitted until week 24.

Period 2 (Observational phase): use of steroids will be permitted after completion of trial-related procedures pertaining to week 24. Patients will be allowed to receive up to 240 mg IM or IA corticosteroid injections if the investigator deems that there is still on-going disease activity until the end of the study period and unless a clinical or imaging assessment is scheduled within the following 6 weeks. The joint(s) injected must be recorded along with the medication taken on the examination section of the corresponding eCRF.

3. NSAIDs

Patients will be permitted to be on non-steroidal anti-inflammatory drugs (NSAIDs) for the duration of the study. Every effort should be made to maintain stable doses of concomitant NSAIDs during the study. In the event of tolerability issues, the NSAID dose may be decreased or discontinued, with the substitution of another NSAID. Data will be collected on NSAID use throughout the trial. NSAIDs should not exceed the maximum recommended dose and patients should be on only one NSAID at a time.

4. Analgesics

Simple analgesics with no anti-inflammatory action may be used.

5. Aspirin

Aspirin at daily doses of up to 150 mg is permitted if indicated for cardiovascular protection.

Any concomitant diseases not included in the exclusion criteria are to be controlled using appropriate medication before the patient enters the study and, if medically appropriate, the medication is to be continued during the entire study period. Concomitant medical conditions, any relevant medications, and any changes to both of these will be documented appropriately in the eCRF. Any new illness or worsening of a previous medical condition is to be recorded as an AE.

After the first 24 weeks (Period 2: Observational phase phase), the addition of DMARDs will be allowed at the discretion of the investigator if it is thought that there is on-going disease activity.

During the double-blind treatment period (week 0 to week 24) any dose adjustment, changes of NSAIDs, and/or introduction of a new NSAID is not permitted, unless required for safety reasons or for rescue therapy.

7.6.3. Prohibited concomitant medications

The following therapies will NOT be permitted during the interventional period (week-0-baseline-visit to week 24):

- PsA and coexisting Pso therapies that are defined as prohibited in the exclusion criteria.

- Any therapy within the washout periods specified in the exclusion criteria (see exclusion criteria 17, section 6.3.3).
- Live vaccines (including BCG)

7.6.4. Surgical procedures

Planned surgery within the study period which is expected to require omission of any study medication of 28 days or more will not be permitted during the course of the study.

7.7 Special warnings and precautions for use

Please consult the SmPC for further details.

7.8 Dose modifications

Patients will receive 50mg of golimumab unless at the time of baseline they are 100 kg of weight or over (see also section 7.4) In this case they will be eligible for 100mg golimumab. Golimumab dose will not be altered throughout the interventional period of the trial (week 0 to 24).

7.9 Assessing subject compliance with trial treatment(s)

Every attempt will be made to select patients who have the ability to understand and comply with study instructions. The investigator is responsible for discussing methods to ensure high treatment compliance with the patient before randomization.

If a patient is noncompliant with any study procedure, the investigator should assess the patient to determine the reason and educate and/or manage the patient as appropriate to improve compliance. Specific instances of non-compliance to trial treatment, which would result in withdrawal, are mentioned in section 7.3.

7.10 Withdrawal of trial treatment

Patients showing an unacceptable degree of disease activity (not achieving a PsARC response) beyond week 12 and before the week 24 assessment may be withdrawn from study medication (i.e.: trial intervention) at the discretion of the chief investigator (or medically-qualified delegate) and treated as clinically indicated. At week 24 patients with MDA will continue with their allocated treatment and undergo further assessments as per protocol (see section 5.1).

Patients **MUST** be withdrawn from the study treatment if any of the following occur:

- Pregnancy
- Grade 4 or 5 systemic toxicity (see appendix 2) or a serious adverse event (SAE) thought to be related to study treatment and not alleviated by symptomatic treatment after cessation of the IMP for up to 2 weeks.
- Recurrent serious infection requiring parenteral (intravenous or intramuscular) antimicrobial agents or hypotension suggestive of impending sepsis syndrome.
- Confirmed blood dyscrasia or a demyelinating disorder (such as multiple sclerosis or optic neuritis)
- Lack of patient compliance with the trial intervention (section 7.3)
- If missing 2 or more consecutive IMP doses.
- When visit attendance during period 1 of the trial (between week 0 and week 24) is delayed by more than 10 days of the mandated window visit date (see also timeline reference in the summary schedule of study assessments, section 8.6)

- Withdrawal of consent (during either interventional period or observational period, see section 8.6)
- Chief Investigator decision

All patients recruited to this study, irrespective of therapy change (as outlined above) will continue to be followed up for the 52 week study duration with imaging and immunological studies as per protocol, with the exception of those who withdraw consent to continue with study assessments.

As far as possible, all examinations scheduled for the final study day must be performed on all subjects who receive the investigational product but do not complete the study according to protocol.

The investigator must make every effort to contact subjects lost to follow-up. Attempts to contact such subjects must be documented in the subject's records (e.g., times and dates of attempted telephone contact, receipt for sending a registered letter).

7.10.1. General/study-related withdrawal criteria

- When personal circumstances mean that the regular visits required by the protocol can no longer be guaranteed
- Inability of the subject to comply with study requirements
- If intercurrent disorders develop which rule out continuation of study medication i.e. determination by the investigator that it is no longer safe for the subject to continue therapy
- If disallowed drugs are administered (see section 7.6.3).
- If a SAE occurs, the patient could be withdrawn at the discretion of the investigator.

METHODS OF ASSESSMENT

8.1 Assessment of primary efficacy variable

PASDAS is a recently developed composite measure of disease activity in Psoriatic arthritis that is represented by a single score and which provides quantitative measures of improvement based on baseline scores and changes from baseline. The PASDAS has been shown to perform well not only in polyarticular but also oligoarticular PsA (34).

The PASDAS will not be performed at the bedside when assessing participants as it is a composite measure. Individual components will be assessed to allow calculation of the PASDAS at the time of data analysis as only an outcome measure. Its formula is calculated as follows:

PASDAS= (((0.18 x √Physician global VAS) + (0.159 x √Patient global VAS) - (0.253 x √SF36 - PCS) + (0.101 x LN (Swollen joint count + 1)) + (0.048 x LN (Tender joint count + 1)) + (0.23 x LN (Leeds Enthesitis Count + 1)) + (0.377 LN (Tender dactylitis count + 1)) + (0.102 x LN (CRP + 1)) +2)*1.5.

8.2 Assessment of secondary efficacy variable(s)

8.2.1. C-Reactive Protein

Standard C-reactive protein (mg/L) will be the selected acute phase reactant.

8.2.2 Tender joint count

The number of tender and painful joints will be determined by examination of 78 joints (39 joints on each side of the patient's body, see appendix 7). Joints will be assessed for tenderness by pressure and joint manipulation on physical examination. The patient will be asked for pain sensations on these manipulations and watched for spontaneous pain reactions. Any positive response on pressure, movement, or both will then be translated into a single tender-versus-non tender dichotomy. The same assessor should preferably perform the TJC and SJC for a given patient particularly during the first 24 weeks of the study to minimize inter-observer variation. Missing, replaced, ankylosed, or arthrodesed joints will be identified by the investigator at the Screening Visit and will be excluded from evaluation during the trial.

8.2.3 Swollen joint count

The number of swollen joints will be determined by examination of 76 joints (38 joints on each side of the patient's body, hip joints not encompassed, see appendix 7). Joints will be classified as either swollen or not swollen. Swelling is defined as palpable fluctuating synovitis of the joint. Swelling secondary to osteoarthritis will be assessed as not swollen, unless there is unmistakable fluctuation. Where possible, the same assessor should preferably perform the TJC and SJC for a given patient particularly during the first 24 weeks of the study to minimize inter-observer variation. Missing, replaced, ankylosed, or arthrodesed joints will be identified by the investigator at the Screening Visit and will be excluded from evaluation during the trial.

8.2.4 Patient's Assessment of Pain Visual Analogue Scale

The patient will be asked to assess their current level of joint pain by marking a vertical line on a 100 mm horizontal VAS where 0 represents no joint pain ("excellent") and 100 represents worst imaginable joint pain ("poor"). The Patient's Assessment of Pain VAS should be administered prior to the TJC and SJC examinations. Results will be expressed in millimetres measured between the left end of the scale and the crossing point of the vertical line; this procedure is applicable for all VAS used in the trial (see appendix 6).

8.2.5 Patient's Global Assessment of Disease Activity Visual Analogue Scale

The patient's overall assessment of their PsA activity will be recorded using the 100 mm horizontal VAS where 0 or left end represents "no disease activity" or "excellent" and 100 or right end represents extremely active disease "poor". The wording proposed by Cauli et al (35) referring specifically to PsA will be used (see appendix 6).

8.2.6 Physician's Global Assessment of Disease Activity Visual Analogue Scale

The Investigator will be asked to give an overall assessment of the severity of the patient's current PsA activity using a 100 mm horizontal VAS, where 0 at the left end represents no disease activity ("Disease not active") and 100 on the right end represents extremely active disease ("Disease extremely active"). The investigator making the assessment must be a rheumatologist or medically qualified physician. The same assessor should preferably perform the Physician's Global Assessment of Disease Activity VAS for a given patient particularly during the first 24 weeks of the study to minimize inter-observer variation.

8.2.7 Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)

The BASDAI is a self-administered questionnaire measure used to answer 6 questions (on a Likaert scale ranging from 0-10) pertaining the 5 major symptoms of axial activity: 1) fatigue, 2) neck, back or hip pain, 3) joint pain/swelling other than neck, back or hips, 4) areas of localized tenderness, 5) overall level of morning stiffness, and 6) duration of morning stiffness (36). To give each symptom equal

weighting, the mean of the 2 scores relating to morning stiffness is taken. The resulting 0 to 50 score is divided by 5 to give a final 0 to 10 BASDAI score.

8.2.8 Leeds Enthesitis Index (LEI)

The LEI has been developed specifically for use in PsA. It measures enthesitis at 6 sites (lateral epicondyle, left and right, medial femoral condyle, left and right, Achilles tendon insertion, left and right) (37). Each site is assigned a score of 0 (absent) or 1 (present); the results from each site are then added to produce a total score (range 0 to 6). The LEI will be administered by a suitably trained member of the research team.

8.2.9 Leeds Dactylitis Index

If a patient has dactylitis, the LDI-will be administered by site personnel. The LDI has been developed to measure the severity of dactylitis. Once the presence of dactylitis is established in each digit, the ratio of the circumference of the affected digit to the circumference of the digit on the opposite hand or foot is measured (38). Each dactylitic digit is defined by a minimum increase of 10% in circumference over the contra-lateral digit. If the same digits on each hand or foot are thought to be involved, the clinician will refer to a table of normative values for a value which will be used to provide the comparison. The calculated ratio is then multiplied by a tenderness score of 0 (non-tender), 1 (tender), 2 (tender and wince) or 3 (tender and withdraw). Tenderness is assessed in the area between the joints. The results of each digit are then added to produce a total score (39).

8.2.10 Health Assessment Questionnaire-Disability Index

The HAQ-DI is a patient-reported standardized questionnaire that is commonly used in PsA to measure disease-associated disability (assessment of physical function). It consists of 24 questions referring to 8 domains: dressing/grooming, arising, eating, walking, hygiene, reach, grip, and other daily activities(40).

The disability section of the questionnaire scores the patient's self-perception on the degree of difficulty (0 = without any difficulty, 1 = with some difficulty, 2 = with much difficulty, and 3 = unable to do), covering the 8 domains. The reported use of special aids or devices and/or the need for assistance of another person to perform these activities is also assessed. The scores for each of the functional domains will be averaged to calculate the functional disability index.

8.2.11 Minimal Disease Activity (MDA)

Minimal disease activity or MDA (27) is defined as any patient who meets at least 5 of the 7 following criteria:

Tender joint count ≤1; Swollen joint count ≤1; PASI ≤1; Patient pain VAS ≤15; Patient global disease activity VAS ≤20; HAQ ≤0.5; Enthesitis count ≤1.

8.2.12 Psoriatic Arthritis Response Criteria (PsARC)

The PsARC (7, 8) is a composite assessment reported in terms of the percentage of patients achieving response according to the following criteria: Physician's Global Assessment of Disease Activity, Patient Global Assessment of Articular Disease Activity, tender joints grading, and swollen joints grading. Overall response is defined by improvement from baseline assessment in 2 of 4 criteria, 1 of which must be a joint count; there must not be worsening in any of the 4 criteria:

1. At least 30% reduction in tender joints grading (grading of 68 joints instructions: as in appendix 7; CMC and DIP of the feet excluded)

2. At least 30% reduction in swollen joints grading (grading of 66 joints instructions: as in appendix 7; CMC, hips and DIP of the feet excluded)
3. At least a 1 point reduction in physician's assessment of articular disease (1-5 Likaert scale)
4. At least a 1 point reduction in patient's assessment of articular disease (1-5 Likaert scale)

8.2 13 American College of Rheumatology 20 Responder Index (ACR20)

ACR20 response (6) is an efficacy measure for which a patient must have:

- ≥20% improvement in both TJC (68 joints count: as in appendix 7; CMC and DIP of the feet excluded) and SJC (66 joints count: as in appendix 7; CMC, hips and DIP of the feet excluded) and
- ≥20% improvement in at least 3 of the following 5 ACR Core set criteria:

    1. Patient's Assessment of Pain on Visual Analogue Scale (VAS)
    2. Patient's Global Assessment of Articular Disease Activity VAS
    3. Physician's Global Assessment of Disease Activity VAS
    4. Patient's Assessment of Physical Function as measured by the HAQ-DI
    5. Acute phase reactant as measured by CRP

ACR50 and ACR70

ACR50 and ACR70 responses are secondary efficacy endpoints and are improvements of at least 50% and of at least 70%, respectively, in the multiple disease assessment ACR criteria. The ACR50 and ACR70 are calculated similarly to ACR20, as described above.

8.2.14 Composite Psoriatic Disease Activity Index

Composite Psoriatic Disease Activity Index is a validated instrument intended to assess composite psoriatic disease activity and response to therapy (30). This instrument assesses individual domains involved as well as the global effect of disease in all dimensions by which each patient may be affected. Domains include peripheral arthritis as assessed by the number of tender (68 joints count: as in appendix 7; CMC and DIP of the feet excluded) and swollen (66 joints count: as in appendix 7; CMC, hips and DIP of the feet excluded) joint and the Health Assessment Questionnaire (HAQ), skin as assessed by the PASI and the DLQI, enthesitis as assessed by the number of sites with enthesitis and the HAQ, dactylitis as assessed by the number of digits affected, and spinal disease as assessed by the BASDAI and ASQoL (41). Scores range from 0 to 15 for assessment including spinal disease (BASDAI and ASQoL) and 0 to 12 for assessment excluding spinal disease, with a higher score indicating higher disease activity.

