GOLMePsA

STATISTICAL ANALYSIS PLAN

Protocol 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
Protocol Number:	RR13/10782
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SAP REVISION HISTORY

Protocol version	Updated SAP nº	Section changed	Description of and reason for change	Date changed
6.0	1.0	N/A	Original SAP dated 23/07/2018	N/A
7.0	1.1	N/A	Amended SAP not finalised as some of the changes to protocol needed to be reversed in a further amendment	16/09/2019
8.0	2.0	Approvals	Statistician signature added to approvals page	08/02/2022
		Abbreviations	List of abbreviations updated	10/03/2022
		3.1	Secondary objectives updated and exploratory objectives added, to match amended protocol	03/02/2022
		3.2	Secondary endpoints updated and exploratory endpoints added, to match amended protocol	03/02/2022
		3.3.2	Efficacy variables updated, to match amended protocol	03/02/2022
		3.3.3	Safety variable wording amended, to match amended protocol	03/02/2022
		4.2	Key exclusion criteria amended, to match amended protocol	03/02/2022
		5.2	Timing of analyses section updated to state that analyses involving only screening and/or baseline data will be performed as soon as all relevant data has been collected, cleaned and locked	03/02/2022
		6	Sample size amended to allow for 5% drop-out instead of 10%; details of sample size required for WB-MRI added now that this is deemed an exploratory endpoint, only available for a subset of patients	03/02/2022
		8.2	Visit window details added; clarification that MI only to be used to primary and secondary outcomes; detail regarding imputation for count data added; detail regarding MI with respect to interactions added; reference to mixed modelling added to match protocol	10/02/2022
		8.7	Derivations of US and MRI variables updated to match protocol	10/02/2022
		10.3.1	Reference to summaries of continuous variables removed as all planned variables are categorical	10/02/2022
		10.3.3	Patient global VAS added to list of PsA specific baseline variables to match protocol	10/02/2022
		11.1	Clarification added that the primary analysis of the primary variable will be based on the adjusted difference between groups; primary analysis now based on randomised stratification status with actual	10/02/2022

Protocol version	Updated SAP nº	Section changed	Description of and reason for change	Date changed
			oligo/polyarthritis status used in sensitivity analysis. Reference to quantile regression removed, heteroscedasticity-robust standard errors added	
		11.2	Details of summary data and confidence intervals added; appropriate modelling for count outcomes added to match updated protocol, generalised linear modelling added for skewed variables; additional detail of quantile regression approach for skewed variables added; explicit description of interpretation of secondary outcomes in the absence of a statistically significant difference in the primary outcome added; details of alternative mixed modelling approach in the instance that MI models fail to converge added; details of analysis methods for associations between US and clinical response, and between post-baseline steroid and US response added	10/02/2022
		11.3	Other efficacy variable analyses updated to reflect exploratory analysis of US and WB-MRI and to match wording in amended protocol	03/02/2022
8.0	3.0	3.2.2	Clarification that the planned comparison of cumulative steroid dose received up to week 12 between groups will not be performed, as all participants who received additional steroid received the same dose, therefore this is already captured in the outcome 'proportion requiring additional steroid therapy'	29/06/2023
		3.2.2.1	Reference to lack of validation of PsARC amended as this outcome is recommended by NICE for this population	11/07/2023
		4.2	Key exclusion criteria amended to include receipt of systemic steroids within 4 weeks prior to screening	20/06/2023
		8.1	Analysis software statement amended to remove 'or later' from the version number	11/07/2023
		8.2	Imputation methods and sensitivity analyses for missing data updated following blind review of final data; reference to sensitivity analysis that amended imputed values removed as full primary outcome data is available when withdrawal visit data is carried forward; reference to splitting imputation by treatment group/stratification variable removed for the same reason	20/06/2023

Protocol version	Updated SAP nº	Section changed	Description of and reason for change	Date changed
		8.6	Added clarification that the assessment of predictors/modifiers of treatment response will be made for response at 24 weeks	27/06/2023
		8.7	Typo in derivation of PASDAS corrected	20/06/2023
			Typo in range of LDI corrected; description of calculation expanded to match development paper	20/06/2023
			MDA criterion corrected to include BSA, to match development paper	20/06/2023
			Joint and entheseal remission criteria corrected to match protocol	20/06/2023
			Definitions of CPDAI 'not involved' category added; typos in criteria for scores of 2 & 3 corrected	20/06/2023
		9.2	Key exclusion criteria for derivation of per protocol population amended to include receipt of systemic steroids within 4 weeks prior to screening	20/06/2023
		11.3	References to exploratory subset analyses using 76/78 joints for the secondary outcomes MDA and ACR response removed, as the intention is to focus solely on PsARC response.	27/06/2023
			Correction to planned correlation between joint counts and total US GLOESS, which will be assessed using screening values rather than baseline values, as US was performed at screening rather than baseline	
		12.4	Initial inspection of ALT results indicates skewed distributions, therefore the planned summaries have been amended accordingly, and details given as to the time-points at which the values will be summarised. References to changes from baseline have been removed in favour of summaries at each time-point.	
8.0	4.0	3.2.4	Unplanned endpoints i.e. PASDAS status and response variables, published since the inception of the trial, added in a separate section: • Very low disease activity (PASDAS<1.9) • PASDAS moderate or good response • PASDAS meaningful change value achieved (improvement >1.29)	09/11/2023 (post-unblinding)
		8.7	Unplanned PASDAS status and response variables, and sensitivity definitions of US remission, defined in the derived variable section	09/11/2023 (post-unblinding)

Protocol version	Updated SAP nº	Section changed	Description of and reason for change	Date changed
		11.4	New 'Additional unplanned analysis' section added to give details of analysis methods for unplanned endpoints and unplanned descriptive summaries	09/11/2023 (post-unblinding)

APPROVALS

Approved By:

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Date: 17/11/2023

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Date: 15/11/2023

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ABBREVIATIONS

ABBREVIATION	DEFINITION
ACR	American College of Rheumatology
AE	Adverse Event
ALT	Alanine Aminotransferase
AS	Ankylosing Spondylitis
ASQoL	Ankylosing Spondylitis Quality of Life questionnaire
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
BSA	Body Surface Area
CANDEN	Canada-Denmark MRI scoring system
CASPAR	Classification Criteria for Psoriatic Arthritis
CPDAI	Composite Psoriatic Disease Activity Index
CTR	Clinical Trial Report
DLQI	Dermatology Life Quality Index
DMARD	Disease-Modifying Anti-Rheumatic Drug
EULAR	European Alliance of Associations for Rheumatology
GLOESS	Global OMERACT-EULAR Score System
GS	Ultrasound Grey Scale
HAQ-DI	Health Assessment Questionnaire Disability Index
HEMRIS	Heel Enthesitis MRI Scoring System
HIMRISS	Hip Inflammation MRI Scoring System
IBD	Inflammatory Bowel Disease
ICC	Intraclass Correlation Coefficient
IM	Intramuscular
IMP	Investigational Medicinal Product
ITT	Intent-To-Treat Population
KIMRISS	Knee Inflammation MRI Scoring System

LDI	Leeds Dactylitis Index
LTHT	Leeds Teaching Hospitals NHS Trust
MDA	Minimal Disease Activity
mNAPSI	Modified Nail Psoriasis Severity Index
MRI	Magnetic Resonance Imaging
MRI-WIPE	OMERACT MRI Whole-Body Score for Inflammation in Peripheral Joints and Entheses
MTX	Methotrexate
OMERACT	Outcome Measures in Rheumatoid Arthritis Clinical Trials
PASDAS	Psoriatic Arthritis Disease Activity Score
PASI	Psoriasis Area and Severity Index
PD	Ultrasound power Doppler
PDUS	Combined US grey scale and power Doppler score (at joint level)
PP	Per-Protocol Population
PsA	Psoriatic Arthritis
PsARC	Psoriatic Arthritis Response Criteria
RA	Rheumatoid Arthritis
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SPARCC	Spondyloarthritis Research Consortium of Canada
TT	Treat-to-Target
US	Ultrasound
VAS	Visual Analogue Scale
WB-MRI	Whole-Body Magnetic Resonance Imaging

1. PREFACE

This Statistical Analysis Plan (SAP) describes the planned analysis and reporting for The Leeds Teaching Hospitals NHS Trust protocol RR13/10782 (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).

