Remission Induction Treatment Strategies in Early Psoriatic Arthritis: A Clinical and Imaging Study

by

Dr. Gabriele De Marco

Submitted in accordance with the requirements for the degree of

Doctor of Philosophy

The University of Leeds

School of Medicine and Health

Leeds Institute of Rheumatic and Musculoskeletal Medicine

September 26th, 2024

Intellectual Property and Publication Statements

The candidate confirms that the work submitted is his own, except where work formed part of jointly authored publications. The contribution of the candidate and other authors to this work is explicitly indicated.

The candidate confirms that, within this thesis, appropriate credit was given where reference was made to the work of others.

List of Publications Arising from this Thesis

Articles Published on Indexed Medical Journals

De Marco, G., Helliwell, P., McGonagle, D. et al. The GOLMePsA study protocol: an investigator-initiated, double-blind, parallel-group, randomised, controlled trial of GOLimumab and methotrexate versus methotrexate in early diagnosed psoriatic arthritis using clinical and whole body MRI outcomes. BMC Musculoskelet Disord 18, 303 (2017). https://doi.org/10.1186/s12891-017-1659-1

De Marco G, Berekméri A, Coates LC, Dubash S, Emmel J, Gladman DD, Lubrano E, McGonagle DG, Mahmood F, Marchesoni A, Mason L, Ogdie A, Wittmann M, Helliwell PS, Marzo-Ortega H. Systematic literature review of non-topical treatments for early, untreated (systemic therapy naïve) psoriatic disease: a GRAPPA initiative. Rheumatol Adv Pract. 2020 Jul 11;4(2):rkaa032. doi: 10.1093/rap/rkaa032. PMID: 33542971; PMCID: PMC7850142.

Dubash SR, **De Marco G**, Wakefield RJ, Tan AL, McGonagle D, Marzo-Ortega H. Ultrasound Imaging in Psoriatic Arthritis: What Have We Learnt in the Last Five Years? Front Med (Lausanne). 2020 Aug 25;7:487. doi: 10.3389/fmed.2020.00487. PMID: 32984374; PMCID: PMC7477070.

Wetterslev M, Maksymowych WP, Lambert RG, Eshed I, Pedersen SJ, Stoenoiu MS, Krabbe S, Bird P, Foltz V, Mathew AJ, Gandjbakhch F, Paschke J, Carron P, **De Marco G**, Marzo-Ortega H, Poulsen AE, Jaremko JL, Conaghan PG, Østergaard M. Joint and entheseal inflammation in the knee region in spondyloarthritis - reliability and responsiveness of two OMERACT whole-body MRI scores. Semin Arthritis Rheum. 2021 Aug;51(4):933-939. doi: 10.1016/j.semarthrit.2021.05.013. Epub 2021 Jun 17. PMID: 34176643.

Wetterslev M, Lambert RG, Maksymowych WP, Eshed I, Pedersen SJ, Bird P, Stoenoiu MS, Krabbe S, Mathew AJ, Foltz V, Gandjbakhch F, Paschke J, **De Marco G**, Marzo-Ortega H, Carron P, Poulsen AE, Jaremko JL, Conaghan PG, Østergaard M. Arthritis and enthesitis in the hip and pelvis region in spondyloarthritis - OMERACT validation of two whole-body MRI methods. Semin Arthritis Rheum. 2021 Aug;51(4):940-945. doi: 10.1016/j.semarthrit.2021.05.006. Epub 2021 May 21. PMID: 34140185.

Presentations at Scientific Congresses

Fourth Update on Psoriatic Disease, Naples (Italy), September 8-9, 2017

The GOLMePsA study protocol: an investigator-initiated, parallel group, randomized, controlled trial of GOLimumab and Methotrexate in early diagnosed Psoriatic Arthritis using clinical and whole body MRI outcomes.

Oral presentation

Not published on indexed medical journal

EULAR Congress 2019, Madrid (Spain), June 12-15, 2019

Non topical pharmacological treatment of early, untreated (DMARD-naïve, systemic therapy-näive) psoriatic disease: a systematic review

Poster

Published as: **Marco GD**, Berekméri A, Coates LC, et al. FRI0429 NON TOPICAL PHARMACOLOGICAL TREATMENT OF EARLY, UNTREATED (DMARD-NAÏVE, SYSTEMIC THERAPY-NAÏVE) PSORIATIC DISEASE: A SYSTEMATIC REVIEW.

Annals of the Rheumatic Diseases 2019; 78: 904.

GRAPPA 2019 Annual Meeting and Trainee Symposium, Paris (France), July 13, 2019

Non topical pharmacological treatment of early, untreated (DMARD-naïve, systemic therapy-naïve) psoriatic disease: a systematic review

Oral presentation

Published as: Goel N, Coates LC, **De Marco G**, Eder L, FitzGerald O, Helliwell PS, Leung YY, Maksymowych WP, Mease PJ, Østergaard M, O'Sullivan D, Poddubnyy D, Ritchlin CT, Gladman DD. GRAPPA 2019 Project Report

J Rheumatol Suppl. 2020 Jun;96:53-57. doi: 10.3899/jrheum.200129.