8.2.15 Measures of skin disease activity

8.2.15.1 Percentage of Body Surface Area (BSA)

The investigator will evaluate the percentage involvement of skin psoriasis (Pso) on each patient's BSA on a continuous scale from 0% = no involvement to 100% = full involvement, where 1% corresponds to the size of the patient's handprint including the palm, fingers, and thumb.

8.2.15.2 Psoriasis Area and Severity Index (PASI 75, PASI 90, PASI 100)

If the patient has skin affected by plaque Pso, the PASI will be administered by site personnel. The PASI combines assessments of the extent of body-surface involvement in 4 anatomical regions (head, trunk, arms, and legs) and the severity of desquamation, erythema, and plaque induration/infiltration (thickness) in each region, yielding an overall score of 0 for no Pso to 72 for the most severe disease

(28). Patients achieving PASI 75, 90, or 100 are defined as having an improvement of at least 75%, 90%, or 100%, respectively, in the PASI compared to baseline.

8.2.15.3 Modified Nail Psoriasis Severity Index (mNAPSI)

A modification to the NAPSI (the modified Nail Psoriasis Severity Index, mNAPSI) removed the division of the nail into quadrants and scores pitting and crumbling on a scale from 0-3. Oil drop discolouration and onycholysis were also combined, as it was felt they represent the same pathology. In the newly modified method, each fingernail is scored for the presence and the severity of pitting, onycholysis/oil-drop dyschromia and nail plate crumbling (score 0-3) and the presence or absence of splinter haemorrhages, leuconychia, red spots in the lunula and nail bed hyperkeratosis (score 1 for each if present). We are planning to assess the oil drop dyschromia or discolouration as an independent feature (0-1) (see appendix 4). This gives a total possible score of 140. Validation as part of the original study found excellent inter-rater reliability, along with good correlation with a physician nail VAS and good intra-rater reliability (29) .

8.2.16 Quality of life and health status measures

8.2.16.1 SF-36

The SF-36 is a multi-purpose, short-form health survey with 36 questions (32). It yields an 8-scale profile of functional health and well-being scores as well as psychometrically-based physical and mental health summary measures and a preference-based health utility index. It is a generic measure, as opposed to one that targets a specific age, disease, or treatment group.

8.2.16.2 Dermatology Life Quality Index

The DLQI is a simple, patient administered, 10 question, validated, quality of life questionnaire that covers 6 domains including symptoms and feelings, daily activities, leisure, work and school, personal relationships and treatment. Response categories include “not at all”, “a lot” and “very much” with corresponding scores of 1, 2 and 3 respectively and unanswered (“not relevant”) responses scored as “0”. Totals range from 0 to 30 (less to more impairment) and a 5-point change from baseline is considered clinically relevant (31).

8.3 Assessment of other efficacy variables

8.3.1 Ultrasound of joints and entheses

Ultrasound (US) of hands and feet and lower and upper limb joints and entheses (Achilles, plantar fascia insertion, quadriceps insertion, patellar tendon origins and insertions and common extensor tendon origins of the elbow) will be performed at week 0, 12, 24 and 36 within ten days before or after the scheduled visit attendance using a multiplanar technique with symmetrical scanning. All scans will be performed, whenever possible, by the same ultrasonographer with specialist training in scanning entheses. The room will be maximally darkened starting from the beginning of the ultrasound assessment. Joints and entheseal sites will be assessed for the presence of grey scale (GS) abnormalities and power Doppler (PD) signal.

Pre-defined joints will be scanned for the presence of synovitis and bone erosions as per established rheumatoid arthritis (RA) protocols as there is currently no validated system for PsA. Synovitis will be scored according to the EULAR-OMERACT definitions for RA (42, 43) for gray scale, power Doppler and a combined PDUS score for each joint (0 if GS=0, otherwise highest of either gray scale or power Doppler score); the total of these individual PDUS scores is the Global OMERACT-EULAR Score System (GLOESS). US enthesopathy will be identified according to OMERACT definitions (44, 45). Enthesopathy is defined as ‘abnormally hypoechoic (loss of fibrillar architecture) and/or thickened

tendon or ligament at its bony attachment (may occasionally contain hyperechoic foci consistent with calcification), seen in two perpendicular planes, which may exhibit Doppler signal and/or bony changes including enthesopathy, erosions or irregularity.'

Entheseal thickening will be evaluated relative to the body of the tendon. When PD signal is detected at the cortical bone insertion, it will be considered entheseal. When PD signal is detected at the tendon body and/or adjacent bursitis, it will be considered perientheseal and therefore not documented.

Thickness and erosion assessments will be scored quantitatively. Thickness findings will be scored on a scale between 0 and 3.

Grade 0: <1mm exceeding the normal threshold

Grade 1: ≥ 1mm but < 2mm exceeding the normal threshold

Grade 2: ≥ 2mm but < 3mm exceeding the normal threshold

Grade 3: ≥ 3mm exceeding the normal threshold

The maximum diameter of erosions will also be scored quantitatively:

Grade 1: >0 but <2mm

Grade 2: ≥2 but <3mm

Grade 3: ≥3mm

Entheseal power Doppler will be scored on a semi-quantitative basis:

Grade 1: Mild changes

Grade 2: Moderate changes

Grade 3: Severe changes

The remainder of the assessments (hypoechogenicity, enthesophytes, calcifications) will be scored present (1) or absent (0).

Once all aspects have been scored, the cumulative totals will be calculated to formulate and 'inflammation score' and a 'chronicity score'

Inflammation score: GS changes related to inflammation (entheseal hypoechogenicity and thickening) will be added to the PD scores.

Chronicity score: GS changes related to chronic findings (calcifications, erosions and enthesophytes) will be totalled.

US scores forming secondary endpoints will include 24 joints (bilateral wrists, MCPs 2&3, PIPs 2&3, knees, MTPs 1-5, ankle) and 10 entheses (bilateral quadriceps insertion, patellar ligament proximal insertion, patellar ligament distal insertion, Achilles tendon, plantar fascia). Exploratory analysis of synovitis and enthesitis will be performed in a subset of patients using scores calculated according to the newly published OMERACT definitions which include 48 joints (bilateral wrists, MCP1-5, PIP1-5, DIP2-5, knees, MTP1-5, tibiotalar, talonavicular and subtalar) and 12 entheses (bilateral lateral

epicondyle, quadriceps insertion, patellar ligament proximal insertion, patellar ligament distal insertion, Achilles tendon, plantar fascia) (42, 43).

Patients will be considered to be in US remission if the maximum score for any of the joints forming part of the established RA scoring protocol, and for any of the entheses scanned in all patients, is GS entheseal hypoechogenicity score <2 and power Doppler score=0. On an exploratory basis this will be repeated using scores calculated in the joints and entheses included in the OMERACT definitions, in the subset of patients with these scores available.

8.3.2 Radiographs of hands and feet

During screening all patients meeting entry criteria will have a single postero-anterior radiographic assessment of the left and right hand/wrist and a single dorso-plantar radiographic image taken of the left and right foot, unless these have been performed within 3 months of the screening visit. Images will be assessed by the study physician and/or radiologist and assessed for the presence of ill-defined ossification near joint margins (excluding osteophyte formation) for the purpose of fulfilment of CASPAR criteria(33).

8.4 Clinical assessments for evaluating safety

8.4.1 Physical examination

A complete physical examination will be performed that will include the examination of general appearance, head, neck, thyroid, ears, nose, throat, cardiovascular apparatus, respiratory apparatus, abdomen, neurological apparatus, skin, musculoskeletal system (related and non-related to PsA). Information for all physical examinations must be included in the source documentation.

8.4.2 Chest x-ray

During screening all patients meeting entry criteria will have a single postero-anterior radiographic assessment of the chest, unless this has been performed within 3 months of the screening visit. Images will be evaluated by the study physician and/or radiologist and assessed for the presence of findings compatible with exclusion criteria.

8.4.3 Electrocardiogram

During screening a standard 12-lead ECG will be performed. The study physician must review and initial the tracing. The tracing must then be stored in the participant's source documents. Tracings will be evaluated by the study physician and assessed for the presence of findings compatible with exclusion criteria. If the ECG findings are clinically relevant and would prevent the patient from participating in the study (taking into account the participant's overall health status as well as the medication profile), the participant should be recorded as screening failure, should NOT be enrolled and should not receive the trial intervention.

8.5 Assessment of exploratory variables

8.5.1 Whole-Body MRI

Whole body MRI scan will be performed to assess for entheseal, bone marrow and synovial involvement of both the axial and peripheral skeleton at baseline and weeks 24 and 36, within ten days before or after the scheduled visit attendance.

Scans will be performed using a commercially available 3T scanner. Fitness to undergo MRI scan will be assessed during the screening process. To comply with MRI guidance, the blood test urea & electrolytes (U&Es) needs to be up-to-date (within 4 weeks of each scan): see also section 8.6.

Participants unable to undergo MRI scanning (due to contraindication) remain eligible to the GOLMePsA trial.

MR sequences

Systematic scanning of the axial and peripheral skeleton will be performed in all subjects, using the following sequences:

- T1-weighted spin echo (SE) before and after an IV Gadolinium contrast injection.
- Short Tau Inversion Recovery (STIR).

It is expected that each scan will take around 60 min to be performed. Images will be acquired in two phases with patients allowed to mobilize from the scanner for a short time.

WB-MRI images will be assessed for incidental abnormalities –and not for scoring- by LTHT radiologists blinded to treatment allocation. Findings unrelated to PsA and implicating safety concerns or conditions requiring clinical (as per NHS guidance) action will be reported to the research team.

Image evaluation and features to be scored

All MRI images produced by GOLMePsA data collection will be assessed and scored using the following reading methods: SPARCC – SPINAL INFLAMMATION (46); SPARCC – SACRO-ILIAC JOINTS INFLAMMATION (47); HIMRISS (48); KIMRISS (49); CANDEN MRI spine scoring system (50); HEMRIS (51); MRI-WIPE (52). Methods are detailed in appendix 8.

8.5.2 Laboratory exploratory biomarkers

In total, this study will require an additional 60 ml of blood to be collected as specified in the schedule of study procedures (section 8.6) time of early discontinuation, and at time of flare for determination of exploratory biomarkers. This will include collection of red-topped clotted tubes, EDTA tubes and lithium heparin green-topped tubes.

A sample of urine will also be collected.

The exploratory biomarker variables include inflammation biomarkers i.e. to explore prediction of response/non-response.

The sampling, handling, and shipment (if appropriate) of samples for the exploratory biomarkers should be performed as per local LIRMM laboratory Standard Operating Procedures.

Patients can opt out of this part of the study, as they will be asked to sign a specific consent form for a Biological Sub-study.

8.5.2.1 Soluble biomarkers

Serum samples collected will also be stored (at baseline and at time-points of sample collection previously stipulated) for future evaluation of disease categorisation, auto-antibodies, inflammatory, immunological and vascular biomarkers and products of synovial, cartilage and bone turnover in this and future studies (subject to ethical review of such studies).

8.5.2.2 Genetic Studies

Diseases such as psoriatic arthritis may be associated with the presence of specific changes in an individual's genetic makeup, contributing to the disease process and predicting susceptibility or severity to the disease and/or response to specific therapies. An aliquot of all DNA samples will ultimately be entered into both national and international genetics studies, since large numbers of samples are required to undertake these studies. However, the genetic information will be used solely for research purposes.

8.5.2.3 Sample Storage

Personal details will be removed from all biological research blood samples after separation into the component parts, and a pseudo-anonymisation code will be generated. It will be possible to link the clinical and laboratory databases through this unique laboratory code so that we can look at long-term disease outcomes and predictors of response to future treatments. Any samples and residual cellular materials that are not used at the end of this study will be stored in an HTA licensed sample repository once project specific approval expires and will be used in future studies within this research remit.

8.6 Summary schedule of study assessments.

Study Period	***Period 1: Double-blind randomised***								***Period 2: Observational****				** *Withdrawal visit*
Study Phase	*Screen*	*Baseline*	*(Safety)*	*(Safety)*	*Secondary outcome*	*(Safety)*	*(Safety)*	*Primary outcome*	*(Safety)*	*Secondary outcome*	*End of study visit*	*Extra Visit*	
Week	***–4 to 0***	***0***	***4*** *(±7 days)*	***8*** *(±7 days)*	***12*** *(±7 days)*	***16*** *(±7 days)*	***20*** *(±7 days)*	***24*** *(±7 days)*	***28*** *(±7 days)*	***36*** *(±7 days)*	***52*** *(±7 days)*	***Y******	***X***
Visit number	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*11*	*98*	*99*
Full informed Consent	X												
Confirmation of on-going consent		X	X	X	X	X	X	X	X	X	X	X	X
PsA CASPAR criteria	X	X											
Inclusion / Exclusion Criteria	X	X											
Randomisation		X											
Adverse events evaluation			X	X	X	X	X	X	X	X	X	X	X
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X
Demographic data (smoking, alcohol intake)	X												
Medical, surgical and family history	X												
PsA-related history (Articular symptoms onset date; PsA diagnosis date; skin psoriasis onset date; psoriasis diagnosis date)	X												
Duration of articular morning stiffness	X	X	X	X	X	X	X	X	X	X	X	X	X
Back pain symptoms		X											
PsA-related comorbidities	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs (blood pressure; heart rate; bodily temperature)	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight	X	X	X	X	X	X	X	X	X	X	X	X	X
Height; body mass index	X												
Physical Examination	X												X