This phase IIIb study is being completed to assess the efficacy of golimumab and methotrexate for the treatment of psoriatic arthritis in patients with early, treatment naïve disease.

The following documents were reviewed in preparation of this SAP:

- Clinical Research Protocol RR13/10782, and amendments issued (July 2017; July 2018; March 2022).
- Case report forms (CRFs) for Protocol RR13/10782.
- ICH Guidance on Statistical Principles for Clinical Trials.

The reader of this SAP is encouraged to also read the clinical protocol for details on the conduct of this study, and the operational aspects of clinical assessments and timing for completing a patient in this study.

2. PURPOSE OF SAP

The purpose of this SAP is to outline the planned analyses to be completed to support the completion of the Clinical Trial Report (CTR) for protocol RR13/10782. The planned analyses identified in this SAP will be included in regulatory submissions and/or future manuscripts. Also, exploratory analyses not necessarily identified in this SAP may be performed to support the clinical development program. Any post-hoc, or unplanned, analyses not identified in this SAP performed will be clearly identified in the respective CTR.

3. STUDY OBJECTIVES AND ENDPOINTS

3.1 Study Objectives

3.1.1 Primary Objective

The primary objective is 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.

3.1.2 Secondary Objectives

Secondary objectives are:

- To assess superiority of combination therapy over standard care in improving ultrasound-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

3.1.3 Exploratory Objectives

- 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

3.2 Study Endpoints

3.2.1 Primary Endpoint

The primary endpoint is clinical disease activity (PASDAS) at 24 weeks.

3.2.1.1 Appropriateness of Primary Endpoint

The PASDAS has been shown to be the most responsive of the available composite disease activity measures for psoriatic arthritis[1].

3.2.2 Secondary Endpoint(s)

Secondary endpoints are:

Efficacy measures

Clinical measures of disease activity

- Disease activity measures:
    - PASDAS at 12, 36 and 52 weeks
    - Enthesitis score(2) at 12, 24, 36 and 52 weeks
    - Dactylitis score(3,4) at 12, 24, 36 and 52 weeks in patients with dactylitis
    - PASI score[5] at 12, 24, 36 and 52 weeks
    - mNAPSI score[6] at 12, 24, 36 and 52 weeks
    - CPDAI score[7] 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
        - GLOESS score(8,9)
        - Inflammatory enthesitis score
        - Chronic enthesitis score
- Acceptable state
    - Proportion achieving US remission (all common joints and entheses (see section 8.7) score GS<2 & PD==0) at 12, 24 and 36 weeks

Patient-reported outcomes

- Patient VAS global disease activity at 24 and 52 weeks
- Quality of life
    - DLQI score[10] at 24 and 52 weeks
- Health status
    - SF-36 mental component summary and physical component summary[11] at 24 and 52 weeks.

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*

*This was originally planned; however, inspection of blinded data indicates that all participants who received additional steroid received one IM dose of 120mg, therefore this analysis will not be performed as this is already captured in the proportion requiring additional steroid therapy

3.2.2.1 Appropriateness of Secondary Endpoints

All secondary endpoints are validated outcomes for use in this patient population with the exception of the PsARC, which is nevertheless widely used in international PsA RCTs and endorsed by EMEA & NICE, and the whole-body MRI assessments, which are novel.

3.2.3 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 of protocol) (in a subset of patients)
    - Imaging measures of disease activity in expanded set of sites (the expanded ultrasound variables will only be available for 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.

3.2.4 Unplanned endpoints

Following unblinding of the trial data, the following unplanned endpoints, published since the inception of the trial, were added to the trial report:

- PASDAS very low disease activity (PASDAS<1.9; Y/N) at 12, 24, 36 & 52 weeks
- PASDAS moderate or good response (Y/N) at 12, 24, 36 & 52 weeks
- PASDAS meaningful change value for improvement achieved (Y/N) at 12, 24, 36 & 52 weeks

3.3 Study variables

3.3.1 Standard variables

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

3.3.2 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 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

3.3.3 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.

4. STUDY METHODS

4.1 Overall Study Design and Plan

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

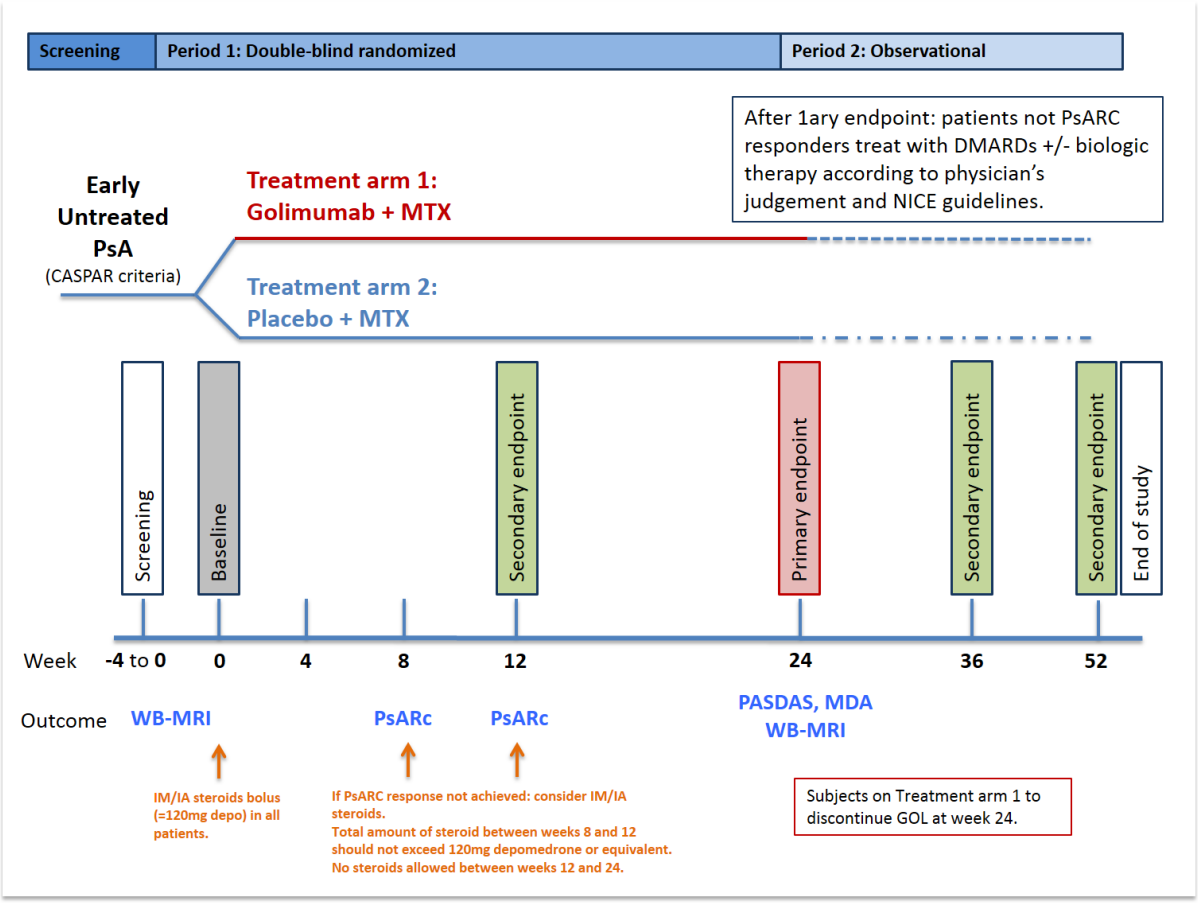
- Treatment-naïve PsA patients classified according to CASPAR criteria[12]
- <24 month diagnosis
- At least 3 swollen and 3 tender joints or 2 swollen and 2 tender joints and one tender enthesis.

The trial will start with a four-week screening phase, and informed consent will be obtained at the screening visit. A 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.