Northern BRC Early Career Researchers Conference, Leeds (UK), November 22, 2023

Remission-induction treatment strategies in Early Psoriatic Arthritis: A clinical and imaging study

Oral presentation

Not published on indexed medical journal

Leeds Institute of Rheumatic and Musculoskeletal Medicine Symposium, Leeds (UK), December 6, 2023

Remission-induction treatment strategies in Early Psoriatic Arthritis: A clinical and imaging study

Oral presentation

Not published on indexed medical journal

British Society for Rheumatology, Annual Conference 2024, Liverpool (UK), April 24-26, 2024

PASDAS demonstrates excellent test-retest reliability in early, untreated PsA

Electronic poster E072

Published as: **Gabriele De Marco**, Elizabeth M A Hensor, Dennis G McGonagle, Ai Lyn Tan, Laura C Coates, Paul Emery, Philip S Helliwell, Helena Marzo Ortega, E072 The psoriatic arthritis disease activity score demonstrates excellent test-retest reliability in early, untreated psoriatic arthritis.

Rheumatology, Volume 63, Issue Supplement 1, April 2024, keae163.299, https://doi.org/10.1093/rheumatology/keae163.299

EULAR Congress 2024, Vienna, Austria, June 12-15, 2024

A treatment strategy combining TNF-inhibitor, methotrexate and steroids is not superior to methotrexate and steroids in early Psoriatic Arthritis: results from the GOLMePsA randomised, double-blind clinical trial

Oral presentation (OP0184)

Annals of the Rheumatic Diseases 2024;83:153-154.

Acknowledgements

First and foremost, I wish to thank the participants to the GOLMePsA trial, without whom this work would have proved impossible to complete.

My supervisors, Prof. Marzo-Ortega, Dr. Tan and Prof. McGonagle overlooked my postgraduate student activity and steadily supported this project. Their precious comments contributed to make this thesis the piece of work it is now.

Dr. Hensor and Dr. Guerra provided statistical and data management support. To them my gratitude for their advice. Dr. Di Matteo, Dr. Eshed, Prof. Maksymowych, Prof. Østergaard and Dr. Wakefield contributed to imaging acquisition and scoring. They also offered valuable insights to this work. Dr. Coates, Dr. Dubash, Dr. Merashli, Dr. Michelena Vegas and Dr. Naraghi collaborated to the clinical data collection underpinning this thesis.

I believe that clinical trials remain the most gratifying and challenging endeavours in medical research and, tough only a few members of staff eventually make the headlines, these projects are impossible to conduct without teamwork. Just as no ship sails the seven seas without its crew. A large number of staff at Chapel Allerton Hospital, Leeds (UK), had a direct role in the delivery, management and administration of the GOLMePsA trial programme. It is unfortunate that I can not mention them all, yet I want to offer my gratitude to Mrs. Alieva, Mrs. Allen, Mr. Armstrong, Mr. Banda, Mr. Bertham, Mr. Biggs, Dr. Bissell, Mr. Chaka, Mr. Clarke, Mrs. Corscadden, Ms. Dibb, Dr. Duquenne, Mr. Evans, Ms. Fisher, Dr. Garcia-Montoya, Mr. Goulding, Mrs. Hallett, Dr. Harrison, Mrs. Harrison, Mr. Harrison, Mr. Higgs, Ms. Horton, Mrs. Hulland, Mrs. Koome, Mr. Lockley-Ault, Mrs. Mallinder, Mrs. Mbara, Ms. Morgan, Ms. Morton, Mrs. Mumba Mdala, Mr. Papageorgiou, Ms. Peake, Mr. Pickles, Ms. Russell, Ms. Sarker, Mrs. Smith, Ms. Smith, Mr. Ward, Mr. Weatherill and Mr. Wordsworth.

Among people who mentored me, I wish to thank Dr. Arnold, Prof. Conaghan, Prof. Emery, Dr. Farrow, Prof. Helliwell, Prof. Keenan, Prof. Marchesoni, Dr. Ogdie-Beatty, Prof. Pandit and Dr. Ponchel. Prof. Buch and Dr. Vital sponsored my admission to the postgraduate programme. The Leeds Institute of Rheumatic and Musculoskeletal Medicine (University of Leeds), the Leeds Teaching Hospitals NHS Trust and the National Institute for Health and Care Research (Leeds Biomedical Research Centre) welcomed me as postgraduate student and member of staff, providing the crucial infrastructure to my research activities.

Personally, I hope my gratitude will be something to my wife and children. We rebuilt a life in the UK and endured the whole process of postgraduate studies together. I would have certainly failed without your relentless love and support.