Study Period	***Period 1: Double-blind randomised***								***Period 2: Observational****				*** Withdrawal visit*
Study Phase	*Screen*	*Baseline*	*(Safety)*	*(Safety)*	*Secondary outcome*	*(Safety)*	*(Safety)*	*Primary outcome*	*(Safety)*	*Secondary outcome*	*End of study visit*	*Extra Visit*	
Week	***–4 to 0***	***0***	***4*** *(±7 days)*	***8*** *(±7 days)*	***12*** *(±7 days)*	***16*** *(±7 days)*	***20*** *(±7 days)*	***24*** *(±7 days)*	***28*** *(±7 days)*	***36*** *(±7 days)*	***52*** *(±7 days)*	***Y******	***X***
Visit number	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*11*	*98*	*99*
76/78 joints Tender and Swollen Joint assessment (count and grading)	X	X		X	X			X		X	X	X	X
PsA type classification		X											
Leeds Dactylitis Index	X	X			X			X		X	X	X	X
Leeds Enthesitis Index	X	X			X			X		X	X	X	X
PASI		X			X			X		X	X	X	X
BSA		X			X			X		X	X	X	X
mNAPSI		X			X			X		X	X	X	X
Psoriasis subtype and site classification		X											
Psoriasis-related symptoms		X											
PsARC				X	X			X		X	X	X	X
Infectious hepatitis serology/ HIV test	X												
Biochemistry (including CRP) / Haematology, ESR	X	X	X	X	X	X	X	X	X	X	X	X	X
Immunology tests[1]: ANA (including dsDNA) anti-CCP and RF	X										X	X	X
Blood and urine collection for biomarkers (Biological Sub-study)		X			X			X		X	X	X	X
Urinalysis[2]	X												
Pregnancy test[3]	X												
Whole-Body MRI (WB-MRI)[4]	X							X		X		X[6]	X[6]

Study Period	***Period 1: Double-blind randomised***								***Period 2: Observational****				** *Withdrawal visit*
Study Phase	*Screen*	*Baseline*	*(Safety)*	*(Safety)*	*Secondary outcome*	*(Safety)*	*(Safety)*	*Primary outcome*	*(Safety)*	*Secondary outcome*	*End of study visit*	*Extra Visit*	
Week	***–4 to 0***	***0***	***4*** *(±7 days)*	***8*** *(±7 days)*	***12*** *(±7 days)*	***16*** *(±7 days)*	***20*** *(±7 days)*	***24*** *(±7 days)*	***28*** *(±7 days)*	***36*** *(±7 days)*	***52*** *(±7 days)*	***Y******	***X***
Visit number	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*11*	*98*	*99*
Musculoskeletal US scan[5]	X				X			X		X		X[7]	X[7]
Chest-X-ray[1], ECG	X												
Plain X-ray of Hands and Feet[1]	X												
X-ray of the orbits[1]	X												
Physician VAS global disease Activity	X	X			X			X		X	X	X	X
Physician Likaert scale, articular disease Activity	X	X		X	X			X		X	X	X	X
Patient VAS global disease Activity	X	X			X			X		X	X	X	X
Patient VAS articular pain	X	X			X			X		X	X	X	X
Patient Likaert scale, articular disease Activity	X	X		X	X			X		X	X	X	X
HAQ	X	X			X			X		X	X	X	X
DLQI		X			X			X		X	X	X	X
SF-36	X	X			X			X		X	X	X	X
ASQoL		X			X			X		X	X	X	X
BASDAI		X			X			X		X	X	X	X
Administration of SC IMP[8]		X	X	X	X	X	X	X					

1. At screening visit; end of study visit (visit 11, week 52); extra visit (week Y); and withdrawal visit (week X), immunology tests should not be repeated if results available within 20 days prior to study visit.

If subjects do not have a chest x-ray or hands/feet x-ray performed within 3 months of screening, an x-ray should be performed after it is certain the subject meets the inclusion/exclusion criteria (in order to minimize exposure to x-ray radiation).

X-ray of the orbits should be performed only in subjects contraindicated to WB-MRI, who report a personal history suggestive of metallic fragments present in the orbits.

2, 3. Urinalysis and Pregnancy test can be repeated in other visits as clinically indicated.

4. WB-MRI (if required) should be performed within ten days before or after the scheduled follow-up visit attendance. To comply with MRI guidance, the blood test urea & electrolytes (U&Es) needs to be up-to-date (within 4 weeks of each scan). Baseline scans should always be performed before randomization.

IMPORTANT: WB-MRI data is being used to support an exploratory endpoint, from a subset of randomised participants; WB-MRI scans will not be performed in any patients once the required sample size has been reached.

5. US should be performed within ten days before or after the scheduled follow-up visit attendance.

6, 7. No imaging (WB-MRI and/or US) to be performed if: a) withdrawal visit (numbered 99) occurs within 6 weeks of last imaging; b) flare visit (numbered 98) occurs after week 36; or if within 6 weeks of last imaging.

8. IMP administration should be every four weeks. In the case of a missed dose of IMP, the IMP can be administered at the next scheduled visit. Exposure to IMP should be captured in the medication workbook. All timed visits should take place within a seven-day window of the ideal target visit date (with the exception of the screening and baseline visits).

* Week 44: Participants will be re-supplied with anti-rheumatic drugs at this time-point, as part of NHS standard of care. The study physician will prescribe the relevant drug(s) according to local procedures. Laboratory tests will be performed according to the prescription-related monitoring requirements. No trial-related data will be collected at this time-point.

**Study week X: withdrawal visit. Subjects who discontinue prematurely during Period 1 should return for assessments associated with Week 24 visit. Participants who withdraw their consent at either period 1 or 2 should return for assessments associated with Week 24 visit (exceptions apply as per points 6,7 of this legend). See also section 6.5

*** Study week Y: extra visit to be performed only in case of flare of psoriatic arthritis. It applies only to period 2 (observational, after week 24 until week 52). For definition and management of flare between week 0 and week 24, refer to section 8.18

8.7 Screening visit

The screening period should not last longer than four weeks. The aim of the screening visit is to identify a patient who might be suitable for inclusion in the study. The following will be performed either at this visit (or during the permitted 4 week screening period) and recorded in the eCRF:

- Full informed consent.

  The patient will have received information, including the Patient Information Sheet, at least 24 hours before the screening visit. Their knowledge of the nature and objectives of the study will be verified and his/her informed consent will be obtained. The screening period will provide further opportunity for a patient to re-consider and consent will be confirmed at the baseline visit.

- Inclusion/exclusion criteria available at this time will be recorded.
- Demographic variables describing the patient (age, sex, and ethnic group), smoking and alcohol intake history
- Medical and surgical history, family history, PsA-related history will be recorded.
- Concomitant medications.
- Duration of articular morning stiffness.
- PsA-related comorbidities.
- Physical examination.
- Measurement of body weight and height; body mass index.
- Vital signs (blood pressure after a 5-minute rest, pulse rate and body temperature).
- 12-lead ECG.
- Articular examination (76 swollen and 78 tender joint counts and grading).
- Laboratory tests:
  - Haematology, blood chemistry.
  - CRP and ESR.
  - Immunology tests (ANA, anti-dsDNA, anti-CCP, RF - (unless already performed within 20 days prior to screening visit)
  - Infectious hepatitis screen (Hep B surface antigen, Hep B core antibody, anti-HCV antibody).
  - QuantiFERON test for TB testing.
  - HIV testing
  - Urinary tests:
    - Pregnancy test in female patients with child-bearing potential (see appendix 1).
    - Urinalysis (dipstick for blood, protein and nitrites).

- Patient-reported outcomes (disease activity and pain VAS, assessment of articular disease on Likaert scale, HAQ, SF-36)
- Physician VAS assessment of global disease activity and assessment of articular disease on Likaert scale.
- LEI and LDI
- MRI eligibility checklist (only to be conducted during WB-MRI subset recruitment period)
- WB-MRI (if in WB-MRI subset; to be performed between screening visit and week 0)
- US (to be performed between screening visit and week 0)
- Radiographs of chest, hands and feet (unless performed within 3 months of screening).
- Radiographs of the orbits, in subjects candidate to WB-MRI who report a personal history suggestive of metallic fragments present in the orbits.

Note: Whenever possible, physician VAS assessments should be performed by the same investigator, and joint examinations should be performed by the same assessor throughout the time course of the study to reduce potential investigator bias.

8.8 Baseline (week 0)

- Check consent has been provided and confirmed with the patient.
- Inclusion/exclusion criteria reviewed and eligibility statement recorded.
- Randomization to treatment arm (see section 6.6.3 - randomisation process).
- Concomitant medication reviewed and recorded.
- Duration of articular morning stiffness.
- Back pain symptoms
- PsA-related comorbidities.
- Vital signs (blood pressure after a 5-minute rest, pulse rate and body temperature).
- Measurement of body weight.
- Joint examination (76/78 swollen and tender joint counts and grading).
- PsA type classification.
- Blood tests:
    - Haematology, blood chemistry.
    - CRP and ESR.
    - Samples for biological research sub-study (see section 8.4.1, section 8.4.2 and section 8.4.3).
- Enthesis, dactylitis, skin and fingernail assessments.
- Psoriasis subtype and site classification, psoriasis-related symptoms.

- Physician VAS assessment of global disease activity and assessment of articular disease on Likaert scale.
- Patient-reported outcomes (disease activity and pain VAS, assessment of articular disease on Likaert scale, HAQ, BASDAI, ASQoL, SF-36, DLQI).
- Dispense study drugs according to treatment arm (see section 7.4.2).
- Administer 120mg intramuscular methylprednisolone if ≥4 synovitic joints (unless contraindicated or not tolerated) or consider intra-articular steroid injections (as per an equivalent dose of methylprednisolone; see section 7.3 and section 7.6.2).
- Prescribe MTX according to instructions in section 7.3.

8.9 Safety/Monitoring Visit (week 4, ± 7 days)

- Confirmation of on-going consent
- Review of previous blood results/reports (from Week 2 – Baseline visit).
- Adverse events evaluation.
- Concomitant medication.
- Duration of articular morning stiffness.
- PsA-related comorbidities.
- Vital signs (blood pressure after a 5-minute rest, pulse rate and body temperature).
- Measurement of body weight.
- Blood tests:
    - Haematology, blood chemistry.
    - CRP and ESR.
- Compliance assessment.
- Dispense study drugs according to treatment arm. MTX (oral or SC) to be increased to 25 mg (section 7.3).

8.10 Week 8 (± 7 days)

- Confirmation of on-going consent
- Adverse events evaluation.
- Concomitant medication.
- Duration of articular morning stiffness.
- PsA-related comorbidities.
- Vital signs (blood pressure after a 5-minute rest, pulse rate and body temperature).
- Measurement of body weight.
- Blood tests:

  - Haematology, blood chemistry.
  - CRP and ESR.

- Compliance assessment
- Response Assessment - Joint examination with swollen and tender joint counts/grading and patient and physician assessments of articular disease on Likaert scale for PsARC assessment.
- Dispense study drugs according to treatment arm.
- Administer 120mg intramuscular methylprednisolone if ≥4 synovitic joints (unless contraindicated or not tolerated) or consider intra-articular steroid injections (as per an equivalent dose of methylprednisolone – see section 7.3 and section 7.6.2) if PsARC response not achieved.

8.11 Week 12, ± 7 days (secondary endpoint)

- Confirmation of on-going consent
- Adverse events evaluation.
- Concomitant medication.
- Duration of articular morning stiffness.
- PsA-related comorbidities.
- Vital signs (blood pressure after a 5-minute rest, pulse rate and body temperature).
- Measurement of body weight.
- Blood tests:
  - Haematology, blood chemistry.
  - CRP and ESR.
- Compliance assessment.
- Response Assessment - Joint examination with swollen and tender joint counts/grading and patient and physician assessments of articular disease on Likaert scale for PsARC assessment.
- US scan (performed as per footnote following summary schedule, section 8.6).
- Enthesitis, dactylitis, nail and skin assessments
- Physician VAS
- Patient-reported outcomes (disease activity and pain VAS, HAQ, SF-36, DLQI, ASQoL, BASDAI)
- Sample collection for biological sub-study.
- Dispense study drugs according to treatment arm.
- Administer 120 mg intramuscular methylprednisolone if ≥4 joints involved (unless contraindicated or not tolerated) or consider intra-articular steroid injections (as per an equivalent dose of methylprednisolone – see section 7.6.2) if PsARC response not achieved.

8.12 Weeks 16 (± 7 days) and 20 (± 7 days)

- Confirmation of on-going consent
- Adverse events evaluation.
- Concomitant medication.
- Duration of articular morning stiffness.
- PsA-related comorbidities.
- Vital signs (blood pressure after a 5-minute rest, pulse rate and body temperature).
- Measurement of body weight.
- Blood tests:
    - Haematology, blood chemistry.
    - CRP and ESR.
- Compliance assessment.
- Dispense study drugs according to treatment arm.

8.13 Week 24, ± 7 days (primary endpoint).

- Confirmation of on-going consent
- Adverse events evaluation.
- Concomitant medication.
- Duration of articular morning stiffness.
- PsA-related comorbidities.
- Vital signs (blood pressure after a 5-minute rest, pulse rate and body temperature).
- Measurement of body weight.
- Blood tests:
    - Haematology, blood chemistry.
    - CRP and ESR.
- Compliance assessment.
- Response Assessment - Joint examination with swollen and tender joint counts/grading and patient and physician assessments of articular disease on Likaert scale for PsARC assessment.
- Imaging: WB-MRI (if in WB-MRI subset) and US (performed as per footnote following summary schedule, section 8.6)
- Physician VAS.
- Enthesitis, dactylitis, skin and nail assessments.
- Sample collection for biological sub-study.

- Patient-reported outcomes (disease activity and pain VAS, HAQ, BASDAI, ASQoL, SF-36, DLQI)
- Dispense study drugs according to treatment arm.

8.14 Subsequent visits (Week 28 [±7 days] and Week 36 [± 7 days]) for both treatment arms:

- Confirmation of on-going consent
- Adverse events evaluation.
- Concomitant medication.
- Duration of articular morning stiffness.
- PsA-related comorbidities.
- Vital signs (blood pressure after a 5-minute rest, pulse rate and body temperature).
- Measurement of body weight.
- Joint examination with swollen and tender joint counts/grading **(WEEK 36 ONLY)**.
- Enthesitis, dactylitis, skin and nail assessments **(WEEK 36 ONLY)**.
- Imaging: WB-MRI (if in WB-MRI subset) and US (performed as per footnote following summary schedule, section 8.6) **(WEEK 36 ONLY)**
- Blood tests:
  - Haematology, blood chemistry.
  - CRP and ESR.
  - Samples for scientific research **(WEEK 36 ONLY)**.
- Response Assessment – taking into account joint examination (with swollen and tender joint counts/grading) and patient and physician assessments of articular disease (Likaert scale for PsARC assessment) **(WEEK 36 ONLY)**.
- Physician VAS **(WEEK 36 ONLY)**
- Patient-reported outcomes (disease activity and pain VAS, HAQ, ASQoL, SF-36, DLQI, BASDAI) **(WEEK 36 ONLY)**.