4.2 Selection of Study Population

Key inclusion criteria (pertinent to primary endpoint)

- Subjects with a diagnosis of psoriatic arthritis as per the Classification for Psoriatic Arthritis (CASPAR) criteria confirmed up to 24 months prior to screening.
- Subjects with active PsA defined as the presence of at least 3/78 tender and at least 3/76 swollen joints or 2 swollen and 2 tender joints plus one affected entheseal site (Achilles tendon and/or plantar fascia) at baseline.

Key exclusion criteria (pertinent to primary endpoint)

- 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).
- Any chronic inflammatory arthritis diagnosed before 16 years old.

- 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.

4.3 Method of Treatment Assignment and Randomization

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 at baseline (oligoarticular: ≤4 joints involved /polyarticular: >4 joints involved). Informed written consent for entry into the trial must be obtained prior to randomisation, subject to the patient meeting the eligibility criteria. Randomization should take place as soon as possible after consent is obtained and must be performed by an authorized member of the clinical team at the site using the LTHT Pharmacy telephone randomisation service.

4.4 Treatment Masking (Blinding)

Pre-filled syringes will be available from pharmacy (provided by Janssen Biologics) 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. This will be provided by Janssen Biologics and will consist of an aqueous medium of histidine sorbitol and polysorbate 80 at pH 5.5.

5. SEQUENCE OF PLANNED ANALYSES

5.1 Interim Analyses

There are no planned Interim Analyses for this study.

5.2 Final Analyses and Reporting

All final, planned, analyses identified in the protocol and in this SAP will be performed only after the last patient has completed the week 52 visit, with the exception of baseline analyses (see below). A blinded data review meeting will be held prior to database lock and completion of the final analyses.

In addition, no database may be locked, random code unblinded, or analyses completed until this SAP has been approved.

Key statistics and study results will be made available to the study team following database lock and prior to completion of the final CTR.

Analyses using either screening and baseline data (PASDAS test-retest reliability) or baseline data only (associations between clinical and imaging assessments at baseline) will be performed as soon as all the relevant patients have completed these visits and the relevant data have been fully validated and locked to further amendment. In the case of MRI, no analyses of the baseline data will be performed until all patients in the subset in whom MRI measurements were obtained at baseline have completed the follow-up MRI visits, and all MRI data have been fully validated, because MRI data from all visits will be scored simultaneously. As these analyses do not involve post-treatment efficacy comparisons and can be performed blind to treatment group there will be no impact on multiplicity and no potential to unblind the trial.

Any, post-hoc, exploratory analyses completed to support planned study analyses, which were not identified in this SAP, will be documented and reported in appendices to the CTR. Any results from these unplanned analyses will also be clearly identified in the text of the CTR.

Analysis of exploratory WB-MRI outcomes may be conducted after the primary and secondary outcomes have been analysed and reported; in which case this analysis will be attached as an addendum to the main CTR.

6. SAMPLE SIZE DETERMINATION

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[13]. 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[14,15] 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 WBMRI 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[1]. This element was added in an amendment and will not be available for all patients; we will aim to obtain data from at least 31 patients.

7. ANALYSIS POPULATIONS

The following analysis populations are planned for the study:

- **Screening Population (SCREEN):** The Screening Population includes all subjects who provide informed consent and provide demographic and/or baseline screening assessments, regardless of the subject's randomization and treatment status in the trial.
- **Safety Population (SAFETY):** The Safety Population includes all patients who receive any amount of planned study medication.
- **Full Analysis Set (EFFICACY):** The Efficacy Population includes all patients who are randomized.
- **Per-Protocol Efficacy (PP-EFFICACY):** The PP-Efficacy includes all patients in the Efficacy Population deemed to fulfil the protocol in terms of eligibility, interventions and outcome assessment (see section 9.2).

8. GENERAL ISSUES FOR STATISTICAL ANALYSIS

8.1 Analysis Software

All analysis will be performed using Stata software version 17.0.

8.2 Methods for Withdrawals, Missing Data, and Outliers

For missing values at baseline, screening values (if available) will be carried forward.

Visits which fall outside ±14 days of the scheduled date will be considered missing for analysis.

For patients who withdraw early, in the primary analysis data from the withdrawal visit will be imputed for subsequent visits for continuous outcomes, and non-response will be imputed for binary outcomes.

Multiple imputation by chained equations will be used to address the remainder of the missing data for primary and secondary outcomes. The number of imputed datasets will be determined by the Monte Carlo (MC) error rate of the resulting combined estimates. A minimum of 20 datasets will be imputed; if the MC errors calculated for the coefficient and standard error for the treatment group term are more than 10% of the estimated standard error the number of imputations will be increased in increments of 5 until the MC error is <10% of the standard error. Continuous interval, count or ordinal outcomes will be imputed using predictive mean matching to 10 nearest neighbours; categorical outcomes will be imputed using binary, ordinal or multinomial logistic regression as appropriate to the data type. Composite measures, including the primary outcome, and the achievement of thresholds of response (e.g. PsARC) will be computed passively following imputation of the underlying score or components, provided sample size is sufficient for the imputation models to converge. If the number of parameters to be estimated exceeds the number of patients, these variables will be directly imputed.

All imputation models will include:

Age at baseline, sex, oligo/polyarticular disease, treatment arm, symptom duration at baseline, baseline values of the variables being imputed (values of components for response variables), other auxiliary variables found to be associated with the outcome to be imputed and/or with the likelihood that it is missing. Only values from the main primary and secondary endpoints (12, 24, 36, 52 weeks) will be included in imputation models. If imputation models continue to fail, mixed modelling will be explored as an alternative – see section 11.2 for details.

Sensitivity analyses relating to missing data will include restricting analysis of the data to the observed values only (1), and using post-treatment-withdrawal data observed for patients who withdrew from study therapy early (where available) rather than carrying forward data from their withdrawal visit (2).

Outliers, defined as values lying more than 3 times the inter-quartile range from the nearest quartile, will be identified during the blind data review. Those that can be confirmed to be due to data entry errors will be corrected in the database. In all other cases outliers will be included in the main analysis but sensitivity analyses will be performed to assess whether the exclusion of these data points affects study conclusions. The same approach will be used for cases identified to be unduly influential during the analysis of continuous outcomes; for example cases for which the studentized residuals from the linear regression model exceed an absolute value of 2.5.

Analysis of exploratory WB-MRI outcomes will be available case only.

8.3 Data Transformations

Data transformations will not be used with the exception of transformations that are required for calculation of composite measures; any severely skewed variables will be compared between groups using non-parametric quantile regression.

8.4 Multicenter Studies

This is a single centre study.

8.5 Multiple Comparisons and Multiplicity

EME guidance states that 'a clinical study that requires no adjustment of the type I error is one that consists of two treatment groups, that uses a single primary variable, and has a confirmatory statistical strategy that pre-specifies just one single null hypothesis relating to the primary variable and no interim analysis.' On this basis, the GOLMePsA trial requires no adjustment.

8.6 Planned Subgroups, Interactions, and Covariates

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 exploratory subgroup analyses will investigate differences in treatment response at week 24

according to oligo/polyarthritis status, symptom 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.

8.7 Derived and Computed Variables

The following derived and computed variables have been initially identified. It is expected that additional variables will be required. The SAP will not be amended for additional variables that are not related to the primary target or key secondary target variables. Any additional derived or computed variables will be identified and documented in the Stata programs that create analysis files.