Abstract

Effective remission-induction strategies are not established in early Psoriatic Arthritis (PsA) and a comprehensive definition of remission is lacking. This thesis explored the effects of combined Methotrexate (MTX), Golimumab (GOL) and steroids in inducing remission in early, treatment naïve PsA; the role of imaging in the assessment of remission; and the potential of newly proposed sets of remission.

Methods

This work firstly presents a systematic review of the literature that identified relevant knowledge gaps: the definition of remission in early PsA; the interventions likely to induce remission across musculoskeletal and cutaneous domains of disease; and the limited scope of current outcome measures, as these fail to assess disease activity across disease domains.

Then new remission criteria for early PsA (three sets) were designed, aimed at assessing disease activity in the musculoskeletal domains (set A). Set B added the skin/nails domain to set A items. Set C added imaging (whole-body ultrasound and magnetic resonance scans) remission items to those of set B ("deep remission").

The GOLMePsA study (a randomized, double-blind placebo-controlled trial of treatment-naïve early PsA) dataset was used as a platform to: 1) formally confirm the test-retest reliability of the Psoriatic ArthritiS Disease Activity Score (PASDAS), the recommended outcome measure for PsA trials; 2) test the prevalence of remission (as defined by sets A, B and C) in GOLMePsA participants following intervention; 3) correlate remission data with PASDAS levels, intended at identifying novel remission subgroups by PASDAS values.

Results and Conclusions

GOLMePsA participants achieved low disease activity following intensive interventions, recording responses across musculoskeletal and cutaneous domains. However, treatment allocation was not associated to remission prevalence (achieved by 8.3%). Remission sets A and B related to novel subgroupings by PASDAS levels (≤1.2 value). Notably, achievement of remission reduced the need for resuming biologic drugs by the end of trial.

Table of Contents

List of Tables

List of Figures

List of Abbreviations

ACR	American College of Rheumatology
ANA	Anti-Nuclear Auto-antibodies
anti-CCP	anti-Cyclic Citrullinated Peptides
ARA	American Rheumatism Association
AS	Ankylosing Spondylitis
ASQoL	Ankylosing Spondylitis Quality of Life Index
AxSpA	Axial Spondyloarthritis
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
bDMARDs	biologic Disease-Modifying Anti-Rheumatic Drugs
BMI	Body Mass Index
BML	Bone Marrow Lesions
BMO	Bone Marrow Oedema
BSA	Body Surface Area
CANDEN	Canada-Denmark MRI Scoring System
CASPAR	ClASsification criteria for Psoriatic ARthritis
CI	Confidence Interval
CMC	Carpal-MetaCarpal joint(s)
CPDAI	Composite Psoriatic Disease Activity Index
CR	Conventional Radiography
csDMARD	conventional synthetic Disease-Modifying Anti-Rheumatic Drugs
CT	Computed Tomography
DAPSA	Disease Activity index for PSoriatic Arthritis
DIP	Distal Inter-Phalangeal joint(s)
DLQI	Dermatology Life Quality Index
DMARDs	Disease-Modifying Anti-Rheumatic Drugs
ESR	Erythrocyte Sedimentation Rate
EU	European Union
EudraCT	European Union Drug Regulating Authorities Clinical Trials Database
EULAR	European Alliance of Associations for Rheumatology

GLOESS	Global OMERACT-EULAR Score System
GOL	Golimumab
GOLMePsA	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
GRAPPA	Group for Research and Assessment of Psoriasis and Psoriatic Arthritis network
HAQ-DI	Health Assessment Questionnaire Disability Index
HEMRIS	Heel Enthesitis MRI Scoring
HIMRISS	Hip Inflammation MRI Scoring System
HLA	Human Leukocyte Antigen
HRA	Health Research Authority
IBD	Inflammatory Bowel Disease
ICC	Intra-Class Correlation Coefficient
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IED	Inflammatory Eye Disease
IM	Intra-Muscular
IMPs	Investigational Medicinal Products
IRR	Incidence-Rate Ratio
KIMRISS	Knee Inflammation MRI Scoring System
LDI	Leeds Dactylitis Index
LEI	Leeds Enthesitis Index
LTHT	Leeds Teaching Hospitals NHS Trust
MC	Monte Carlo
MCPs	MetaCarpal-Phalangeal joints
MCS	Mental Component Score
MDA	Minimal Disease Activity
MHRA	Medicines & Healthcare products Regulatory Agency
mNAPSI	modified Nail Psoriasis Severity Index
MRI	Magnetic Resonance Imaging
MRI-WIPE	MRI Whole-Body Score for Inflammation in Peripheral Joints and Entheses in Inflammatory Arthritis