8.15 Withdrawal visit (week X)

- Confirmation of consent for continued data collection after withdrawal procedures.
- Adverse events evaluation.
- Concomitant medication.
- Duration of articular morning stiffness.
- PsA-related comorbidities.
- Physical examination.
- Vital signs (blood pressure after a 5-minute rest, pulse rate and body temperature).

- Measurement of body weight.
- Blood tests:
    - Haematology, blood chemistry.
    - CRP and ESR.
- Immunology tests (ANA, anti-dsDNA, anti-CCP, RF)
- Response Assessment – taking into account joint examination (with swollen and tender joint counts/grading) and patient and physician assessments of articular disease (Likaert scale for PsARC assessment).
- Physician VAS.
- Enthesitis, dactylitis, skin and nail assessments.
- Patient-reported outcomes (disease activity and pain VAS, HAQ, BASDAI, ASQoL, SF-36, DLQI)
- Sample collection for biological sub-study.
- WB-MRI (if in WB-MRI subset) and US (not required if withdrawal visit occurs within 6 weeks of last imaging; perform as per footnote following summary schedule, section 8.6).

8.16 Extra visit (week Y) (*Applicable to period 2 (observational) only*)

- Confirmation of on-going consent
- Adverse events evaluation.
- Concomitant medication.
- Duration of articular morning stiffness.
- PsA-related comorbidities
- Vital signs (blood pressure after a 5-minute rest, pulse rate and body temperature).
- Measurement of body weight.
- Blood tests:
    - Haematology, blood chemistry.
    - CRP and ESR.
    - Immunology tests (ANA, anti-dsDNA, anti-CCP, RF)
- Response Assessment - taking into account joint examination (with swollen and tender joint counts/grading) and patient and physician assessments of articular disease (Likaert scale for PsARC assessment).
- Physician VAS.
- Enthesitis, dactylitis, skin and nail assessments.
- Patient-reported outcomes (disease activity and pain VAS, HAQ, BASDAI, ASQoL, SF-36, DLQI)

- Sample collection for biological sub-study.
- WB-MRI (if in WB-MRI subset) and US (not required if flare visit occurs after week 36 or if within 6 weeks of last imaging).

8.17 Completion visit (week 52, ± 7 days)

- Confirmation of on-going consent
- Adverse events evaluation.
- Concomitant medication.
- Duration of articular morning stiffness.
- PsA-related comorbidities.
- Vital signs (blood pressure after a 5-minute rest, pulse rate and body temperature).
- Measurement of body weight.
- Blood tests:
    - Haematology, blood chemistry.
    - CRP and ESR.
    - Immunology tests (ANA, dsDNA, anti-CCP, RF)
- Response Assessment - Joint examination with swollen and tender joint counts/grading and patient and physician assessments of articular disease on Likaert scale for PsARC assessment.
- Physician VAS.
- Enthesitis, dactylitis, skin and nail assessments.
- Sample collection for biological sub-study.
- Patient-reported outcomes (disease activity and pain VAS, HAQ, BASDAI, ASQoL, SF-36, DLQI)
- Patients will be given a follow up appointment in the normal rheumatology clinic as per routine clinical practice.

8.18 Definition and Management of Disease Flare

Flare is defined as an increase in disease activity compared to previous assessment in a patient previously improving or stable, requiring a change in treatment. For patients on MDA, flare would be defined as a loss of MDA.

Flares of disease activity can be managed, at the investigators discretion, as follows:

- By altering analgesics.
- Steroids are only permitted at certain time points (weeks 8 and 12 and after week 24.).

Prior to Week 24: *Treatment Arms 1 and 2:* patients that are judged as clear non-responders (not achieving a PsARC response at week 12) or are intolerant of GOL/MTX may receive change in therapy (at the physician's discretion) but will be withdrawn from the interventional part of the study. A repeat WB-MRI may be performed at this stage (according to section 8.6). If they consent, patients will continue to be observed until the end of the study (week 52) and to undergo all the procedures as set per protocol timeline. Steroids IM/IA will be allowed only until week 12. From week 12 to week 24 only analgesics can be used.

- **After Week 24:** Subjects on both treatment arms will have IMP SC injections discontinued (GOL or placebo) at week 24. After this, participants will be observed for the remaining of the study period (i.e. until week 52). Disease flares occurring after week 24 and until week 52 will be treated according to normal clinical protocols and NICE guidelines.
- Other procedures at the time of flare: A response assessment will be carried out including a joint examination with swollen and tender joint counts/grading and patient and physician assessments of articular disease on Likaert scale for PsARC assessment; MDA (where applicable); blood testing for ESR, CRP; and patient-reported outcomes (disease activity and pain VAS, HAQ, BASDAI, ASQoL, SF-36, DLQI), physician's VAS (disease activity).

Blood samples will be taken for use in the biological sub-study.

PHARMACOVIGILANCE

9.1 Defining adverse events

An **adverse event** (AE) is any untoward medical occurrence in a patient during or following administration of an investigational product and which does not necessarily have a causal relationship with treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporarily associated with the use of the trial drugs, whether or not considered related to the trial drugs. As the sponsor of the study, the Sponsor Institution and the CI or their research team, shall be the solely responsible for complying, within the required timelines, with any safety reporting obligation towards the competent Health Authorities, and the REC, as defined in the applicable laws and regulations.

9.2 Defining serious adverse events (SAEs)

A **serious adverse event** (SAE) is an adverse event which is defined as serious, i.e. that it:

- Results in death. Death may occur as a result of the basic disease process. Nevertheless, all deaths occurring within 24 hours of the last administration of the study agent must be treated as an SAE and reported as such. All deaths which may be considered as related to the trial agent, regardless of the interval, must be treated as a SAE and reported as such if occurred during the trial period.
- Is life-threatening.
- Requires inpatient (overnight) hospitalization or prolongation of an existing hospitalization.
- Results in a persistent or significant disability or incapacity.
- Results in a congenital anomaly or birth defect.

Additionally, important medical events that may not result in death, be life-threatening, or require hospitalization may be considered SAEs when, based on appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Any other significant clinical event, not falling into any of the criteria above, but which in the opinion of the Investigator requires reporting.

Other Reportable Information: Certain information, although not considered an SAE, must be recorded, reported, and followed up as indicated for an SAE. This includes the following:

- Pregnancy exposure to an IMP, except for exposure to prenatal vitamins.
- Lactation exposure to an IMP, with or without an AE.
- Overdose of an IMP as specified in this protocol, with or without an AE.
- Inadvertent or accidental exposure to an IMP, with or without an AE.

9.3 AEs of special interest

9.3.1 Pregnancy

Pregnancy is considered a form of SAE. If a pregnancy is confirmed, use of the IMP must be discontinued immediately. Both maternal and paternal exposures are considered other reportable information. Paternal exposure occurs when there is a possibility of intrauterine exposure to drug via semen from the male partner who is taking the Study Product (IMP) at the time of conception, thereby possibly exposing the foetus to the product. For example, a male patient's partner becomes pregnant while the male patient is using the Study Product (IMP). For exposure involving the female partner of a male subject, the necessary information must be collected from the subject, while respecting the confidentiality of the partner. All pregnancies will be followed up until birth.

9.3.2 Lactation

Lactation exposure of an IMP as specified in this protocol, with or without an AE.

9.3.3 Overdose

Overdose of an IMP as specified in this protocol, with or without an AE.

9.3.4 Accidental exposure to an IMP

Inadvertent or accidental exposure to an IMP, as specified on this protocol with or without an AE.

9.3.5 Product Quality Complaint

Any discrete concern that questions the identity, quality, durability, reliability, safety, efficacy or intended performance of a drug product. A complaint may allege an adverse reaction, injury or malfunction associated with the used of the drug product. It may also involve the design, literature, packaging, advertising, availability, physical appearance or promotion of the drug product. Any product quality complaint (PQC), with or without an AE (including reports of suspicion of counterfeiting, diversion or tampering, and suspected transmission of pathogens) will be transmitted by the Institution or Chief Investigator in an electronic format (as supplied by Janssen) to Janssen Biologicals BV within 24 hours of becoming aware of the events.

9.4 Defining unexpected and suspected unexpected serious adverse reactions (SUSARs)

An **Unexpected Adverse Event** is any adverse event, the specificity or severity of which is not consistent with the current labelling for the product.

A **Suspected Unexpected Serious Adverse Reaction** (SUSAR) is a serious adverse event suspected to have a reasonable causal relationship to the investigational medicinal product where the nature or severity of the reaction is inconsistent with the available product information (referring to the Summary Product Characteristics (SmPC)). All SAEs assigned by the CI (or delegated clinician) as both *suspected* to be related to the trial drugs and *unexpected* are subject to expedited reporting.

9.5 Exemptions from safety reporting

9.5.1 Efficacy endpoints and disease progression events

All events that are unequivocally due to progression of moderate to severe psoriatic arthritis or lack of response should not be recorded or reported as an AE or SAE. This type of information will be captured in the study assessments. Disease progression would include: increased joint pain, musculoskeletal pain, generalized body aches, uncontrolled PsA, joint swelling, increased stiffness, limited motion, joint aspirations (in or out of the hospital), and hospitalizations for PsA-related procedures (joint replacement surgery, joint arthroscopy, synovectomy).

9.6 Recording and reporting of AEs

9.6.1 Recording and reporting of all AEs

Determination of AEs should be based on the signs or symptoms detected during the physical examination and on clinical evaluation of the subject, and should be assessed and recorded at every visit. Signs and symptoms must be recorded using standard medical terminology.

AEs and SAEs will be collected from first dose of protocol treatment until week 52 (visit 11). The Investigator must instruct the subject to report AEs and SAEs during this time period.

All adverse events must be evaluated by a medically qualified and authorised member of the study research team, and graded (in terms of severity) in accordance with the Common Terminology Criteria for Adverse Events (CTCAE) (see appendix 2).

During the time period specified above, the Investigator will:

- Record all AEs and SAEs on source documents.
- Record all AEs and SAEs in the eCRF for subjects who are not screen failures.
- Report all SAEs on a 'Serious Adverse Event/Expedited Report from a Clinical Trial'. Instructions on where to send this form will be provided by the Sponsor.

The Investigator must follow up on all AEs and SAEs until the events have subsided, returned to baseline, or, in case of permanent impairment, until the condition has stabilized whilst the subject remains under follow up as per study protocol. All adverse events that are still ongoing when the patient finishes study follow-up will be coded as 'ongoing' in the eCRF , after which time appropriate follow up will be organized as per standard clinical care.

The Sponsor will maintain detailed records of all AEs and SAEs reported by an Investigator in accordance with good clinical practice and applicable local regulations.

9.6.2. SAE and SUSAR reporting requirements

Where applicable, all SAEs assessed by Investigators as being both suspected to be related to protocol-treatment and unexpected, will be reviewed by the Chief Investigator (CI).

If the SAE is suspected to be related to the study treatment/s and is deemed to be unexpected against the Reference Safety Information (RSI) (*specifically Section 4.8 'Undesirable effects' of the SmPc*), the SAE qualifies as a Suspected Unexpected Serious Adverse Reaction (SUSAR) and requires expedited reporting.

The expectedness assessment can be undertaken by the CI or other medically qualified delegate. In absence of both the CI/delegated investigator, a SUSAR must nevertheless be reported to the Sponsor and the regulator within the legislatively specified timelines.

All SAEs, other information reportable as SAEs and follow-up information must be reported to the Sponsor and to Janssen Biologics BV within 24 hours of the research team becoming aware of them as follows:

9.6.2.1 SAE/SUSAR reporting to the Sponsor

The investigator or named delegate must report the SAE/SUSAR to the Sponsor QA office immediately and within 24 hours of awareness using the CTT21 SAE report form outlined in SOP QCRES_01 via email to the following address:

SPONSOR E-MAIL ACCOUNT FOR

SERIOUS ADVERSE EVENT/EXPEDITED REPORT

leedsth-tr.sponsorqa@nhs.net

9.6.2.2 SAE/SUSAR reporting to Janssen

The investigator or named delegate must report the SAE/SUSAR to 'Janssen Biologics" to the following number:

JANSSEN BIOLOGICALS FAX NUMBER FOR

SERIOUS ADVERSE EVENT/EXPEDITED REPORT

+44 149 456 7799 or +44 800 389 3644

Identifiable patient data, other than linked anonymised data required by the SAE form, must not be included when reporting SAEs and SUSARs.

Suspected adverse reactions that are both serious and unexpected are subject to expedited reporting to the REC and MHRA.

The Sponsor then will inform the MHRA via the MHRA eSUSAR web portal and the Main Research Ethics Committee (Main REC) of SUSARs within the required expedited reporting timescales.

1. All SUSARs must be reported to the Sponsor QA office within 1 working day of the event being reported to the CI (or their research team).
2. SUSARs must be reported to the REC / MHRA within 7 calendar days of the CI (or their research team) being informed of the event, if they result in Death or are deemed to be life-threatening. Follow-up information must be reported within 8 calendar days.
3. Any SUSARs not resulting in death or deemed to be life-threatening must be reported to the REC / MHRA within 15 Calendar days of the CI (or their research team) being informed of the event. Follow-up information must be reported within 8 calendar days.

SUSARs will be reported in accordance with the requirements and provisions of the applicable national laws. They will all be signed off by the Chief Investigator or, in their absence, by a delegated individual.

9.7 Urgent safety measures

If the research team becomes aware of information affecting the risk/benefit balance of the trial they may take immediate action to ensure patient safety. Urgent safety measures deemed necessary must be reported immediately by telephone to the MHRA (in conjunction with the Sponsor) and to the main REC for the trial, and must be followed within three days by notice in writing setting out the reasons for the urgent safety measures and the plan for further action. The REC co-ordinator will acknowledge within 30 days.

9.8 Serious breaches of protocol

A **serious breach** is a breach which is likely to affect to a significant degree either:

- The safety or physical or mental integrity of the subjects of the trial; or
- The scientific value of the trial.

Serious breaches of GCP, the trial protocol or the Clinical Trial Authorisation will be reported to the Sponsor QA office within 3 working days from the time the research team becomes aware of the incident.

9.9 Laboratory measurements

In total, this study will require an additional 60 ml blood (alongside with a sample of urine) to be taken for the purposes of the biological sub-study at baseline and weeks 12, 24, 36, 52, withdrawal visit, and at time of flare (extra visit, during the observational period).

This will include storage of serum, white cell pellets, peripheral blood mononuclear cells (PBMCs), whole blood and urine. These may be used for soluble biomarkers, flow cytometry, functional studies or DNA/RNA extraction using methods/techniques applicable to the study.