Table 1: Derived and computed variables

Variable Name	Description	Valid Values (Ranges)	Computation Methods, Notes or Equations
AGE at baseline	Subject age in years	18-100	=Truncate[number of days between DateOfBirth and DateOfBaseline/365.25] (0 d.p.)
BMI	Body Mass Index	10 to 60	=[Weight (Kg)/Height (m^2)]
PASDAS	Primary endpoint: Psoriatic arthritis disease activity score	0 to 10	(((0.18 x √Physician global VAS) + (0.159 x √Patient global VAS) – (0.253 x √SF36-PCS) + (0.101 x LN (66 swollen joint count + 1)) + (0.048 x LN (68 tender joint count + 1)) + (0.23 x LN (Leeds Enthesitis Count + 1)) + (0.37 x LN (Tender dactylitis count + 1)) + (0.102 x LN (CRP + 1)) +2)*1.5 See section 15 for details of SF36 PCS calculation
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index	0 to 10	BASDAI=((sum Q1:Q4)+((Q5+Q6)/2))/5
Enthesitis score	Leeds Enthesitis Index	0 to 6	Each of six sites scored (0=absent, 1=present) for enthesitis: medial femoral condyle (2), Achilles tendon (2), plantar fascia insertion (2)
Dactylitis score	Leeds Dactylitis Index	0 to approx. 400	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. If the contralateral digit is also affected then the sex-specific standard reference value corresponding to the digit is used instead. The digit result is then obtained by subtracting 1 from the ratio, multiplying by 100, then multiplying the result by the tenderness score for that digit. The results of each digit are then added to produce a total score
PASI score	Psoriasis area and severity index	0 to 72	Each of four body areas (head & neck, upper limbs, trunk, lower limbs) is scored 0-4 (absent-very severe) for severity of erythema, induration and desquamation. The three scores are summed for each region, then multiplied by the surface area of each region (0.1, 0.2, 0.3 & 0.4 respectively). Each region is also scored for area of psoriasis from 0 (nil) to 6 (90-100%). The severity score is multiplied by the area score and these subtotals are added across the four regions.
mNAPSI score	Modified Nail Psoriasis Severity Index	0 to 140	Each fingernail is scored for the presence and the severity of pitting, onycholysis and nail plate crumbling (score 0-3) and the presence or absence of splinter haemorrhages, leukonychia, red

Variable Name	Description	Valid Values (Ranges)	Computation Methods, Notes or Equations
			spots in the lunula, oil spot dischromia and nail bed hyperkeratosis (score 1 for each if present). This gives a total possible score of 140.
CPDAI score	Composite psoriatic disease activity index	0 to 15	See Table 2 (below) for calculation of CPDAI including the spine
DLQI	Dermatology life quality index	0 to 30	Total of 10 questions across 6 domains scored 0 to 3
HAQ	Health assessment questionnaire disability index	0 to 3	Mean of 8 domains each scored 0-3; within each domain the maximum score is taken. If this is <2 and the patient has reports requiring help or devices for that domain, score for that domain is increased to 2.
ASQoL	Ankylosing spondylitis quality of life scale	0 to 18	Total of 18 responses (0 “No” or 1 “Yes”)
SF36-PCS	Short form 36 physical component score	0 to 100	Scoring of SF36 is complex; see section 15 for syntax which corresponds to command: sf36, natver(US) stub(SF)
SF36-MCS	Short form 36 physical component score	0 to 100	Scoring of SF36 is complex; see section 15 for syntax which corresponds to command: sf36, natver(US) stub(SF)
MDA	Minimal disease activity	0 (No) to 1 (Yes)	At least 5 of the 7 following criteria: Tender joint count (/68) ≤1 Swollen joint count (/66) ≤1 PASI ≤1 or BSA≤3 Patient pain VAS ≤15 Patient global disease activity VAS ≤20 HAQ ≤0.5 Enthesitis count ≤1.
PsARCResponse	Psoriatic arthritis response criteria	0 (No) to 1 (Yes)	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 joint grade (total of 68 joints graded 0-3) 2. At least 30% reduction in swollen joint grade (total of 66 joints graded 0-3) 3. At least a 1 point reduction in physician’s assessment of articular disease (1-5 Likert scale) 4. At least a 1 point reduction in patient’s assessment of articular disease (1-5 Likert scale)
PsARCResponseSens	Psoriatic arthritis response criteria	0 (No) to 1 (Yes)	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 joint grade (total of 78 joints graded 0-3) 2. At least 30% reduction in swollen joint grade (total of 76 joints graded 0-3)

Variable Name	Description	Valid Values (Ranges)	Computation Methods, Notes or Equations
			3. At least a 1 point reduction in physician's assessment of articular disease (1-5 Likert scale) 4. At least a 1 point reduction in patient's assessment of articular disease (1-5 Likert scale)
ACR20/50/70	American college of rheumatology responder index 20 / 50 / 70	0 (No) to 1 (Yes)	The patient must have: ≥20/50/70% improvement in both TJC (68 joints count: as in appendix 8, minus CMC and DIP of the feet) and SJC (66 joints count: as in appendix 8, minus CMC and DIP of the feet) and ≥20/50/70% improvement in at least 3 of the following 5 ACR Core set criteria: 1. Patient's Assessment of Pain Visual Analogue Scale (VAS) 2. Patient's Global Assessment of 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
PASI75	PASI 75% response	0 (No) to 1 (Yes)	Patients achieving PASI 75 are defined as having an improvement of at least 75% in the PASI compared to baseline.
US_TotalGS	US total grey scale scores across all common joints	0 to 72	Total of GS scores (0-3) for 24 joints: bilateral wrists, MCPs 2&3, PIPs 2&3, knees, MTPs 1-5, ankle
US_TotalGS_Subset	US total grey scale scores across OMERACT list of joints	0-144	Total of GS scores (0-3) for 48 joints: bilateral wrists, MCP1-5, PIP1-5, DIP2-5, knees, MTP1-5, tibiotalar, talonavicular and subtalar
US_TotalPD	US total power Doppler scores across all common joints	0-72	Total of PD scores (0-3) for 24 joints: bilateral wrists, MCPs 2&3, PIPs 2&3, knees, MTPs 1-5, ankle
US_TotalPD_Subset	US total power Doppler scores across OMERACT list of joints	0-144	Total of PD scores (0-3) for 48 joints: bilateral wrists, MCP1-5, PIP1-5, DIP2-5, knees, MTP1-5, tibiotalar, talonavicular and subtalar
US_GLOESS	US total PDUS scores across all common joints	0-72	Total of PDUS scores (0-3) for 24 joints: bilateral wrists, MCPs 2&3, PIPs 2&3, knees, MTPs 1-5, ankle

Variable Name	Description	Valid Values (Ranges)	Computation Methods, Notes or Equations
US_GLOESS_Subset	US total PDUS scores across OMERACT list of joints	0-144	Total of PDUS scores (0-3) for 48 joints: bilateral wrists, MCP1-5, PIP1-5, DIP2-5, knees, MTP1-5, tibiotalar, talonavicular and subtalar
US_JointRemission	US number of common joints with GS>1 & PD>0 =0 (Y/N)	0-24	Count of joints with GS>1 or PD>0 in 24 joints: bilateral wrists, MCPs 2&3, PIPs 2&3, knees, MTPs 1-5, ankle = 0 (1 if yes, 0 if no)
US_JointRemission_Subset	US number of joints in OMERACT list with GS>1 & PD>0=0 (Y/N)	0-48	Count of joints with GS>1 or PD>0 in 48 joints: bilateral wrists, MCP1-5, PIP1-5, DIP2-5, 8 knee, MTP1-5, tibiotalar, talonavicular and subtalar = 0 (1 if yes, 0 if no)
US_NenthGS	US number of common entheses with GS abnomalities	0-10	Count of GS=1 for 10 entheses: Bilateral quadriceps insertion, patellar ligament proximal insertion, patellar ligament distal insertion, Achilles tendon, plantar fascia
US_NenthGS_Subset	US number of entheses in OMERACT list with GS abnomalities	0-12	Count of GS=1 for 12 entheses: Bilateral lateral epicondyle, quadriceps insertion, patellar ligament proximal insertion, patellar ligament distal insertion, Achilles tendon, plantar fascia
US_TotalEnthPD	US total power Doppler score across common entheses	0-30	Total of PD scores (0-3) for 10 entheses: Bilateral quadriceps insertion, patellar ligament proximal insertion, patellar ligament distal insertion, Achilles tendon, plantar fascia
US_TotalEnthPD_Subset	US total power Doppler score across OMERACT list of entheses	0-36	Total of PD scores (0-3) for 12 entheses: Bilateral lateral epicondyle, quadriceps insertion, patellar ligament proximal insertion, patellar ligament distal insertion, Achilles tendon, plantar fascia
US_EnthRemission	US number of common entheses with GS>1 & PD>0=0 (Y/N)	0-10	Count of entheses with GS>1 or PD>0 in 10 entheses: bilateral quadriceps insertion, patellar ligament proximal insertion, patellar ligament distal insertion, Achilles tendon, plantar fascia=0 (1 if yes, 0 if no).
US_EnthRemission_Subset	US number of entheses in OMERACT list with GS>1 & PD>0=0 (Y/N)	0-1	Count of entheses with GS>1 or PD>0 in 12 entheses: bilateral lateral epicondyle, quadriceps insertion, patellar ligament proximal insertion, patellar ligament distal insertion, Achilles tendon, plantar fascia=0 (1 if yes, 0 if no).