MSK	Musculoskeletal
MTPs	MetaTarsal-Phalangeal joints
MTX	Methotrexate
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIMPs	Non-Investigational Medicinal Products
NSAID	Non-Steroidal Anti-Inflammatory Drug
OA	Osteoarthritis
OMERACT	Outcome Measures in Rheumatoid Arthritis Clinical Trials
OR	Odds Ratio
PASDAS	Psoriatic ArthritiS Disease Activity Score
PBO	Placebo
PCS	Physical Component Summary
PD	power-Doppler
PET	Positron Emission Tomography
PICO	Patient Intervention Comparator Outcome
PICs	Participant Identification Centres
PROMs	Patient Reported Outcome Measures
PsA	Psoriatic Arthritis
PsARC	Psoriatic Arthritis Response Criteria
PsD	Psoriatic Disease
PsO	Psoriasis
QoL	Quality of Life
RA	Rheumatoid Arthritis
REC	Research Ethics Committee
RF	Rheumatoid Factor
SAEs	Serious Adverse Events
SARS-CoV-2	Severe Acute Respiratory Syndrome CoronaVirus 2
SC	Subcutaneous
SD	Standard Deviation
SE	Spin Echo
SEC	Synovial-Entheseal Complex

SF-36	Short Form-36
SJC	Swollen Joint Count
SpA	Spondyloarthropathies
SPARCC	Spondyloarthritis Research Consortium of Canada
sPGA	static Physician Global Assessment of Psoriasis
STIR	Short Tau Inversion Recovery
T2T	Treat To Target
TJC	Tender Joint Count
TNFi	Tumor Necrosis Factor α inhibitor
US	Ultrasound Scan
VAS	Visual Analogue Scale
VLDA	Very Low Disease Activity
WB-MRI	Whole-Body Magnetic Resonance Imaging

Ἀσπίδι μὲν Σαΐων τις ἀγάλλεται, ἣν παρὰ θάμνῳ
ἔντος ἀμώμητον κάλλιπον οὐκ ἐθέλων·
αὐτὸν δ' ἔκ μ' ἐσάωσα· τί μοι μέλει ἀσπὶς ἐκείνη;
Ἐρρέτω· ἐξαῦτις κτήσομαι οὐ κακίω.

One among the Saians now enjoys the shield that I -reluctantly- cast aside
By a bush, for a fine one indeed it is.
Back then, though, I had to save myself. So why should I now care for that Shield?
Blast it! Another one I will own, and no way worse.

Archilochus

Chapter 1

This chapter presents the background of the subject discussed in this thesis. The initial considerations related to Psoriatic Arthritis (PsA) offer the opportunity to introduce the important concepts of clinical heterogeneity of disease manifestations and of remission. Then the chapter focuses on early PsA, the treatment of early PsA, the identified gaps in current knowledge, the concept of remission in early PsA and the use of imaging as means of inflammatory burden detection. The rationale for utilising data collected in one in-house, double-blind, randomised clinical trial as basis for this thesis will also be outlined in chapter one.

At the end of this chapter, the reader will find the thesis plan (Table 4).

1.1 Introduction

The disease entity known as PsA is a relatively common form of chronic, inflammatory rheumatic disease that -for classification purposes- belongs to the group of Spondyloarthropathies (SpA, Figure 1) (Moll et al., 1974; Ritchlin, C.T. et al., 2017). Though variations in prevalence and geographically clustered reporting gaps are described in the literature, PsA is a health problem that affects human beings worldwide (Karmacharya et al., 2021; Maharaj and Adebajo, 2021).

PsA is associated with the chronic dermatitis known as Psoriasis (PsO) -itself one of the most common cutaneous affections in Europe (Richard et al., 2022)- and usually symptoms of PsA present seven to ten years (Gladman, D.D. et al., 1987; Ritchlin, C.T. et al., 2017) following the clinical onset of PsO. However, in a substantial proportion (15%) of cases, PsA precedes -or presents simultaneously with- the onset of cutaneous manifestations (Ritchlin, C.T. et al., 2017). In a minority of cases (3.1% to 5.5%) PsA stands alone without apparent clinical manifestations of skin involvement [the so-called “PsA sine psoriasis” (Scarpa et al., 2003; Ziade et al., 2022)].