9.10 Annual reports

An annual report describing the general progress and any relevant safety data related to the trial must be submitted to the main REC, MHRA and the Sponsor on the anniversary of the Clinical Trial Authorisation being granted. The annual report should follow the format of a Developmental Safety Update Report (DSUR). A template and guidance for the completion of this report is available from the Sponsor office. An annual report of AEs will also be sent to Janssen Biologics. The CI must review and sign / date the report.

9.11 End of trial report

Upon completing the trial, as defined in section 6.6.7, an end of trial report must be submitted to the MHRA within one year of the end of the trial by the Sponsor or Sponsor-delegated individual. A copy of this end of trial report should also be supplied to all support departments involved in the study, for example pharmacy and or radiology.

The CI must review and sign / date the report.

STUDY MANAGEMENT AND ADMINISTRATION

10.1 Good clinical practice (GCP) and regulatory compliance

This clinical trial, which involves the use of an investigational medicinal product, has been designed and will be run in accordance with the Principles of GCP and the current regulatory requirements, as detailed in the Medicines for Human Use (Clinical Trials) Regulations 2004 (UK S.I. 2004 / 1031) and any subsequent amendments of the clinical trial regulations.

10.2 Adherence to protocol

The Investigator should not deviate from the protocol. In medical emergencies, the Investigator may use his/her medical judgment and may remove a study patient from immediate hazard before notifying the Sponsor, the MHRA and the REC in writing regarding the type of emergency and the course of action taken.

10.3 Monitoring, audit and inspection

The Sponsor reserves the right to monitor and/or audit the site (i.e. where the trial is being conducted) at any time. The Sponsor will visit the study centre to check the completeness of patient records, accuracy of entries on paper documents and eCRFs, and the adherence to the protocol and to GCP.

The site may be monitored or audited, by the Sponsor (or their appointed representative) or internally by the LIRMM Clinical Research Associate.

The trial may be subject to inspection by the MHRA in order to ensure compliance with UK Trials regulations, and the Investigator should allow direct access to trial documentation.

10.3.1. Procedures for monitoring subject compliance

Patient compliance with the trial intervention will be assessed at each visit. Further reference is presented in sections 6.5, 7.3, 7.6, 7.9, 7.10.1. A patient will be considered overall compliant for each study period if he/she is missing no more than 20% of the expected doses and not missing 2 consecutive doses of IMP.

10.3.2. Definition of source data

Source documents are original records in which raw data are first recorded, as defined by the source data location document kept in the study Trial Master File. These may include, e.g. hospital/clinic/general practitioner records, charts, diaries, x-rays, laboratory results, printouts, pharmacy records, care records, ECG or other printouts, completed scales, or Quality of Life Questionnaires. Source documents should be kept in a secure, limited access area.

Electronic data records such as x-ray, US and MRI records will be saved and stored in an appropriately secure centralised location.

Source data verification ensures accuracy and credibility of the data obtained. During monitoring reported data are reviewed with regard to being accurate, complete, and verifiable from source documents (e.g. subject files, recordings from automated instruments, ECG tracings, x-ray films, laboratory notes). All data reported on the eCRF should be supported by source documents. Data Verification will be carried out by the investigators and members of the study team who will check the case report forms for completeness and clarity, and crosscheck them with source documents.

A Source Data Location Sheet (SDLS) specific to the GOLMePsA trial can be found in a dedicated section on the study TMF.

10.3.3. Quality assurance

Investigators will promptly notify the Sponsor Quality Assurance Office of the following within the required timeframe:

- Serious breaches of GCP
- Urgent safety measures
- Protocol violations

- Any amendments to the trial
- Any changes to the Sponsor's Clinical Trial Risk Assessment (form A).
- Any other issues as stated in the study contract or agreement

10.3.4. Trial oversight: trial steering committee

Independent oversight of the study will be conducted by the Trial Steering Committee. Amongst its members will be an independent chair, a lay individual (from the NIHR Leeds Biomedical Research Centre and Patient Advocacy Group), a clinician who is independent of the study research team, and a representative of the LIRMM study management team. They are expected to meet at least annually. For its terms of reference see appendix 5.

10.4 Data handling

10.4.1. Paper-based data collection tools and electronic (e) CRF completion

The research team is responsible for prompt reporting of accurate, complete, and legible data in the paper based source documents and in all required reports. Any change or correction to the paper-based documents should be dated, initialled, and explained (if necessary) and should not obscure the original entry. Use of correction fluid (e.g. Tipp-Ex) is not permitted.

Designated investigator staff will enter the data required by the protocol into an electronic (e) CRF system. Any change or correction to the eCRF will be time-stamped and documented within the data storage system, with all previous versions of the form retained. The Investigator should maintain a list of personnel authorized to enter data into the eCRF.

10.4.2. Database entry and reconciliation

Data will be entered via an eCRF into a validated electronic data collection system. Computerized data cleaning checks will be used in addition to manual review to check for discrepancies and to ensure consistency of the data.

After the eCRF has been submitted initially, an electronic audit trail system will be maintained within the data collection system to track all data changes in the database. Regular backups of the electronic data will be performed in line with local SOPs for the backup of systems.

10.4.3. Screening and enrolment logs

Patients screening will be recorded in the Patient Screening Log which will contain a record of the date of informed consent signing and the date of randomisation. The Investigator will also keep a list containing all patients enrolled and randomized into the study (Subject Identification [ID] Log). This list remains with the Investigator, kept in the Trial Master File and is used for unambiguous identification of each patient. The list contains the patient identification number, full name, date of birth and the hospital number and/or National Health Service number, if applicable. In addition a Pre-screening log will be kept to record all patients approached as possible study candidates.

The patient's consent and enrolment in the study must be recorded in the patient's medical record. These data should identify the study and document the dates of the patient's participation.

10.5 Archiving and data retention

In line with the principles of GCP/UK Clinical Trial Regulations, at the end of the trial, essential documents will be securely archived for a minimum of 15 years. Arrangements for confidential destruction will then be made. If a patient withdraws consent for their data to be used, it will be

confidentially destroyed immediately. No records/study documentation/data may be destroyed without first obtaining written permission from the Sponsor.

Essential documents include (this list is not exhaustive):

- Signed informed consent documents for all subjects.
- Patient Screening Log, Subject Identification Log and Pre-Screening Log.
- Record of all communications between the Investigator, the REC and the Sponsor.
- List of sub-investigators and other appropriately qualified persons to whom the Investigator has delegated significant trial-related duties, together with their roles in the study and their signatures.
- Copies of case report forms and documentation of corrections for all subjects.
- Investigational product accountability records.
- All other source documents (subject medical records, hospital records, laboratory records, etc.).
- All other documents as listed in section 8 of the ICH E6 Guideline for Good Clinical Practice (Essential Documents for the Conduct of a Clinical Trial).

*European Union legislation requires this list to be maintained for a minimum of 15 years.

10.6 Study suspension, termination and completion

Suspension or termination of the study may occur at any time for any reason, following discussion between the Investigator and the Sponsor. In the case of early study termination the Sponsor or Sponsor-delegated individual will be responsible for completing a premature end of study report to the Medicines and Healthcare products Regulatory Agency (MHRA) and the Research Ethics Committee (REC) within 15 days. Upon study completion, the Sponsor or Sponsor-delegated individual will be responsible for sending the Declaration of the End of a Clinical Trial to the MHRA within 90 days. The Sponsor or Sponsor-delegated individual will be responsible for providing the End of Trial Report to the MHRA within 1 year of the end of the trial.

DATA EVALUATION

11.1 Responsibilities

The Leeds Institute of Rheumatic and Musculoskeletal Medicine statistician will be responsible for producing the final data report.

11.2 Hypotheses

The analysis of the primary endpoint will test the following hypothesis:

H0: The difference* between the two treatment arms in the PASDAS score at week 24 is equal to zero.

H1: The difference* between the two treatment arms in the PASDAS score at week 24 is not equal to zero.

*adjusted for the baseline PASDAS value and stratification factor (oligo/polyarthritis)

11.3 General statistical considerations

In general, analyses will be adjusted for the randomisation stratification factor(s) and baseline values of the outcome measure; 2-tailed tests will be performed and will be considered statistically significant if $p<0.05$. A final analysis plan will be completed prior to the final data lock before unblinding. Any deviations from this plan will be documented in the final data report.

Unless otherwise specified, the last valid measurement before study medication administration will be utilized as the baseline value. In general, summary statistics [n (number of available measurements), arithmetic mean, standard deviation, median, minimum, and maximum] for quantitative variables and absolute and relative frequency tables for qualitative data will be presented.

Wherever possible the trial will be reported in accordance with the recommendations of the CONSORT (Consolidated Standards of Reporting Trials) statement (53-55).

11.4 Analysis populations

- Full Analysis Set (FAS): The full analysis set will include all patients
- Safety Set (SS): The safety set will include all patients who received at least one dose of study medication
- Per Protocol Set (PPS): The per protocol set will include all patients deemed to fulfil the protocol in terms of eligibility, interventions and outcome assessment.

11.5 Planned efficacy analyses

11.5.1. Primary endpoint analysis

The primary endpoint will be assessed in the Full Analysis Set, with patients assigned to the study arms to which they were originally randomised (intention-to-treat analysis).

Full descriptive data will be provided for the PASDAS score at week 24. Unadjusted and adjusted estimates of the treatment effect will be obtained; the unadjusted estimate will be considered supplementary to the primary adjusted estimate. We will present the difference between treatment group means and the 95% confidence interval around the difference. Analysis of covariance by multiple linear regression will be used to compare PASDAS between the two treatment groups at week 24, controlling for the PASDAS values at baseline, and whether or not the patient had clinical polyarthritis at baseline (stratification factor).

11.5.2. Secondary endpoint analyses

Full descriptive data will be provided for all secondary endpoints. Adjusted estimates of effect size will be obtained for binary secondary endpoints using multiple binary logistic regression; odds ratios and 95% confidence intervals will be presented. Continuous interval outcomes will be analysed using multiple linear regression; differences between treatment group means and 95% confidence intervals will be presented. Count outcomes will be analysed using an appropriate generalised linear model; incident rate ratios and 95% confidence intervals will be presented. Severely skewed outcomes for which an appropriate generalised linear model cannot be identified will be analysed using quantile regression; differences between medians and 95% confidence intervals will be presented. All analyses will control for the stratification factor and baseline values of the outcome. Where the aim is to relate clinical or imaging responses to baseline joint counts or to symptom duration, these variables will be added to the relevant models as covariates after the initial estimate of the treatment effect has been obtained; interactions between each variable and treatment will be assessed and will be considered substantive if found to be significant at the 10% level. Planned subgroup analyses will investigate

differences in treatment response according to oligo/polyarthritis status, disease duration at baseline. The total amount of steroids received by week 12, as a post-randomisation variable, will not be adjusted for in the analysis but will instead be compared between groups.

11.5.3. Other analyses

A number of sensitivity analyses will be conducted. These will include restricting analysis of the data to the observed values only, imputing non-response for patients who withdraw for any reason, using post-withdrawal data observed for patients who withdrew from study therapy early rather than carrying forward data from their withdrawal visit, and amending imputed values for continuous variables to investigate the robustness of response estimates to a variety of deviations from the missing at random assumption. A per protocol analysis will also be performed, repeating the primary endpoint analysis in the PPS. Further details of these sensitivity analyses will be set out in the statistical analysis plan.

In a subset of patients, total synovitis and enthesitis scores calculated in expanded sets of joints defined in the newly published OMERACT definitions will be compared between groups according to the same methods as for secondary outcomes. In addition, for patients in the WB-MRI subset the MRI outcomes will be compared between groups on an exploratory basis using the same methods as for secondary outcomes. However, the focus will be on quantifying the potential treatment effect. A range of confidence intervals (75%, 85%, 95%) around the difference between the treatment arms will be calculated, to indicate the level of confidence with which we could say there was potential for a substantive difference between groups.

An assessment of the test-retest reliability of the PASDAS will be performed, by calculating the intraclass correlation coefficient between PASDAS measurements collected a screening and baseline with a 95% confidence interval.

11.6 Safety analyses

Line listings of all SAEs will be provided in the end of trial report. Safety analyses will be conducted in the SS. The frequency of all SAEs during the study period will be presented for each treatment group separately. The data will be displayed as number of subjects experiencing the SAEs, percentage of subjects, and number of SAEs. Data will also be corrected for exposure by 100 patient-years. Quarterly listings of SAEs will be sent to Janssen Biologics.

11.7 Handling of dropouts and missing data

The primary analysis will include all patients, as originally randomised (ITT analysis). This will require missing data to be imputed. For patients who withdraw early, data from the withdrawal visit will be imputed for subsequent visits for continuous outcomes, and non-response will be imputed for binary outcomes. For all other instances of missing data, multiple imputation will be used to obtain at least 20 full datasets; this number may be increased should Monte Carlo error estimates indicate instability of model coefficients. Outcomes will be imputed according to data type; in general for measures of disease activity the achievement of thresholds of response (e.g. PsARC) will be computed passively following imputation of the underlying score or components via predictive mean matching, provided sample size is sufficient for the imputation models to converge. Analyses from the imputed datasets will be combined according to Rubin's rules. Should multiple imputation not prove possible due to the level of attrition, mixed models will be investigated as an alternative.

11.8 Planned interim analysis and data monitoring

There are no interim analyses planned. The biostatistician will conduct an initial inspection of the data prior to breaking of the blind to identify any issues with data quality, which will be resolved in the RDMS before the database is locked for final analysis.

11.9 Determination of sample size and randomization method

Using in-house unpublished data we estimated the minimum clinically important difference to be 0.7 units on the PASDAS; this is similar to a published value for smallest detectable difference of 0.8 units (11). We will aim to detect a difference of at least 1 unit between the treatment arms in this study. The standard deviation of PASDAS in the TICOPA MTX rapid escalation arm (56, 57) at 24 weeks (restricted to patients who remained on methotrexate throughout) was 1.57. Assuming $\delta=1$, $\sigma=1.57$, at alpha=0.05 and 1-Beta=0.8 this would require 78 patients. Originally the sample size for the trial was adjusted to account for 10% drop-out, requiring a total of 88 (44 per group). However, because recruitment had been slower than anticipated, in part due to the SARS-CoV-2 pandemic, drop-out was reassessed once 76 participants had the opportunity to reach the primary endpoint. Only 4 (5%) had withdrawn from follow-up prior to that point. Therefore, the total required sample size was revised down to 84 (42 per group) i.e. allowing for 5% drop-out.