Variable Name	Description	Valid Values (Ranges)	Computation Methods, Notes or Equations
US_NenthCalc	US number of common entheses with calcification	0-10	Count of calcification=1 for 10 entheses: bilateral quadriceps insertion, patellar ligament proximal insertion, patellar ligament distal insertion, Achilles tendon, plantar fascia
US_NenthEnth	US number of common entheses with enthesophytes	0-10	Count of enthesophyte=1 for 10 entheses: bilateral quadriceps insertion, patellar ligament proximal insertion, patellar ligament distal insertion, Achilles tendon, plantar fascia
US_EnthThick	US total thickness score across common entheses: see table 3	0-30	Total of thickness scores (0-3) for 10 entheses: bilateral quadriceps insertion, patellar ligament proximal insertion, patellar ligament distal insertion, Achilles tendon, plantar fascia
US_EnthThick_Subset	US total thickness score across OMERACT list of entheses: see table 3	0-36	Total of thickness scores (0-3) for 12 entheses: bilateral lateral epicondyle, quadriceps insertion, patellar ligament proximal insertion, patellar ligament distal insertion, Achilles tendon, plantar fascia
US_EnthEro	US total erosion score across common entheses	0-30	Total of erosion scores (0-3) for 10 entheses: bilateral quadriceps insertion, patellar ligament proximal insertion, patellar ligament distal insertion, Achilles tendon, plantar fascia
US_EnthEro_Subset	US total erosion score across OMERACT list of entheses	0-36	Total of erosion scores (0-3) for 12 entheses: bilateral lateral epicondyle, quadriceps insertion, patellar ligament proximal insertion, patellar ligament distal insertion, Achilles tendon, plantar fascia
US_EnthInf	US total enthesis inflammation score across common entheses	0-70	=US_NenthGS+ US_TotalEnthPD +US_EnthThick
US_EnthInf_Subset	US total enthesis inflammation score across OMERACT list of entheses	0-84	=US_NenthGS_Subset+ US_TotalEnthPD _Subset+US_EnthThick_Subset
US_EnthChron	US total enthesis chronicity score across common entheses	0-50	=US_NenthCalc+US_EnthEro+US_NenthEnth

Variable Name	Description	Valid Values (Ranges)	Computation Methods, Notes or Equations
US_EnthChron	US total enthesis chronicity score across common entheses	0-60	=US_NenthCalc_Subset+US_EnthEro_Subset+US_NenthEnth_Subset
US_Remission	US remission in common joints	0 (No) to 1 (Yes)	=US_JointRemission==1 & US_EnthRemission==1 if US_JointRemission<. & US_EnthRemission<. (Equates to all common joints and entheses scoring GS<2 and PD==0)
US_Remission_Subset	US remission in OMERACT joint list	0 (No) to 1 (Yes)	=US_JointRemission_Subset==1 & US_EnthRemission_Subset==1 if US_JointRemission_Subset<. & US_EnthRemission_Subset<. (Equates to all scanned joints and entheses scoring GS<2 and PD==0)
US_JointRemissionSens	US remission in common joints (alternative definition)	0 (No) to 1 (Yes)	Count of joints with GS>2 or PD>0 in 24 joints: bilateral wrists, MCPs 2&3, PIPs 2&3, knees, MTPs 1-5, ankle = 0 (1 if yes, 0 if no)
US_EnthRemissionSens	US remission in common entheses (alternative definition)	0 (No) to 1 (Yes)	Count of entheses with GS>0 or PD>0 in 10 entheses: bilateral quadriceps insertion, patellar ligament proximal insertion, patellar ligament distal insertion, Achilles tendon, plantar fascia=0 (1 if yes, 0 if no).
US_ImagingRemissionSens1	US remission (alternative definition 1)	0 (No) to 1 (Yes)	=0 if US_EnthRemissionSens==0 or US_JointRemissionSens==0 =1 if US_EnthRemissionSens==1 & US_JointRemissionSens==1
US_ImagingRemissionSens2	US remission (alternative definition 2)	0 (No) to 1 (Yes)	=0 if US_EnthRemission==0 or US_JointRemissionSens==0 =1 if US_EnthRemission==1 & US_JointRemissionSens==1
US_ImagingRemissionSens3	US remission (alternative definition 3)	0 (No) to 1 (Yes)	=0 if US_EnthRemissionSens==0 or US_JointRemission==0 =1 if US_EnthRemissionSens==1 & US_JointRemission==1
PASDASVLOW	PASDAS very low disease activity	0 (No) to 1 (Yes)	=0 if PASDAS≥1.9 =1 if PASDAS<1.9

Variable Name	Description	Valid Values (Ranges)	Computation Methods, Notes or Equations
PASDASRespMODGOOD	PASDAS moderate or good response	0 (No) to 1 (Yes)	=0 if improvement≤0.8 or (PASDAS≥5.4 & improvement≤1.6) =1 if (PASDAS≤3.2 & improvement>1.6) or (PASDAS≤3.2 & improvement≤1.6 & improvement>0.8) | (PASDAS>3.2 & PASDAS<5.4 & improvement>0.8) | (PASDAS≥5.4 & improvement>1.6)
PASDASMCVImp	PASDAS meaningful change value for improvement achieved	0 (No) to 1 (Yes)	=0 if improvement ≤1.29 =1 if improvement >1.29

Table 2: CPDAI calculation

CPDAI domain	Not involved (0)	Mild (1)	Moderate (2)	Severe (3)
Peripheral arthritis	SJC66=0 & TJC68=0	≤4 Joints (swollen or tender); normal function (HAQ <0.5)*	≤4 Joints but function impaired; or > 4 joints, normal function	>4 Joints and function impaired
Skin disease	'Does the patient currently have skin psoriasis'=No	PASI ≤10 and DLQI ≤10	PASI ≤10 but DLQI >10; or PASI >10 but DLQI ≤10	PASI >10 and DLQI >10
Enthesitis	0 sites involved	≤3 Sites; normal function (HAQ <0.5)*	≤3 Sites but function impaired; or >3 sites but normal function	>3 Sites and function impaired
Dactylitis	0 digits affected	≤3 Digits; normal function (HAQ <0.5)*	≤3 Digits but function impaired; or >3 digits but normal function	>3 Digits and has function impaired
Spinal disease	**	BASDAI <4; normal function (ASQol <6)	BASDAI ≥4 but normal function; BASDAI <4 but function impaired	BASDAI ≥4 and function impaired

*Health assessment questionnaire (HAQ) only counted if clinical involvement of domain (joint/enthesis/dactylitis) present **Lack of axial involvement determined according to the Calin inflammatory back pain criteria i.e. <4 of the following satisfied: Back pain onset at age 40 or less; Back pain duration (> 3 months); Back pain onset insidious; Morning stiffness in back; Back pain improves with exercise

Table 3: Thresholds for US entheseal thickening scores

Enthesis	Thickness	Score
Elbow – lateral epicondyle	<5.9mm	0
	≥5.9mm & <6.9mm	1
	≥6.9mm & <7.9mm	2
	≥7.9mm	3
Knee – quadriceps insertion	<7.1mm	0
	≥7.1mm & <8.1mm	1
	≥8.1mm & <9.1mm	2
	≥9.1mm	3
Knee – proximal patellar ligament insertion	<5.0mm	0
	≥5.0mm & <6.0mm	1
	≥6.0mm & <7.0mm	2
	≥7.0mm	3
Knee – distal patellar ligament insertion	<5.0mm	0
	≥5.0mm & <6.0mm	1
	≥6.0mm & <7.0mm	2
	≥7.0mm	3
Ankle – Achilles tendon	<6.29mm	0
	≥6.29mm & <7.29mm	1
	≥7.29mm & <8.29mm	2
	≥8.29mm	3
Foot – plantar fascia	<5.4mm	0
	≥5.4mm & <6.4mm	1
	≥6.4mm & <7.4mm	2
	≥7.4mm	3

9. STUDY SUBJECTS

9.1 Disposition of Subjects and Withdrawals

All subjects who provide informed consent will be accounted for in this study. The frequency and percent of subjects in each population, study withdrawals, subgroups, and major protocol violations will also be presented. The following will be presented:

- Total number of subjects screened (=subjects who gave informed consent)
- Number of randomized subjects.
- Number of randomized subjects who completed the study in each treatment group.
- Number of subjects who discontinued after randomization, grouped by treatment and main reason.
- Number of enrolled/screened, randomized, and analysis populations.