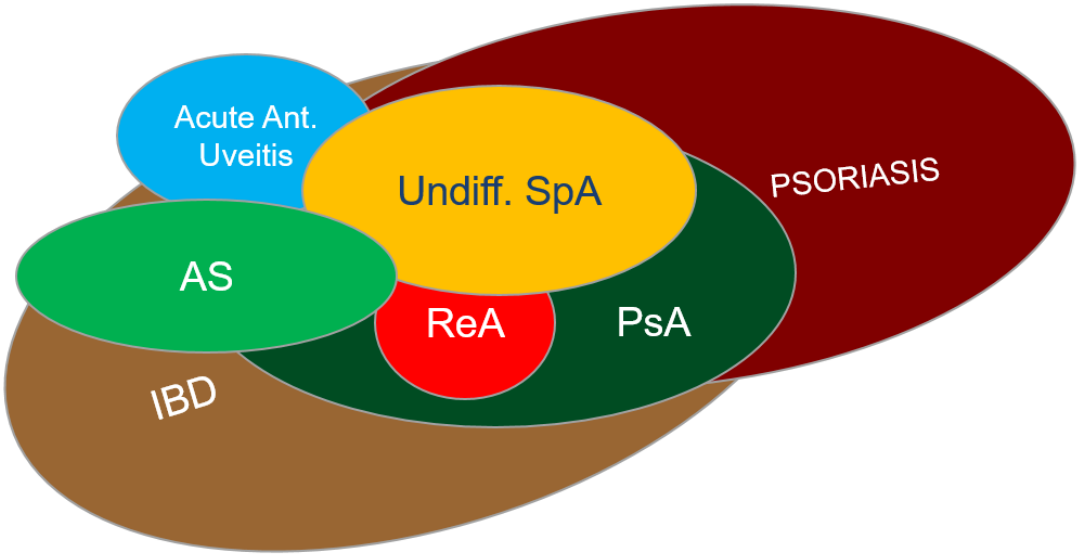

Figure 1 The Heterogeneous Clinical Spectrum of Spondyloarthropathies

Clinical manifestations associated with the Spondyloarthropathies (SpA) span across different domains, including the skin (Psoriasis, mainly), the gut [Inflammatory Bowel Diseases (IBD)], the eye (Iritis, or Acute Anterior Uveitis). Within the rheumatic features associated with SpA, additional heterogeneity occurs in terms of diverse clinical presentation across cases of SpA [these may occur as Psoriatic Arthritis (PsA), Undifferentiated SpA, Ankylosing Spondylitis (AS) and Reactive Arthritis (ReA)].

An additional source of heterogeneity is represented by the variation of clinical course within individual cases. Namely, the initial manifestations dominating the clinical picture (more frequently, peripheral arthritis) are followed by -or become associated to- symptoms and signs of spondylitis, enthesitis and dactylitis.

Although archaeological evidence points to the possibility that PsA affected human beings for centuries (Espinoza, 2018), historically PsA used to be considered a mere clinical variant of Rheumatoid Arthritis (RA) in people who presented PsO in association. Only in the twentieth century research conducted by the Leeds group shed new light into the PsA disease and provided descriptions of distinctive clinical features (Wright, 1959; Moll and Wright, 1973a; Moll and Wright, 1973b; Moll et al., 1974), leading the American Rheumatism Association (ARA, now American College of Rheumatology – ACR) to classify PsA as an entity separate from RA (Espinoza, 2018). More importantly, research from Moll and Wright contributed to highlight the familial recurrence of -as well as the clinical heterogeneity of- PsA, at a time preceding the discovery of the association between Ankylosing Spondylitis (AS) and the Human Leukocyte Antigen (HLA) B27 (Schlosstein et al., 1973). Although the association between PsO and PsA stands out as a factor pointing to the complexity of a condition capable of affecting a diverse range of health domains and tissues -such as the skin and the musculoskeletal (MSK) system- even more variety characterizes the manifestations associated with the SpA spectrum and the PsA spectrum. For example, Moll's and co-workers' publications further highlighted how fluid (both in terms of clinical presentation and of clinical course) and heterogeneous the rheumatic manifestations of PsA -namely, peripheral arthritis, dactylitis, enthesitis, spondylitis and sacro-iliitis- could be (Moll and Wright, 1973b). In their early classification attempts, these authors described subgroups of PsA clinically indistinguishable from RA [except for the negativity for the Rheumatoid Factor (RF) test] or other, more distinctive forms of inflammation affecting digits entirely (dactylitis) and distal interphalangeal joints of the fingers and toes. Clinicians indeed can observe a "constellation" of features in patients affected by PsA (Figure 2), with instances of deformities due to the destruction of joints ("arthritis mutilans") in severe cases.

The heterogeneity characterizing the clinical manifestations of PsA at presentation, as well as the absence of diagnostic biomarkers (Wirth et al., 2022), are relevant problems, in that they represent a challenge for the healthcare professionals who aim at establishing the diagnosis (Rida and Chandran, 2020). To an extent, therefore, it is not surprising that the medical literature reports a substantial diagnostic delay (35.1 months) in PsA (Kilic et al., 2023). The matter of diagnostic delay is of paramount importance, due to its association with worse disease outcomes (Tillett et al., 2013; Theander et al., 2014; Haroon et al., 2015).