For the whole-body MRI subset, published rules of thumb for pilot studies indicate that between 12 and 30 patients per group should be included. We will aim to continue recruiting patients into the WB-MRI subset until there are at least 30 patients (15 per group) with scans available at both baseline and week 24, at which point WB-MRI will cease to be performed in the remaining patients.

To estimate the ICC between two repeated readings of the PASDAS composite index with a confidence interval of width 0.2, we would need 31 patients assuming the ICC is 0.85. For the patient's global assessment of disease activity VAS, which provides the greatest loading on the PASDAS score, ICC = 0.87(35). We will aim to obtain data from at least 31 patients.

11.10 Procedure for un-blinding the study prior to analysis

Prior to un-blinding the statistician will conduct an initial review of the data (see section 11.8); the final statistical analysis plan will be signed off by the CI and a copy will be stored in the trial master file. Once all of these steps have been completed the randomisation status of each patient will be requested from pharmacy and treatment allocation will be stored in the database prior to export for analysis.

ETHICS AND REGULATORY REQUIREMENTS

12.1 Good Clinical Practice

This study will be conducted in accordance with applicable laws and regulations including, but not limited to, the International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice (GCP) and the recommendations guiding ethical research involving human subjects adopted by the 18th World Medical Assembly, Helsinki, Finland, 1964, amended at the 48th General Assembly, Somerset West Republic of South Africa, October 1996. The Research Ethics Committee (REC) and MHRA must review and approve the protocol and informed consent form before any subjects are enrolled. Before any protocol-required procedures are performed, the subject must sign and date the REC-approved informed consent form. The right of a patient to refuse participation without giving reasons must be respected. The patient must remain free to withdraw at any time from the study without giving reasons and without prejudicing his/her further treatment. The study will be submitted

to and approved by a main Research Ethics Committee (REC) and the appropriate regulatory authorities prior to entering patients into the study.

12.2 Delegation of Investigator duties

The Investigator should ensure that all persons assisting with the trial are adequately qualified and informed about the protocol, any amendments to the protocol, the study treatments, and their trial-related duties and functions.

The Investigator should maintain a delegation log of co-investigators and other appropriately qualified persons to whom he or she has delegated significant trial-related duties.

12.3 Subject information and informed consent

Before being enrolled in the clinical study, subjects must consent to participate after the nature, scope, and possible consequences of the clinical study have been explained in a form understandable to them.

An informed consent document (Patient Information Leaflet (PIS)) that includes both information about the study and the consent form will be prepared and given to the subject at least 24 hours prior to the screening visit. This document will contain all the elements required by the ICH E6 Guideline for Good Clinical Practice and any additional elements required by local regulations.

Where English is not the patient's first language, every effort will be made to provide a Trust interpreter in accordance with normal Trust procedures. The document (PIS) will be translated verbally (by a Trust appointed interpreter) into a language understandable to the subject. Additionally in such instances, the completed informed consent document must specify the name of the individual translating and informing the subject.

At the screening visit, patients will be given the opportunity to ask questions and the nature and objectives of the study will be explained. A research nurse may help in this process but the study doctor is responsible for the informed consent discussions.

After reading the informed consent document, the subject must give consent in writing. The subject's consent must be confirmed at the time of consent by the personally dated signature of the subject and by the personally dated signature of the person conducting the informed consent discussions, the study doctor.

The original signed consent document will be retained in the Trial Master File. Further copies of the consent form are required:

- One copy of the informed consent document will be kept in the patient's clinical notes.
- One copy will be given to the patient.

Consent is an ongoing process and will be reassessed at each study visit.

The Investigator will not undertake any measures specifically required only for the clinical study until valid consent has been obtained.

The Investigator must inform the subject's primary physician about the subject's participation in the trial if the subject has a primary physician and if the subject agrees to the primary physician being informed.

12.4 Subject confidentiality

If a subject's name (or any other personally identifiable information) appears on any document (e.g. laboratory report), it will first be redacted on a copy of the document before being supplied to anyone outside the clinical care team (for the purposes of the trial).

The subjects will be informed that representatives of the Sponsor, Research Ethics Committee (REC) or regulatory authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence.

All information collected during the course of the trial will be kept strictly confidential.

Information will be held securely on paper and electronically at the Leeds Institute of Rheumatic and Musculoskeletal Medicine (LIRMM). LIRMM will comply with all aspects of the Data Protection Act 2018.

Upon a patient providing informed consent to participate in the study, the research team will maintain a personal patient identification list in the form of a 'Subject ID Log' held in the Trial Master File (TMF). This log will consist (at a minimum) of subject ID numbers with the corresponding patient name, date of birth and NHS/hospital number) to enable research records/data to be cross-referenced and identified.

12.5 Approval of clinical study protocol and amendments

Before the start of the study, the clinical study protocol, informed consent document, and any other appropriate documents will be submitted to the REC, the MHRA and the Sponsor with a cover letter or a form listing the documents submitted, their dates of issue, and the site (or region or area of jurisdiction, as applicable) for which approval is sought. If applicable, the documents will also be submitted to the authorities, in accordance with local legal requirements.

Investigational products can only be supplied Sponsor after documentation on all ethical and legal requirements for starting the study has been received by the product provider.

Before the first subject is enrolled in the study, all ethical and legal requirements must be met, including approval of the study by the NHS, the Sponsor Research and Development department, the REC and the MHRA.

Amendments must be evaluated to determine whether formal approval must be sought and whether the informed consent document should be revised, thus all protocol amendments and administrative changes must first be discussed with and approved by the Sponsor before being submitted to the REC and the MHRA, in accordance with legal requirements.

The Investigator must keep a record of all communication with the REC, the MHRA, and the Sponsor. This also applies to any communication between the Investigator and the authorities.

12.6 Protocol amendments

Requests for any amendments to the study must be sent to the Sponsor by the Chief Investigator. The Sponsor will determine whether said amendments are substantial or non-substantial prior to their submission to the appropriate bodies for approval.

Patients should be re-consented to the study if the amendments affect the information they have received, patient safety, or if the change alters the type or quality of the data collected for the study. Patients should only be re-consented AFTER an amendment has been fully approved.

12.7 On-going information for MHRA/REC

Unless otherwise instructed by the MHRA, REC and the Sponsor, the Investigator must submit to the MHRA, REC and the Sponsor:

- Information on serious or unexpected adverse events (SUSARs) from the Investigator's site, as soon as possible and within 24 hours (one business day) of the research team becoming aware of them.
- Expedited safety reports, as soon as possible.
- Annual reports on the progress of the study, both DSURs and REC progress reports.
- The Declaration of the End of a Trial form

13. FINANCE AND INSURANCE

13.1 Indemnity and insurance

Clinical negligence indemnification will rest with The Leeds Teaching Hospitals NHS Trust, under standard NHS arrangements. As Sponsor, the Trust does not provide indemnification against claims arising from non-negligent harm.

Further details of liability and insurance provisions for this study are given in separate agreements.

13.2 Financial disclosure

None of the investigators or members of the research team have any financial involvement with the sponsorship or funding bodies or will receive personal benefits, incentives or payment over and above normal salary.

14. PUBLICATION

The trial will be registered with an authorised registry, according to ICMJE Guidelines, prior to the start of recruitment.

The success of the trial depends upon the collaboration of all patients. For this reason, credit for the main results will be given to all those who have collaborated in the trial, through authorship and contributor ship. Uniform requirements for authorship for manuscripts submitted to medical journals will guide authorship decisions. These state that authorship credit should be based only on substantial contribution to:

- conception and design, or acquisition of data, or analysis and interpretation of data
- drafting the article or revising it critically for important intellectual content, and
- final approval of the version to be published, and
- that all these conditions must be met (www.icmje.org).

In light of this, the Chief Investigator, and relevant staff will be named as authors in any publication. In addition, all collaborators will be listed as contributors for the main trial publication, giving details of roles in planning, conducting and reporting the trial.

To maintain the scientific integrity of the trial, data will not be released prior to the end of the trial, either for trial publication or oral presentation purposes, without the permission of the Trial Steering Committee or the Chief Investigator. In addition, individual collaborators must not publish data

directly relevant to the questions posed in the trial until the main results of the trial have been published and following written consent from the Sponsor.

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APPENDICES

APPENDIX 1: Definition of Women of Childbearing Potential (WCBP)

A woman of childbearing potential (WCBP) is defined as one who is biologically capable of becoming pregnant. This includes women who are using contraceptives or whose sexual partners are either sterile or using contraceptives. Sexually active women participating in the study must use a medically acceptable form of contraception during the study and for 6 months after the last dose of study medications. Medically acceptable forms of contraception for women include oral contraception, injectable or implantable methods, intrauterine devices, or properly used barrier contraception.

APPENDIX 2: Common Terminology Criteria for Adverse Events (CTCAE) Grading

Grade	Definition
Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental ADL*.
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**.
Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death related to AE.

Activities of Daily Living (ADL):

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

**Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Reference: *CTCAE v4.03 - June 14, 2010*

US National Cancer Institute, https://evs.nci.nih.gov/ftp1/CTCAE/About.html

APPENDIX 3: CASPAR Classification Criteria for PsA

Taylor W, Gladman D, Helliwell P, Marchesoni A, Mease P, Mielants H; CASPAR Study Group. Classification criteria for psoriatic arthritis: development of new criteria from a large international study. Arthritis Rheum, 2006. 54(8): p. 2665-73.

The CASPAR criteria

Inflammatory articular disease (joint, spine, or entheseal) with 3 or more points from the following**:**

1. Evidence of psoriasis (one of a, b, c)

(a) Current psoriasis *

*Psoriatic skin or scalp disease present today as judged by a rheumatologist or dermatolo*gist

(b) Personal history of psoria*sis*

*A history of psoriasis that may be obtained from patient, family doctor, dermatologist, rheumatologist or other qualified health-care prov*ider

(c) Family history of psoria*sis*

A history of psoriasis in a first or second degree relative according to patient report

2. Psoriatic nail dyst*rophy*

Typical psoriatic nail dystrophy including onycholysis, pitting and hyperkeratosis observed on current physical examination

3. A negative test for rheumatoid f*actor*

By any method except latex but preferably by ELISA or nephelometry, according to the local laboratory reference range

4. Dactylitis (one of a, b)

(a) C*urrent*

*Swelling of an entir*e digit

(b) H*istory*

A history of dactylitis recorded by a rheumatologist

5. Radiological evidence of juxta-articular new bone for*mation*

Ill-defined ossification near joint margins (but excluding osteophyte formation) on plain xrays of hand or foot

* Current psoriasis scores 2 whereas all other items score 1 CASPAR

APPENDIX 4: mNAPSI Score

Does the patient have nail disease? Yes ☐ No ☐ Assessment not possible ☐ (give reason)

Features (circle appropriate number)		**Fingernails Right**					**Fingernails Left**				
		5	**4**	**3**	**2**	**1**	**1**	**2**	**3**	**4**	**5**
Onycholysis	0 = none	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
	1 = 1-10% of nail surface	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
	2 = 11-30% of nail surface	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
	3 = >30% of nail surface	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Pitting	0 = 0	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
	1 = 1-10 pits	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
	2 = 11-49 pits	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
	3 = >50 pits	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Nail plate crumbling	0 = none	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
	1 = 1-25% of nail	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
	2 = 26-50% of nail	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
	3 = >50% of nail	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

Features (tick if present)	**Fingernails Right**					**Fingernails Left**				
	5	**4**	**3**	**2**	**1**	**1**	**2**	**3**	**4**	**5**
Leukonychia	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Splinter haemorrhage	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Nail bed hyperkeratosis	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Red spots in lunula	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Oil spot dyschromia	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Total										

APPENDIX 5: Trial Steering Committee (TSC)

Trial Steering Committee Terms of Reference:

1. To monitor and supervise the progress of the trial towards its interim and overall objectives.
2. To review, at regular intervals, relevant information from other sources (e.g. other related trials).
3. To consider the recommendations of the Data Monitoring and Ethics Committee if applicable.
4. In the light of 1, 2 and 3, to inform the Sponsor (The Leeds Teaching Hospitals NHS Trust) on the progress of the trial.

Specifically, the Trial Steering Committee will be responsible for monitoring the following (See MRC Guidelines for Good Clinical Practice in Clinical Trials 1998 document)

- Patient safety
- Progress of the Trial
- Adherence to Protocol
- Consideration of New Information

APPENDIX 6: Visual Analogue Scales (VAS)

Patient Global Assessment of Disease Activity

The patient's perception of disease will be a 0-100 mm VAS as a global score encompassing both joints and skin. The left end corresponds to "no activity" or "excellent" and the right end to 'poor' (35). The patients will mark their own assessment on the scales in the case report forms by themselves by placing a single vertical line through the bar.

Patient Assessment of Pain

The patient is instructed to rate their level of pain corresponding to their arthritis. The wording of the question asks about the way the patient feels. This is the wording proposed by Cauli et al which been validated in psoriatic arthritis (35). The left end corresponds to no pain or "excellent" state and the right end to the worst pain imaginable or "poor". The patients will mark their own assessment on the scales in the case report forms by themselves by placing a single vertical line through the bar.

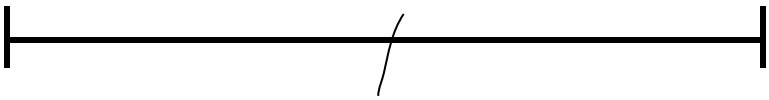
Physician Global Assessment of Disease Activity

The investigator's evaluation of psoriatic disease activity should be completed before the patient's global assessment is received. The investigator will assess the patient's psoriatic arthritis condition taking into account not only impressions from the assessments made in the study, but also any other information available. A 100 mm VAS is used: the left end corresponds to "Disease not active" (0) and the right end to "Disease extremely active" (100).

Visual Analogue Scales (VAS)

Visual analogue scales

Please tell us about how you are feeling <u>today</u> by placing a vertical mark on each line to represent your answer, like this for example:



Patient Global Assessment of Disease Activity:

In all the ways in which your PSORIASIS and ARTHRITIS, as a whole, affects you, how would you rate the way you felt over the past week?

Excellent  Poor

Patient Global Assessment of Pain

In all the ways your ARTHRITIS affects you, how would you rate the way you felt over the past week?