9.2 Protocol Violations and Deviations

The following will be considered major protocol violations and patients meeting any of these criteria will be excluded from the per protocol set. Decisions as to which patients meet these criteria will be made during a blind data review prior to final analysis.

- Patients receiving prohibited prior and/or concomitant medications
- Patients not meeting the following inclusion / meeting exclusion criteria (i.e. those included in error)
    - Inclusion:
        - Subjects with a diagnosis of psoriatic arthritis as per the Classification for Psoriatic Arthritis (CASPAR) criteria confirmed up to 24 months prior to screening.
        - Subjects with active PsA defined as the presence of at least 3/78 tender and at least 3/76 swollen joints or 2 swollen and 2 tender joints plus one affected entheseal site (Achilles tendon and/or plantar fascia) at baseline.
        - Subjects who are treatment naïve to DMARDs.
    - Exclusion:
        - Received previous treatment with any DMARDs at therapeutic dose.
        - Received previous treatment with golimumab or other tumour necrosis factor inhibitor (TNFi) or other biologic drugs.
        - Any chronic inflammatory arthritis diagnosed before 16 years old.

    - 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.
- Patients who missed >20% or 2 or more consecutive doses of golimumab
- Patients whose methotrexate treatment was paused for >28 days
- Patients who did not receive the study treatment to which they were randomised (including patients who did not receive steroid bolus at baseline)
- Patients in whom more than one study visit (up to week 24) was outside the 7 day window
- Patients who withdrew from study treatment for any reason
- Patients without primary endpoint data available

The number of study subjects with each violation will be presented in the CTR.

9.3 Inclusion and Exclusion Criteria

The number and percent are to be presented for subjects meeting each Inclusion and Exclusion Criteria. Generally, it is expected that the overall percentage will be 100% for inclusion and exclusion criteria, except when data review indicates that inclusion or exclusion criteria have been violated. Exceptions to 100% will be presented as absolute and relative frequencies both overall and within each treatment group. For any patients included in error a narrative will be provided.

10. DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

Baseline characteristics will be compared descriptively between randomised arms at baseline; no inferential tests will be performed.

10.1 Demographics

Age, gender and ethnicity will be reported. Descriptive data will be presented as appropriate to the data type; mean (SD) for age, absolute and relative frequencies for gender and ethnicity.

10.2 Prior and Concurrent Medications

Absolute and relative frequencies of patients receiving prior and concomitant NSAIDs will be tabulated overall and by treatment group.

10.3 Baseline and Screening Conditions

10.3.1 Baseline Medical History

The following will be summarized as absolute and relative frequencies, by treatment group:

- Family history of autoimmune disease (RA, AS, PsA, IBD)
- Family history of premature cardiovascular disease
- Smoking status (never, current, previous)

10.3.2 Baseline Physical Exam

Baseline physical exam findings will be summarised according to data type (mean (SD) for normally-distributed continuous, median (inter-quartile range) for skewed continuous, absolute and relative frequencies for categorical), by treatment group. The following will be summarized:

- BMI (kg/m^2)
- Abnormalities
    - Cardiovascular
    - Respiratory
    - Abdomen
    - Neurological
    - Dermatological
    - Hypertension
    - Diabetes
    - Hypercholesterolaemia

10.3.3 PsA Specific Baseline and Screening History

Baseline PsA-specific findings will be summarised according to data type (mean (SD) for normally-distributed continuous, median (inter-quartile range) for skewed continuous, absolute and relative frequencies for categorical), by treatment group. The following will be summarized:

- Percentage of body surface area affected (%)
- PASI score
- mNAPSI
- CPDAI
- PASDAS
- Leeds enthesitis index
- Imaging scores (see Section 3.3.2 for detailed list of WB-MRI & US variables)
- Patient VAS global disease activity
- DLQI score
- SF-36 physical component score
- SF-36 mental component score

10.4 Measurement of Treatment Compliance

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. Golimumab is administered by the study team and will be fully reported; methotrexate compliance is monitored verbally at each visit.

11. EFFICACY ANALYSES

11.1 Primary Efficacy Variable 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 values at baseline, and whether or not the patient had clinical polyarthritis at baseline (stratification factor). In the primary analysis the actual stratification status will be used; in a sensitivity analysis the stratification status used at randomisation (irrespective of actual status) will be used if this differs from the actual status. If visual inspection of model residuals indicate that the data violate the assumptions of linear regression, heteroscedasticity-robust standard errors will be specified.

The analysis of PASDAS at week 24 will include the following test of hypothesis:

H0: $\mu 1 = \mu 2$

The alternative hypothesis is:

H1: $\mu 1 \neq \mu 2$

Where $\mu 1$ and $\mu 2$ represent the covariate-adjusted average in arms 1 and 2 respectively

Acceptance of H1 in favour of treatment arm 1 (Golimumab + MTX) at two-sided significance $p<0.05$, for the Full Analysis Set, will be considered to be a successful demonstration of efficacy.

11.2 Secondary Efficacy Variable Analysis

Full descriptive data will be provided for all secondary endpoints. Adjusted estimates of effect size will be provided for binary secondary endpoints using multiple binary logistic regression; odds ratios and 95% confidence intervals will be presented. This applies to MDA, PsARC response, ACR 20/50/70, PASI75, US remission, steroid therapy required up to week 12 (Y/N). Continuous interval outcomes will be analysed using multiple linear regression; differences between treatment group means and 95% confidence intervals will be presented. This applies to PASDAS, CPDAI, patient global VAS, SF36 PCS and MCS, US outcomes. Count outcomes will be analysed using an appropriate generalised linear model (see Table 11.2.1); incident rate ratios and 95% confidence intervals will be

presented. If negative binomial regression is used, the mean dispersion parameter will be applied. In the case of missing scores for individual joints, the exposure will be amended to indicate the number of joints/entheses assessed. This applies to the Leeds enthesitis index, the Leeds dactylitis index, & mNAPSI. Severely skewed outcomes for which an appropriate generalised linear model cannot be identified will be analysed using quantile (median) regression; differences between medians and 95% confidence intervals will be presented. If the median is 0 in both groups then alternative point of comparison will be attempted in the following sequence until model convergence is achieved: 75th percentile, 90th percentile, 95th percentile. This applies to PASI & DLQI. All analyses will control for the stratification factor and baseline values of the outcome where relevant. Two-sided significance at $p<0.05$ will be the criterion applied to all secondary outcomes. If a statistically significant difference is not found for the primary outcome, all secondary outcomes will be considered exploratory.

Table 11.2.1: Models to be used for analysis of secondary outcomes

The appropriateness of these models has been determined following initial blind review of the data. In the event that, once allocation is known, the specified model fails to converge, an alternative model will be used and this deviation from the SAP will be highlighted in the trial report

Outcome(s)	Model
LEI	Negative binomial
LDI	Negative binomial
PASI	Quantile (median) regression
mNAPSI	Negative binomial
DLQI	Quantile (median) regression

If multiple imputation models fail to converge due to the level of attrition and/or complexity of the models relative to the number of patients, mixed modelling will be explored as an alternative. For each outcome, a mixed effects model will be specified which mirrors the planned generalised linear or logistic model specified above. The mixed models will include all observations of each outcome, and the same covariates as specified above, in addition to a categorical variable for time. Random intercepts and random slopes for the time variable will be included. In the primary analysis an interaction between treatment group and time will be specified; for planned subgroup analyses a three-way interaction will be specified between treatment group, time, and oligo/polyarthritis status

or symptom duration at baseline. The covariate-adjusted treatment effect will be estimated at each visit via marginal means.