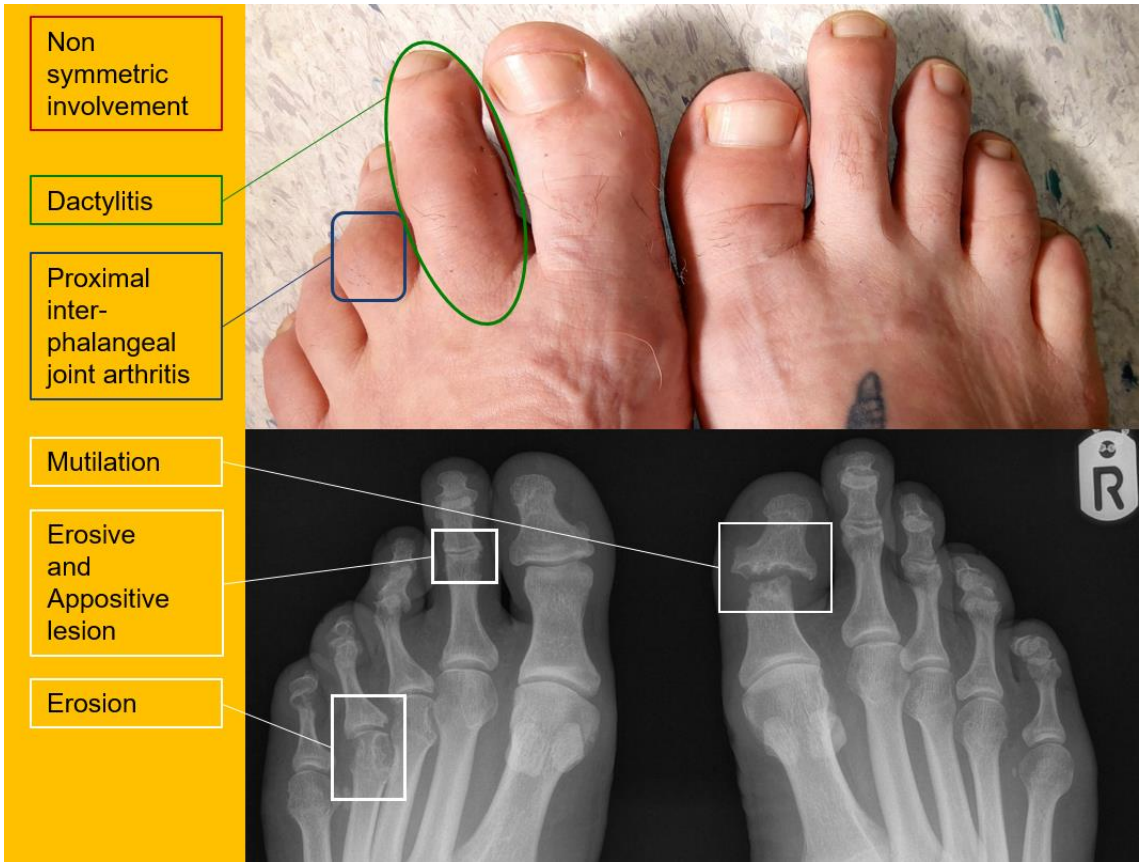

Figure 2 Psoriatic Arthritis, a Constellation of Rheumatic Manifestations

Patients affected by Psoriatic Arthritis may present -at clinical onset or later in the course of disease- with simultaneous rheumatic features of peripheral arthritis (top panel, proximal interphalangeal joint of toe number three, left foot - blue square); enthesitis (bottom panel white square, second proximal interphalangeal joint of the left toe) and dactylitis (top panel, toe number two, left foot - green circle). The lack of clinical symmetric involvement is apparent and the toe number one of the right foot (top panel) is obviously shorter in length than the contra-lateral.

The top panel depicts the clinical presentation; the bottom panel offers the radiographic evaluation of the same person, performed on the same day. Erosive and early destructive features are apparent on the X-rays image. Whiskering, a form of appositive lesion that reflects enthesitis, is visible at the proximal interphalangeal joint of the second toe (left foot).

Of note, the patient was not on treatment at the time of the evaluation.

Image courtesy of the author, taken with verbal consent of the patient -for educational purposes- at the Rheumatology Outpatient Clinic, Leeds Teaching Hospitals NHS Trust (UK).

Evidence from one recent review (De Marco, G. et al., 2023) suggests that the most frequent pattern of clinical presentation of PsA is non-symmetric oligo-arthritis (that is, clinical signs of inflammation in ≤4 peripheral joints). Such finding was concordant with earlier reports: the descriptions left by Moll and Wright (Moll and Wright, 1973b) did highlight that the majority (70%) of cases in their series was affected by peripheral arthritis in "a few" fingers or toes and in "asymmetrical" fashion. Findings of this kind (Wright, 1959) initially led to consider PsA a mostly benign condition, "*often… sufficiently mild not to require treatment*".

Over time, however, appreciation of the severity of PsA underwent substantial re-evaluation, following the publication of observational cohort studies from the research group of Toronto, Canada (Gladman, D.D. et al., 1987; Bond et al., 2007). Gladman, Bond and their co-authors produced evidence that, in their tertiary centre, peripheral polyarthritis (that is, clinical signs of inflammation in ≥5 peripheral joints) affected 61% of the patients described in their series, this being indeed the more frequent pattern of clinical articular involvement. In addition to this, they found that 40% of their patients presented with erosive arthropathy and articular deformities. Further, the amount of joints affected by active inflammation was associated with progression of articular damage on X-rays. The findings from the Canadian group were fundamental in emphasizing that PsA has potential for generating severe damage to the MSK apparatus and its burden -by all means similar to that experienced by RA patients (Michelsen et al., 2015)- could be ameliorated by improved treatment strategies.