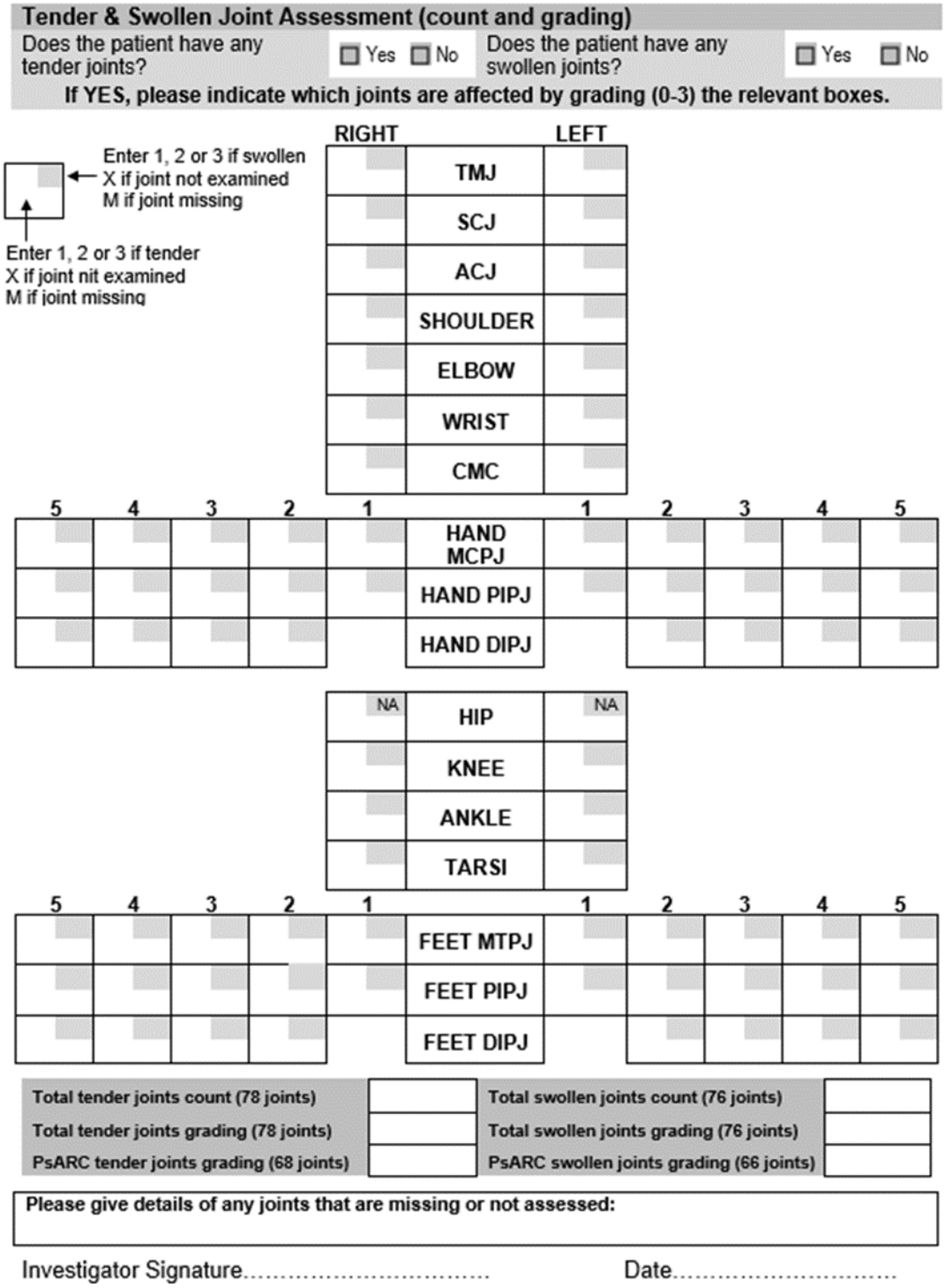
Excellent  Poor

Physician Global Assessment of Disease Activity:

What is your assessment of the patient's current disease activity?

Disease not active  Disease extremely active

APPENDIX 7: Tender and swollen joints assessments instructions



76/78 joints list encompasses all the joints depicted in the above mannequin (TMJ; SCJ/ACJ/Shoulder; Elbow; Wrist; CMC; MCPJ; hand PIPJ; hand DIPJ; HIP; Knee; Ankle (that is: tibio-tarsal joint); Tarsi; feet MTPJ; feet PIPJ; feet DIPfJ). 66/68 joints list encompasses all the above mentioned joint **with the exception of CMC and feet DIPJ**. HIPs are always excluded from the assessment of articular swelling.

Total grading for tender joints ranges 0-234; total grading for articular swelling ranges 0-228. The grading range of tender joints for PsARC calculation is 0-204 (CMC and feet DIPJ excluded). The grading range of articular swelling for PsARC calculation is 0-198 (CMC and feet DIPJ excluded).

Definitions of articular grading

Articular grading (tenderness)	Articular grading (swelling)
0 = none	0 = no swelling
1 = mild (positive response on questioning)	1 = mild (detectable synovial thickening without loss of bony contours)
2 = moderate (spontaneous response elicited)	2 = moderate (loss of distinctiveness of bony contours)
3 = severe (withdrawal on examination)	3 = severe (bulging synovial proliferation with cystic characteristics)

APPENDIX 8: Magnetic Resonance Imaging (MRI) scoring methods planned for GOLMePsA trial

SPARCC – SPINAL INFLAMMATION

Original citation:

Arthritis Rheum 2005 Aug 15;53(4):502-9. doi: 10.1002/art.21337.

Spondyloarthritis Research Consortium of Canada magnetic resonance imaging index for assessment of spinal inflammation in ankylosing spondylitis

Description:

Scoring of MRI lesions | The scoring method (www.altarheum.com/research.html) for active inflammatory lesions in the spine relied on the use of a T2-weighted sequence that incorporated suppression of normal marrow fat signal. We opted for the STIR sequence, which offered greater reliability when using large fields of view compared with T2 spin echo with spectral presaturation. Signal from marrow fat frequently obscures signal emanating from BME associated with inflammation. Consequently, the use of fat suppression improves sensitivity for detection of abnormal water content.

To score lesions in defined regions of the spine, the following definition of a discovertebral unit was used: the region between 2 virtual lines through the middle of each vertebra and includes the intervertebral disc and the adjacent vertebral endplates. Each vertebral endplate was scored independently for BME. T1 spin echo images were included for anatomic reference only and were not scored. For each lesion, a total of 3 consecutive sagittal slices were assessed. This allowed assessment of the extent of the lesion in the coronal and the sagittal planes. Discal lesions were not scored because they are often abnormal in patients with mechanical low back pain and degenerative disc disease.

Definition of abnormal STIR signal | Bone marrow signal in the center of the vertebra constituted the reference for designation of normal signal.

Scoring of depth and intensity | The signal from cerebrospinal fluid constituted the reference for designating an inflammatory lesion as intense. A lesion was graded as deep if there was a homogeneous and unequivocal increase in signal >1 cm. Assessment of depth was made possible by including a scale on the image.

Scoring method | Each discovertebral unit was divided into 4 quadrants: upper anterior endplate, upper posterior endplate, lower anterior endplate, and lower posterior endplate. The presence of increased STIR signal in each of these 4 quadrants was scored on a dichotomous basis: 1 = increased signal, 0 = normal signal. This was repeated for each of 3 consecutive sagittal slices resulting in a maximum score of 12 per discovertebral unit. On each slice, the presence of a lesion exhibiting intense signal in any quadrant was given an additional score of 1. Similarly, the presence of a lesion exhibiting depth ≥1 cm in any quadrant was given an additional score of 1, leading to a maximum additional score of 6 for each specific vertebral unit and bringing the total maximum score to 18 per unit. Because our preliminary analyses indicated that scoring only 6 discovertebral units would be sufficient (see below), this brought the total maximum score for SPARCC-spinal inflammation method to 108.

SPARCC – SACRO-ILIAC JOINTS INFLAMMATION

Original citation:

Arthritis Rheum 2005 Oct 15;53(5):703-9. doi: 10.1002/art.21445.

Spondyloarthritis research Consortium of Canada magnetic resonance imaging index for assessment of sacroiliac joint inflammation in ankylosing spondylitis

Description:

Scoring of MRI lesions | The scoring method for active inflammatory lesions in the SI joint relied on the use of a T2-weighted sequence that incorporates suppression of normal marrow fat signal. In other sequences, signal from marrow fat frequently obscures signal emanating from marrow edema associated with inflammation. Consequently, the use of fat suppression improves sensitivity for detection of abnormal water content.

Scoring of the SI joints was confined to those coronal slices depicting the synovial portion of the joint. In a preliminary overview of SI joint MR images from other patients with AS, the synovial portion was consistently evident in 6 consecutive coronal slices. Of the 12 acquisitions from posterior to anterior, this was typically slices 4 to 9. We therefore scored 6 consecutive coronal slices from posterior to anterior. T1-weighted SE images were included for anatomic reference only and were not scored. All lesions within the iliac bone and within the sacrum up to the sacral foramina were scored. Increased signal within the sacroiliac joint space or in the ligamentous portion of the joint was not scored.

Definition of abnormal lesion on STIR sequence | Sacral interforaminal bone marrow signal formed the reference for assignment of normal signal in the joint.

Scoring of depth and intensity | The signal from presacral blood vessels defined a lesion that was scored as intense. A lesion was graded as deep if there was a homogeneous and unequivocal increase in signal extending over at least 1 cm from the articular surface. Assessment of depth was made possible by including a scale on the image.

Scoring method | Each SI joint is divided into 4 quadrants: upper iliac, lower iliac, upper sacral, and lower sacral. The presence of increased signal on STIR in each of these 4 quadrants was scored on a dichotomous basis, where 1 = increased signal and 0 = normal signal. The maximum score for abnormal signal in the 2 SI joints of 1 coronal slice was therefore 8. Joints that included a lesion exhibiting intense signal were each given an additional score of 1 per slice that demonstrated this feature. Similarly, each joint that included a lesion demonstrating continuous increased signal of depth ≥1 cm from the articular surface was also given an additional score of 1. This brought the maximal score for a single coronal slice to 12. The scoring was repeated in each of the 6 consecutive coronal slices leading to a maximum score of 72.

HIMRISS

Original citation:

J Rheumatol 2014 Feb;41(2):370-8. doi: 10.3899/jrheum.131083. Epub 2013 Nov 15.

Preliminary validation of 2 magnetic resonance image scoring systems for osteoarthritis of the hip according to the OMERACT filter

Description:

Bone Marrow Lesion (BML) is defined as increased signal within bone on STIR sequences, excluding bone cysts. The contralateral hip is the normal reference signal for this assessment using bladder signal and T1 images to assist with identification of cysts. The closest normal bone marrow is used if the contralateral hip is significantly abnormal or arthroplasty is present.

BML in the femoral head is scored in 5 central slices as well as the 5 slices that are anterior and 5 that are posterior to these central slices. The image where the femoral head is largest defines the most central slice of the 5 central slices. On each central slice the femoral head is considered a circle that is segmented into 8 equal sectors (octants) of 45° of arc with a ninth sector being an inner circle representing one-half the diameter of the femoral head. BML is scored dichotomously in each of these sectors, giving a scoring range of 0–45. For each of the anterior and posterior slices, the slice is divided into 2 sectors, superior and inferior, and BML is scored dichotomously in sectors defined as anterosuperior, anteroinferior, posterosuperior, and posteroinferior so that the total scoring range for the sum of anterior and posterior slices is 0–20 and total femoral BML score is 0–65. For assessment of acetabular BML, a 2-cm radius from the rim of the acetabulum is evaluated if the rim can be identified on the image. A part of the BML must contact the articular surface/subchondral bone plate at some stage within the set of images to be evaluated. If rim is not identifiable (out of the field of view), then the 2- cm radius limit is taken from the template horizontal line (that will traverse the center of the femoral head).

The acetabulum is scored in the same slices, the 5 central slices being divided into 3 sectors (superolateral, superomedial, and medial), and 5 anterior and 5 posterior slices being divided into superior and inferior halves so that the total scoring range for acetabular BML is 0–35.

The total BML scoring range per subject is 0–100.

Effusion and synovitis are scored together according to a 0–2 grading scheme [0 = 0–1.9 mm (normal), 1 = 2–3.9 mm, 2 = ≥ 4 mm] on the same central, anterior, and posterior slices, resulting in a scoring range of 0–30. The fluid signal contacting a part of the femoral head and/or neck is assessed at the greatest short axis dimension perpendicular to the underlying bone (which will be femoral neck or femoral head). If no bone is visible (it is just off the slice being measured), the greatest short axis diameter of the synovial recess is measured. A transparency outlining the sectors was developed and used as an overlay being placed over the femoral head so that the outer circle approximates the femoral head.

KIMRISS

Original description:

RMD Open 2017 Jan 18;3(1):e000355. doi: 10.1136/rmdopen-2016-000355. eCollection 2017.

Preliminary validation of the Knee Inflammation MRI Scoring System (KIMRISS) for grading bone marrow lesions in osteoarthritis of the knee: data from the Osteoarthritis Initiative

Description:

The KIMRISS web interface is accessible free to registered users at www.carearthritis.com. This site includes a customized HTML5 DICOM viewer which allows users to upload and score their own DICOM data sets, an introductory slide presentation explaining KIMRISS and demonstrating examples of proper use and pitfalls, and for training purposes, several fully scored sample cases prepared by two expert musculoskeletal radiologist readers. Readers can practice scoring these cases and instantly review their performance slice-by-slice compared to the expert readings.

KIMRISS Overlay placement | The tibia is scored with the template positioned and locked once on the "central slice" where the ACL and PCL are seen to cross on a single image. If the knee is ACL or PCL deficient the central slice is placed where the intact ligament is best seen. Ten segments can be defined for each slice (5 immediately subarticular and 5 deeper). Using 3 mm MRI slice thickness, we have found in pilot work that knees are covered by 29 slices containing the tibia (10 medial, 10 lateral, and 9 central), resulting in a maximum score of 290 for the tibia (i.e., scoring range 0-290).

The femur is scored with the template positioned and locked three times: once outlining the femoral trochlea on the "central slice" (as chosen for the tibia) and once for each femoral condyle, outlining the respective condyle where the cross-sectional area appears largest. The web-based interface will automatically adjust the template position between "locked" positions to best match the femoral contour, using interpolation between the "lock" points. As for the tibia, 29 3-mm slices provide full coverage of the femur (10 slices for each condyle and 9 central slices for the trochlea). Each slice contains 13 segments, resulting in a maximum score of 377 for the femur.

The patella is scored with the template positioned and locked once on the slice with the largest patellar cross-sectional area, and kept in that position to score all slices that contain the patella (maximum of 12 3-mm slices in pilot work). We define 8 segments per slice (4 immediately subarticular and 4 deeper), resulting in a maximum score of 96 for the patella.