11.3 Other Efficacy Variable Analyses

A number of sensitivity analyses will be conducted. In addition to sensitivity analyses relating to missing data or outliers (see section 8.2) and stratification status (see section 11.1), a per protocol analysis will be performed, repeating the primary endpoint analysis in the Per Protocol Set. In addition, comparisons will be made between PsARC response status calculated using the 68/66 tender/swollen counts originally specified by the criteria and response status calculated using the extended 78/76 joint counts. McNemar's tests will be used to compare response status according to the reduced and expanded joint counts. This will be performed in the observed data (i.e. without imputation).

See section 8.6 for details of planned exploratory analysis of baseline predictors of response to treatment.

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. This will be conducted in the subset of participants with for whom the expanded joint scores were collected at screening. In addition, for patients in the WB-MRI subset the WB-MRI lesion scores 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. The biomarker sub-study data (available in a subset of patients) are to be analysed separately as part of a number of collaborative projects with other centres. Analysis plans for these projects will be produced separately.

An assessment of the test-retest reliability of the PASDAS will be performed, by calculating the intraclass correlation coefficient ($ICC_{(1,1)}$) between PASDAS measurements collected at screening and baseline; a 95% confidence interval will be constructed.

If sufficient patients in each group receive additional steroid injections at week 8, g-methods will be used to investigate the extent to which this is associated with total PDUS (US GLOESS) score at week 12.

Pearsons product-moment correlation or Spearman's rank correlation, according to data type, will be used to quantify the extent of association between tender joint count, swollen joint count and total PDUS (US GLOESS) at screening. In specific joints for which both clinical examination and ultrasound scan were performed, sensitivity and specificity of tenderness, swelling and both tenderness and swelling for detecting joints scoring more than GS<2 and PD=0 will be calculated, together with associated 95% confidence intervals via the Wilson method.

To assess the extent of association between clinical and US imaging responses to therapy, an extended Cochran-Mantel-Haenszel test, stratified on poly/oligoarthritis and randomised treatment, will be performed on 24 week MDA versus 24 week US remission.

11.4 Additional unplanned analysis

After breaking the blind, we made the decision to additionally report PASDAS status and response variables that had been published since the inception of the trial. These were PASDAS very low disease activity, PASDAS moderate or good response, and PASDAS meaningful change value for improvement achieved (Y/N). These will be analysed according to the same methods indicated for the binary response variables i.e. adjusted estimates of effect size will be provided for binary secondary endpoints using multiple binary logistic regression; odds ratios and 95% confidence intervals will be presented. All analyses will control for the stratification factor and baseline values of the outcome where relevant. Two-sided significance at $p<0.05$ will be the criterion applied to indicate potential differences between treatment arms; however, as these comparisons were unplanned they will be considered exploratory.

In addition to these unplanned additional endpoints, unplanned additional descriptive summaries of total USGS and USPD will be presented, to help further illustrate that the lack of substantive change in US GLOESS (combined GS and PD score) was similarly observed for its sub-components.

Unplanned descriptive summaries of alternative definitions of US remission will be presented as the proportions achieving remission were very low, possibly because the criteria for joint remission were very strict.

Unplanned descriptive summaries of tender dactylitis count and 'any' dactylitis count will be presented to give further context to the LDI results, which only counts tender dactylitis.

12. SAFETY AND TOLERABILITY ANALYSES

12.1 Drug Exposure

- The following will be summarised descriptively within each treatment group
  - Total cumulative dose of golimumab
  - Total cumulative dose of methotrexate
  - Total steroid (IA/IM injection) dose received between weeks 0 and 12
- Summaries will also be presented corrected for patient-years of exposure

12.2 Adverse Events

12.2.1 Serious Adverse Events

Line listings of all SAEs will be provided in the end of trial report. Safety analyses will be conducted in the SS. A summary of incidence rates (frequencies and percentages) of SAEs by treatment group, System Organ Class, and Preferred Term will be prepared for the Safety Population. No statistical tests will be performed. 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.

12.2.2 Adverse Events Leading to Withdrawal

A summary of incidence rates (frequencies and percentages) of AEs leading to withdrawal, by treatment group, System Organ Class, and Preferred Term, will be prepared for the Safety Population. No statistical tests will be performed.

A data listing of AEs leading to withdrawal will also be provided, displaying details of the event(s) captured on the CRF.

12.2.3 Deaths

If any patients die during the study, relevant information will be supplied in a data listing, and appropriate SAE narratives.

12.2.4 Other AE Assessments

No additional Adverse Event analysis is planned.

12.3 Pregnancies

Pregnancy data will be shown in a data listing. No special analysis will be performed on the pregnancy data. Patients are to be discontinued from the study if they become pregnant.

12.4 Clinical Laboratory Evaluations

Liver function test results (ALTs) will be presented both graphically and in tables.

Descriptive summaries (median, 1st quartile, 3rd quartile, minimum, and maximum) of values at baseline, 2, 4, 6, 8, 10, 12, 16, 20, 24, 28, 36 & 52 weeks will be presented by treatment for the Safety Population.

The number of patients with clinical laboratory values above the normal range pre-procedure versus post-procedure will be tabulated for the Safety Population by treatment group.

Values that are outside the normal range will also be flagged in the data listings, along with the corresponding normal range. Any out-of-range values that are identified by the investigator as being clinically significant will also be shown in a data listing.

13. OTHER PLANNED ANALYSES

13.1 Pharmacokinetic Analysis

No pharmacokinetic analyses are planned for this study.

13.2 Pharmacodynamic Analysis

No pharmacodynamic analyses are planned for this study.

13.3 Quality of Life Analysis

Quality of Life (QOL) was assessed using the DLQI and SF36 and will be analysed according to section 11.2.

13.4 Health Outcomes Analysis (Pharmacoeconomics)

No Health Outcomes (Pharmacoeconomics) analyses are planned for this study.

13.5 Genetic Analyses

No Genetic analyses are planned for this study.