It is interesting to note, though, that despite the use of Disease-Modifying Anti-Rheumatic Drugs (DMARDs), the course of PsA disease is also characterized by heterogeneity of response to therapy (Kane et al., 2003). Specifically, the data generated by Kane et al. showed that disease activity amelioration in peripheral arthritis induced by DMARDs monotherapy was not consistently matched by improvement in other domains –such as dactylitis and enthesitis activity- over a follow-up of two years.

Despite the limitations mentioned above, one way to improve the treatment strategies for PsA would be an approach of administering therapies at the early stages of the disease. Evidence currently available emphasizes the benefits of treating PsA as early as possible in the disease course, with results comparable to those achieved in RA in terms of effectiveness, drug retention and durability of clinical response (Lindstrom et al., 2023). It is important to note, however, that no comparison of the effects of early PsA treatment against late-stage treatment is available from the medical literature.

The current armamentarium of drugs licensed for PsA is ample and guidance on its management is abundant (Gossec et al., 2020; Coates, L.C. et al., 2022b;

Gossec et al., 2024). However, no consensus is available yet on optimal treatment strategies in early PsA. Notably, this guidance gap is wide and involves drug choices (that is, no specific compound is superior to others when used as first line option), treatment timing (no consensus about the specific ideal interval between onset of symptoms and therapy inception is available) and treatment composition (that is, provision of therapy administering one compound at a time or combinations of more than one compound or sequencing different compounds over time). Further, regulatory limitations to the use of drugs confine the use of many potent agents [for example, the biologic DMARDs (bDMARDs)] to later stages in the disease course, mainly based on cost-related considerations. These constrains result in a tiered treatment system -in real terms, implemented worldwide- that allows the prescription of more expensive therapies only upon failure of cheaper ones. In the opinion of this candidate, the evidence underpinning such practice is now out-of-date (Mease et al., 2000; Antoni et al., 2005; Mease et al., 2005), as all PsA participants recruited in the first bDMARDs trials experienced long lasting, refractory and late-stage disease. The byproduct of such practice is that -nowadays- it contributes to delaying the prescription of potent combination therapies for PsA cases who are in their early stages of the disease course. It is postulated, then, that the tiered prescription system deferring the use of advanced combination treatment does compound with the diagnostic delay and hampers the timely establishment of effective treatment for early PsA. In this regard, it is important to highlight that bDMARD treatment inhibits radiographic progression in PsA, regardless of disease severity levels experienced by patients (Landewe et al., 2019).

The current evidence on efficacious interventions for PsA is also limited in scope, as clinical trials conducted so far focused mainly on outcome measures assessing the effects of tested interventions solely on peripheral arthritis. Uncommonly, some trials did assess the primary effect of interventions on other MSK domains such as dactylitis (Palominos et al., 2023) or enthesitis (Araujo et al., 2019), though such evidence remains underrepresented within the body of medical literature. Further, to date no clinical trial in PsA adopted -as primary end-point- composite outcome measures that assess disease activity simultaneously across the PsA disease spectrum, let alone ones that concomitantly assess across the skin and MSK domain.

Finally, treating early PsA offers the chance to exploit a “therapeutic window of opportunity” that could result in improved disease outcomes (Theander et al., 2014; Snoeck Henkemans et al., 2024). For example, in the TICOPA trial the adoption of Minimal Disease Activity (MDA) as treatment target, as part of a tight control strategy for the management plan of PsA, demonstrated that better

outcomes were a realistic goal (Coates, L.C. et al., 2015). The achievement of PsA disease remission, the modalities to obtain it and its long-term ramifications are understudied, though, and no validated definition of remission in early or established PsA is available to date (Kane et al., 2003; Cantini et al., 2012; Theander et al., 2014; Alharbi et al., 2020). From a theoretical perspective, induction -and maintenance- of remission in early PsA would offer the chance to virtually nullify the symptomatic burden of the disease and suppress the clinical manifestations of inflammation in the MSK system (Mease and Coates, 2018). Parallel, analogous effect on the cutaneous manifestations of Psoriatic Disease (PsD) would ideally further increase such benefits. These effects on systemic inflammation would in turn result in restoration of altered physical function (itself negatively conditioned by inflammation, at all disease stages). Another theoretical advantage linked to induction -and maintenance- of remission at the early stage of PsA would be the prevention of structural damage progression in MSK tissues associated with disability (Kerschbaumer et al., 2017). However, such a deep effect of ablation could go undetected by means of clinical evaluation, as cases of subclinical inflammatory activity in early PsA are reported (Freeston et al., 2014). The use of advanced techniques such as Ultrasound Scan (US) and Magnetic Resonance Imaging (MRI) to assess a state of “deep remission” would offer valuable insight in the evaluation of the total (clinical and subclinical) inflammatory burden that people affected by early PsA experience.