Overall maximum score is 290 (tibia) + 377 (femur) + 96 (patella) = 763.

In the rare event that a BML is missed due to being outside the limit of the 29 femur/tibia slices and/or the 12 patellar slices, the template center can be adjusted to include the missed BML. This did not occur in any of the 80 subjects in this study. MRI slices less than 3 mm in thickness should be post-processed to 3 mm prior to scoring.

For ease of use, the KIMRISS BML score at a region is automatically recorded as 1 when a user simply clicks a mouse or touches a touch-screen within that region. Scores are automatically populated into a data table which is maintained in the computer memory cache and can be exported when the scan has been fully reviewed. An overall KIMRISS score can be calculated by summing each segment(s) containing a BML, for each bone (tibia, patella, femur), region (e.g., trochlea, medial condyle, lateral condyle), or subregions. This allows several permutations of region based analysis or calculation of a "total score" for each knee.

CANDEN MRI spine scoring system

Original citation:

RMD Open 2019 Oct 13;5(2):e001057. doi: 10.1136/rmdopen-2019-001057. eCollection 2019.

Canada-Denmark MRI scoring system of the spine in patients with axial spondyloarthritis: updated definitions, scoring rules and inter-reader reliability in a multiple reader setting

Description:

Scoring rules

CANDEN MRI spine inflammation score	The following lesions are scored as 0 (absent) or 1 (present): aCIL, pCIL, NIL, aLIL, pLIL, FIL, TIL, RIL, SPIL and STIL. A score of 1 is added for large aCIL and pCIL. Non-corner lesions (NIL) are scored as 0 (absent) or 2 (present), and a score of 2 is added for large non-corner lesions (NIL). The CANDEN MRI spine inflammation score has a total scoring range of 0–614. The vertebral body subscore has a score range of 0–464 (11 cervical endplates from C2 to C7, each with a maximum score of 4, 35 thoracic/lumbar endplates from T1 to S1 each with a maximum score of 12). The posterior elements subscore has a score range of 0–150 (facet joints at all 23 levels from C2/C3 to L5/S1, transverse process at 17 levels from T1 to L5, rib at 12 levels from T1 to T12, spinous process at 23 levels from C2 to L5, soft tissue inflammation at 23 levels from C2/C3 to L5/S1). The CANDEN MRI spine inflammation score may also be divided into the following four subscores: • A, 'Vertebral body corner inflammation subscore', defined as the sum of the anterior and posterior corner lesions, and anterolateral and posterolateral vertebral body lesions (posterolateral vertebral body lesions only at levels T12/L1 to L5/S1), which may predominantly represent enthesitis related to the anterior and posterior longitudinal ligament and the annulus fibrosus (range 0–254). • B, 'Spondylodiscitis subscore', defined as the sum of non-corner vertebral body lesions, which may predominantly represent inflammation from the disc or endplate itself (range 0–162). • C, 'Facet joint inflammation subscore', defined as the sum of facet joint lesions, representing inflammation of the synovial facet joints (range 0–46). • D, 'Posterolateral elements inflammation subscore', defined as the sum of rib, transverse process, spinous process, soft tissue inflammation and posterolateral vertebral body lesions (posterolateral vertebral body only at levels C7/T1 to T11/T12 because pLIL in the thoracic spine is considered to be related to the costovertebral joint), representing inflammation related to these synovial joints and enthesitis of ligaments of the posterior elements of the spine (range 0–152).

CANDEN MRI spine fat score	The following lesions are scored as 0 (absent) or 1 (present): aCFAT, pCFAT, aLFAT, pLFAT and FFAT. A score of 1 is added for large aCFAT and pCFAT. Non-corner lesions (NFAT) are scored as 0 (absent) or 2 (present), and a score of 2 is added for large non-corner lesions (NFAT). The total scoring range for the CANDEN MRI spine fat score is 0–510. The range for the vertebral body subscore is 0–464 (11 cervical endplates each with a maximum score of 4, 35 thoracic/lumbar endplates each with a maximum score of 12). The range for the fat posterior elements subscore is 0–46 (facet joints at all 23 levels).
CANDEN MRI spine bone erosion score	The following lesions are scored as 0 (absent) or 1 (present): aCOBE, pCOBE and FABE. A score of 1 is added for large aCOBE and pCOBE. The total scoring range for the CANDEN MRI spine bone erosion score is 0–208. The range for the vertebral body subscore is 0–162 (11 cervical endplates each with a maximum score of 2, 35 thoracic/lumbar endplates each with a maximum score of 4). The range for the posterior elements subscore is 0–46 (facet joints at all 23 levels).
CANDEN MRI spine new bone formation score	Anterior corner, posterior corner and non-corner ankylosis are scored as 0 (absent) or 6 (present). Anterior corner, posterior corner and non-corner bone spurs are scored as 0 (absent) or 2 (present). Facet joint ankylosis is scored as 0 (absent) or 1 (present). The total scoring range for the CANDEN MRI spine new bone formation score is 0–460. The range for the vertebral body subscore is 0–414 (23 levels with a maximum score of 18). The range for the posterior elements subscore is 0–46 (facet joints at all 23 levels).

- aCFAT, anterior corner fat lesion; aCIL, anterior corner inflammatory lesion; aCOBE, anterior corner bone erosion; aLFAT, anterolateral vertebral body fat lesion; aLIL, anterolateral vertebral body inflammatory lesion; CANDEN, Canada-Denmark; FABE, facet joint bone erosion; FFAT, facet joint fat lesion; FIL, facet joint inflammatory lesion; NFAT, non-corner fat lesion; NIL, non-corner inflammatory lesion; pCFAT, posterior corner fat lesion; pCIL, posterior corner inflammatory lesion; pCOBE, posterior corner bone erosion; pLFAT, posterolateral vertebral body fat lesion; pLIL, posterolateral vertebral body inflammatory lesion; RIL, rib inflammatory lesion; SPIL, spinous process inflammatory lesion; STIL, soft tissue inflammatory lesion; TIL, transverse process inflammatory lesion.

HEMRIS

Original citation:

J Rheumatol 2019 Sep;46(9):1232-1238. doi: 10.3899/jrheum.181093. Epub 2019 Feb 1.

The OMERACT MRI in Enthesitis Initiative: Definitions of Key Pathologies, Suggested MRI Sequences, and a Novel Heel Enthesitis Scoring System

Description:

MRI sequences: STIR/T2wFS or, alternatively T1w post-Gd; T1w without contrast (not mandatory if only inflammation is assessed)

***Imaging planes*:** Achilles tendon: Sagittal and preferably axial; Plantar aponeurosis: Sagittal and preferably coronal

***Area to score*:** At the heel region, the entheses are evaluated within 1 cm from the tendon/aponeurosis insertion.

Scoring procedure:

Entheseal soft tissue inflammation

- If T1w post-Gd images are available, entheseal soft tissues are assessed on these and the intratendon/peritendon/bursal hypersignal is defined as above-normal post-gadolinium enhancement on T1w images
- If only STIR/T2wFS images are available, entheseal soft tissues are assessed on these and the intratendon/peritendon/bursal hypersignal is defined as high signal intensity on STIR/T2wFS images
- Grading scale is 0-3 based on thirds of the maximum potential volume of enhancing soft tissue: Score 0 – normal; 1 – mild; 2 – moderate and 3 – severe.

Entheseal osteitis

- If STIR/T2wFS images are available, entheseal osteitis is assessed on these defined as a lesion within the entheseal bone marrow with ill-defined margins and high signal intensity on STIR/T2wFS images ("bone marrow edema")
- If only T1w-post Gd images are available, entheseal osteitis is assessed on these, and defined as a lesion within the entheseal bone marrow, with ill-defined margins, which shows above-normal enhancement on T1w-post-Gd images ("bone marrow post-contrast enhancement")
- Grading scale is 0-3 based on the proportion of bone with edema, compared to the 'assessed bone volume', judged on all available images: 0 – no edema; 1: 1-33% of the bone is edematous; 2: 34-66% of the bone is edematous; 3: 67-100% of the bone is edematous.

Entheseal structural damage variables

- Entheseal structural damage variables are scored based on T1w pre-Gd images.

For Achilles tendon and plantar fascia entheses, the possible range of the HEMRIS inflammation sum score will be 0–12 and 0–9, respectively, and the corresponding range of the HEMRIS structural sum scores will be 0–9, respectively.

MRI-WIPE

Original citation:

J Rheumatol . 2019 Sep;46(9):1215-1221. doi: 10.3899/jrheum.181084. Epub 2019 Feb 15.

Development and Validation of an OMERACT MRI Whole-Body Score for Inflammation in Peripheral Joints and Entheses in Inflammatory Arthritis (MRI-WIPE)

Description:

Inflammation in joints (arthritis) and at entheses (enthesitis) are both assessed separately for soft tissues (synovitis at joints, soft tissue inflammation at entheses) and bone (osteitis).

Preferably, synovitis and soft tissue inflammation are assessed on T1-post-Gd images and osteitis on short-tau inversion recovery (STIR)/T2-weighted fat-sat (T2FS) images. But if STIR/T2FS is the only method available, synovitis and soft tissue inflammation can be assessed based on it. Each component is scored on a semiquantitative scale of 0–3 (none/mild/moderate/severe). In total, 83 peripheral joints and 33 entheses are assessed. The MRI-WIPE score is derived by adding all scores together; the total range is 0–738 (joints 0–537; entheses 0–201).

Further Details on the Scoring Methodology	
Osteitis	Osteitis should be assessed in the bone from the articular surface/entheseal insertion to a depth of 1 cm on all available images. Grading scale: The scale is 0-3 based on the proportion of bone with edema, compared to the "assessed bone volume", judged on all available images: 0: no edema; 1: 1-33% of bone edematous; 2: 34-66% of bone edematous; 3: 67-100%.
Synovitis	Synovitis should be assessed in the entire synovial compartment on all available images. Grading scale: Score 0 is normal, while 1-3 is mild, moderate, severe, by thirds of the maximum potential volume of enhancing tissue in the synovial compartment.
Soft tissue inflammation	Soft tissue inflammation should be assessed inside the dense fibrous connective tissue part of the enthesis (which is continuous with and indistinguishable from the ligament/tendon) and in its immediate surroundings to a distance of 1 cm from the entheseal insertion. Grading scale: Score 0 is normal, while 1-3 is mild, moderate, severe, by thirds of the maximum potential volume of enhancing tissue. A distance of 1 cm was chosen by consensus in the OMERACT MRI in Arthritis Working Group with the aim of capturing inflammation that originates from the enthesis and not capturing tendinopathy.
Positive vs. negative score	A positive score of 1 should only be made when the reader is confident that there is an abnormality. All synovial joints contain normal joint fluid; this should not be scored. The scoring system aims at scoring inflammation. If the reader is hesitating whether to score a possible lesion 1 (mild) or 0 (none), it should probably be scored 0 (none).
Lesion judged borderline between two scores	If the lesion is judged borderline 1 vs. 2 or 2 vs. 3, lesion intensity may be taken into account. E.g. if a lesion is borderline between 1 (mild) and 2 (moderate), it may be scored 1 (mild) if not judged intense. Similarly, e.g. if a lesion is borderline between 2 (moderate) and 3 (severe), it may be scored 3 (severe) if judged intense. When there is an increased amount of synovial tissue, not just effusion, and the lesion is judged borderline between two scores, the higher score may be assigned.
No detailed rules for scoring each specific joint or enthesis	To allow a feasible scoring, we did not introduce detailed rules for how to score each specific joint or enthesis, as we aimed at only having generic rules, e.g. to assess soft tissue changes until 1 cm from insertional site irrespective of enthesis. Therefore, if e.g. the retrocalcaneal bursa is inflamed and it partly lies within 1 cm of the Achilles tendon insertion, that part should be considered when assessing soft tissue inflammation.
Choice of MRI sequences	Preferentially, synovitis and soft tissue inflammation are assessed on T1-post-Gd images and osteitis on Short Tau Inversion Recovery (STIR)/T2-Weighted Fat-Sat (T2FS) images, but if only STIR/T2FS is available, synovitis and soft tissue inflammation can be assessed based on this.

List of Sites Assessed		
JOINTS	No. Sites (synovitis)	No. Sites (osteitis)
Acromioclavicular joint	2	2
Sternoclavicular joint†	2	4
Manubriosternal joint†	1	2
Glenohumeral joint	2	2
Distal radioulnar joint	2	2
Radiocarpal joint	2	2
Intercarpal/carpometacarpal joints 2-5	2	2
Carpometacarpal joint 1	2	2
Metacarpophalangeal joints 1-5	10	10
Interphalangeal joint 1 (hands)	2	2
Proximal interphalangeal joints 2-5 (hands)	8	8
Distal interphalangeal joints 2-5 (hands)	8	8
Hip joint†	2	4
Knee joint†	2	10
Talocrural joint	2	2
Posterior talocalcaneal joint	2	2
Talocalcaneonavicular/calcaneocuboid joints	2	2
Tarsal/tarsometatarsal joints	2	2
Metatarsophalangeal joints 1-5	10	10
Interphalangeal joint 1 (feet)	2	2
Proximal interphalangeal joints 2-5 (feet)	8	8
Distal interphalangeal joints 2-5 (feet)	8	8
TOTAL NO. OF SITES	83	96
SCORE RANGE	0-249	0-288
ENTHESES	No. Sites (soft tissue infl)	No. Sites (osteitis)
Supraspinatus tendon	2	2
Costosternal joint 1	2	2
Costosternal joint 2	2	2
Costosternal joint 3-7	2	2
Posterior superior iliac spine	2	2
Iliac crest	2	2
Anterior superior iliac spine	2	2
Ischial tuberosity	2	2
Pubic symphysis†	1	2
Greater trochanter	2	2
Quadriceps femoris tendon insertion into patella	2	2
Patellar tendon insertion into patella	2	2
Patellar tendon insertion into tibial tuberosity	2	2
Medial femoral condyle	2	2
Lateral femoral condyle	2	2
Achilles tendon	2	2
Plantar fascia	2	2
TOTAL NO. SITES	33	34
SCORE RANGE	0-99	0-102

†Osteitis of the sternoclavicular joint is assessed separately for sternum and clavicle. Osteitis of the manubrosternal joint is assessed separately for manubrium and body of sternum. Osteitis of the hip joint is assessed separately for acetabulum and femur. Osteitis of the knee join is assessed separately for lateral femur, medial femur, lateral tibia, medial tibia, and patella. Osteitis of the pubic symphysis is assessed separately for left and right pubic bone.