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15. APPENDIX

```
///Scoring of SF36 component scales///

rename SF1 GH1
rename SF2 HT
rename SF3 PF1
rename SF4 PF2
rename SF5 PF3
rename SF6 PF4
rename SF7 PF5
rename SF8 PF6
rename SF9 PF7
rename SF10 PF8
rename SF11 PF9
rename SF12 PF10
rename SF13 RP1
rename SF14 RP2
rename SF15 RP3
rename SF16 RP4
rename SF17 RE1
rename SF18 RE2
rename SF19 RE3
rename SF20 SF1
rename SF21 BP1
rename SF22 BP2
rename SF23 VT1
rename SF24 MH1
rename SF25 MH2
rename SF26 MH3
rename SF27 VT2
rename SF28 MH4
rename SF29 VT3
rename SF30 MH5
rename SF31 VT4
rename SF32 SF2
rename SF33 GH2
rename SF34 GH3
rename SF35 GH4
rename SF36 GH5

//PHYSICAL FUNCTIONING//

egen PFNUM=rownonmiss(PF1 PF2 PF3 PF4 PF5 PF6 PF7 PF8 PF9 PF10)
egen PFMEAN=rowmean(PF1 PF2 PF3 PF4 PF5 PF6 PF7 PF8 PF9 PF10)

foreach i of numlist 1 2 3 4 5 6 7 8 9 10 {
replace PF`i'=PFMEAN if PF`i'==.
}

egen RAWPF=rowtotal(PF1 PF2 PF3 PF4 PF5 PF6 PF7 PF8 PF9 PF10) if
PFNUM>=5 & PFNUM<.
gen PF=((RAWPF-10)/(30-10))*100

label variable PF "SF36 PHYSICAL FUNCTIONING 0-100"
```

```
label variable RAWPF "RAW SF36 PHYSICAL FUNCTIONING"

//ROLE PHYSICAL//

egen RPNUM=rownonmiss(RP1 RP2 RP3 RP4)
egen RPMEAN=rowmean(RP1 RP2 RP3 RP4)

foreach i of numlist 1 2 3 4 {
replace RP`i'=RPMEAN if RP`i'==.
}

egen RAWRP=rowtotal(RP1 RP2 RP3 RP4) if RPNUM>=2 & RPNUM<.
gen RP=((RAWRP-4)/(8-4))*100

label variable RP "SF36 ROLE-PHYSICAL 0-100"
label variable RAWRP "RAW SF36 ROLE-PHYSICAL"

//PAIN//

gen RBP1=.
gen RBP2=.
replace RBP1=6 if BP1<. & BP2<. & BP1==1
replace RBP1=5.4 if BP1<. & BP2<. & BP1==2
replace RBP1=4.2 if BP1<. & BP2<. & BP1==3
replace RBP1=3.1 if BP1<. & BP2<. & BP1==4
replace RBP1=2.2 if BP1<. & BP2<. & BP1==5
replace RBP1=1 if BP1<. & BP2<. & BP1==6

replace RBP2=6 if BP2==1 & BP1==1
replace RBP2=5 if BP2==1 & BP1>=2 & BP1<=6
replace RBP2=4 if BP2==2 & BP1>=1 & BP1<=6
replace RBP2=3 if BP2==3 & BP1>=1 & BP1<=6
replace RBP2=2 if BP2==4 & BP1>=1 & BP1<=6
replace RBP2=1 if BP2==5 & BP1>=1 & BP1<=6

replace RBP1=6 if BP2==. & BP1==1
replace RBP1=5.4 if BP2==. & BP1==2
replace RBP1=4.2 if BP2==. & BP1==3
replace RBP1=3.1 if BP2==. & BP1==4
replace RBP1=2.2 if BP2==. & BP1==5
replace RBP1=1 if BP2==. & BP1==6
replace RBP2=RBP1 if BP1<. & BP2==.

replace RBP2=6 if BP1==. & BP2==1
replace RBP2=4.75 if BP1==. & BP2==2
replace RBP2=3.5 if BP1==. & BP2==3
replace RBP2=2.25 if BP1==. & BP2==4
replace RBP2=1 if BP1==. & BP2==5
replace RBP1=RBP2 if BP1==. & BP2<.

egen BPNUM=rownonmiss(BP1 BP2)
egen RAWBP=rowtotal(RBP1 RBP2) if BPNUM>=1 & BPNUM<.
gen BP=((RAWBP-2)/(12-2))*100

label variable BP "SF36 PAIN INDEX 0-100"
```

```
label variable RAWBP "RAW SF36 PAIN INDEX"

//GENERAL HEALTH//

gen RGH1=.
replace RGH1=5 if GH1==1
replace RGH1=4.4 if GH1==2
replace RGH1=3.4 if GH1==3
replace RGH1=2 if GH1==4
replace RGH1=1 if GH1==5

gen RGH3=6-GH3
gen RGH5=6-GH5

egen GHNUM=rownonmiss(GH1 GH2 GH3 GH4 GH5)
egen GHMEAN=rowmean(RGH1 GH2 RGH3 GH4 RGH5)

replace RGH1=GHMEAN if RGH1==.
replace GH2=GHMEAN if GH2==.
replace RGH3=GHMEAN if RGH3==.
replace GH4=GHMEAN if GH4==.
replace RGH5=GHMEAN if RGH5==.

egen RAWGH=rowtotal(RGH1 GH2 RGH3 GH4 RGH5) if GHNUM>=3 & GHNUM<.
gen GH=((RAWGH-5)/(25-5))*100

label variable GH "SF36 GENERAL HEALTH PERCEPTIONS 0-100"
label variable RAWGH "RAW SF36 GENERAL HEALTH PERCEPTIONS"

//VITALITY//

gen RVT1=7-VT1
gen RVT2=7-VT2

egen VITNUM=rownonmiss(VT1 VT2 VT3 VT4)
egen VITMEAN=rowmean(RVT1 RVT2 VT3 VT4)

replace RVT1=VITMEAN if RVT1==.
replace RVT2=VITMEAN if RVT2==.
replace VT3=VITMEAN if VT3==.
replace VT4=VITMEAN if VT4==.

egen RAWVT=rowtotal(RVT1 RVT2 VT3 VT4) if VITNUM>=2 & VITNUM<.
gen VT=((RAWVT-4)/(24-4))*100

label variable VT "SF36 VITALITY 0-100"
label variable RAWVT "RAW SF36 VITALITY"

//SOCIAL FUNCTIONING//

gen RSF1=6-SF1
egen SFNUM=rownonmiss(SF1 SF2)
egen SFMEAN=rowmean(RSF1 SF2)

replace RSF1=SFMEAN if RSF1==.
```

```
replace SF2=SFMEAN if SF2==.

egen RAWSF=rowtotal(RSF1 SF2) if SFNUM>=1 & SFNUM<.
gen SF=((RAWSF-2)/(10-2))*100

label variable SF "SF36 SOCIAL FUNCTIONING 0-100"
label variable RAWSF "RAW SF36 SOCIAL FUNCTIONING"

//ROLE EMOTIONAL//

egen ROLMNUM=rownonmiss(RE1 RE2 RE3)
egen ROLMMEAN=rowmean(RE1 RE2 RE3)

replace RE1=ROLMMEAN if RE1==.
replace RE2=ROLMMEAN if RE2==.
replace RE3=ROLMMEAN if RE3==.

egen RAWRE=rowtotal(RE1 RE2 RE3) if ROLMNUM>=2 & ROLMNUM<.
gen RE=((RAWRE-3)/(6-3))*100

label variable RE "SF36 ROLE-EMOTIONAL 0-100"
label variable RAWRE "RAW SF36 ROLE-EMOTIONAL"

//MENTAL HEALTH//

gen RMH3=7-MH3
gen RMH5=7-MH5

egen MHNUM=rownonmiss(MH1 MH2 MH3 MH4 MH5)
egen MHMEAN=rowmean(MH1 MH2 RMH3 MH4 RMH5)

replace MH1=MHMEAN if MH1==.
replace MH2=MHMEAN if MH2==.
replace RMH3=MHMEAN if RMH3==.
replace MH4=MHMEAN if MH4==.
replace RMH5=MHMEAN if RMH5==.

egen RAWMH=rowtotal(MH1 MH2 RMH3 MH4 RMH5) if MHNUM>=3 & MHNUM<.
gen MH=((RAWMH-5)/(30-5))*100

label variable MH "SF36 MENTAL HEALTH INDEX 0-100"
label variable RAWMH "RAW SF36 MENTAL HEALTH INDEX"

//PHYSICAL AND MENTAL HEALTH INDICES//

gen PF_Z=(PF-84.52404)/22.89490
gen RP_Z=(RP-81.19907)/33.79729
gen BP_Z=(BP-75.49196)/23.55879
gen GH_Z=(GH-72.21316)/20.16964
gen VT_Z=(VT-61.05453)/20.86942
gen SF_Z=(SF-83.59753)/22.37642
gen RE_Z=(RE-81.29467)/33.02717
gen MH_Z=(MH-74.84212)/18.01189

//RAW FACTOR SCORES//
```

```
gen PRAW=(PF_Z*0.42402)+(RP_Z*0.35119)+(BP_Z*0.31754)+(SF_Z*-
0.00753)+(MH_Z*-0.22069)+(RE_Z*-
0.19206)+(VT_Z*0.02877)+(GH_Z*0.24954)
gen MRAW=(PF_Z*-0.22999)+(RP_Z*-0.12329)+(BP_Z*-
0.09731)+(SF_Z*0.26876)+(MH_Z*0.48581)+(RE_Z*0.43407)+(VT_Z*0.23534)
+(GH_Z*-0.01571)

//STANDARDIZED SCORES//

gen PCS=(PRAW*10)+50
gen MCS=(MRAW*10)+50

label variable PCS "STANDARDIZED PHYSICAL COMPONENT SCALE"
label variable MCS "STANDARDIZED MENTAL COMPONENT SCALE"
```