1.2 Psoriatic Arthritis - Considerations

1.2.1 Epidemiology of Psoriatic Arthritis

Although the estimated prevalence of PsA in the general population (0.1%–1%) is slightly lower than that of RA, the prevalence among cases of PsO is up to 30% according to some publications (Gladman, D.D., 2009; Ritchlin, C.T. et al., 2017; Karmacharya et al., 2021). Therefore, PsA represents a substantial source of chronic pain and disability and its impact on the wider society and the healthcare provision services worldwide – in terms of financial resources allocated, utilization of healthcare, loss of work-related productivity and assistance required because of reduction of personal autonomy- is relevant (Helliwell, P.S. and Ruderman, 2015).

1.2.2 Pathogenesis of Psoriatic Arthritis

Despite the epidemiological relevance and societal impact of PsA, the pathogenetic mechanisms underpinning this condition remain understudied and far from being fully disentangled.

Cases of PsA feature substantial familial aggregation with PsO, as well as with other conditions such as AS and Inflammatory Bowel Diseases (IBD) (Moll et al., 1974). One foundation stone in understanding SpA and PsA was the discovery of a link between this group of conditions and the HLA-B27 (Schlosstein et al., 1973). This discovery was the first in a row about genetic predisposing factors associated to PsA, eventually establishing the rationale for further differentiation between PsA and RA, as well as providing the basis for a justification of the heterogeneity of the clinical manifestations observed in PsA (FitzGerald et al., 2015; McGonagle, D. et al., 2015).

Another milestone was reached at the end of the twentieth century, when imaging data emphasized the importance of enthesitis in PsA as a potential *primum movens* in the pathogenetic process (McGonagle, D. and Emery, 1999; McGonagle, D. et al., 1999). Later, a breakthrough came with the theorization of the Synovial-Entheseal-Complex (SEC) (McGonagle, D. et al., 2007). Initially building on insights from findings detected by advanced imaging techniques such as MRI (McGonagle, D. and Emery, 1999; Benjamin and McGonagle, 2001), the SEC was then further elaborated as a unifying concept for the broad spectrum of SpA entities and for further linking these MSK conditions to PsO, to Inflammatory Eye Diseases (IED) such as anterior uveitis and to IBD. Further imaging and immunopathology research, on both animal models (Lories et al., 2004; Melis and Elewaut, 2009; Aydin et al., 2010) and human tissues (McGonagle, D. et al., 2009), kept shedding more light onto the molecular pathogenetic mechanisms underpinning the clinical heterogeneity of PsA (Benjamin and McGonagle, 2007). It remains uncertain, though, how specifically genetic predisposition to PsA combines with acquired immune dysregulation and environmental factors (such as the “deep Koebner phenomenon”) in determining the diverse clinical features of PsA and in influencing the severity of the disease and its response to treatment.

1.2.3 Clinical Presentation and Clinical Course of Psoriatic Arthritis

Clinical features of PsA are diverse and can affect virtually any area within the MSK apparatus of the human body. The archetype manifestation is enthesitis [that is, inflammation at the site of attachment of ligaments, tendons and capsules onto bones (D'Agostino and Olivieri, 2006)]. The occurrence of soft (that is, “non-bony”) swelling, tenderness and prolonged stiffness located at the distal insertion

of the Achilles' tendon onto the calcaneus is a classic presentation. Other localizations of enthesitis, however, could challenge even the experienced clinician (Marchesoni et al., 2018). Dactylitis [that is, contemporary inflammatory involvement of joints, entheses, tendons and surrounding soft tissues of one entire digit (Girolimetto et al., 2021)] is also considered typical of PsA and useful in distinguishing it from other forms of inflammatory arthropathies. Arthritis, the eponymic clinical manifestation of PsA, is characterised by articular swelling, pain, stiffness and loss of function. The clinical patterns of arthritic involvement across people affected by PsA usually vary, adding more complexity to the clinical heterogeneity of the condition. Lastly, spondylitis (that is, inflammation of the vertebras), sacro-iliitis (inflammation of the sacroiliac joints), costovertebral arthritis and costochondritis are features of the axial skeleton pattern of involvement in PsA.

To underscore again the complexity of this condition, the range of clinical features briefly described above may either present in isolation or in combination. They also can affect patients at one time or affect them over consecutive years through the course of the disease. Further, one or more features may dominate the severity of the clinical picture at one point in time, only to eventually remit and give way to different ones later on. Furthermore, genuinely MSK features may occur alongside diverse, non-MSK affections -PsO, IBD, IED- in a kaleidoscope of iterations broadly deteriorating the health and Quality of Life (QoL) of patients, either at one time or in temporal sequence. Such clinical phenomena of co-occurrence and complex clinical iteration underpin the concept of PsD.

1.2.3.1 The Concept of Psoriatic Disease as a Tool to Encapsulate the Heterogeneity Related to Psoriatic Arthritis

PsD is a complex chronic condition characterized by a range of cutaneous and MSK inflammatory manifestations (Scarpa et al., 2006; Scarpa et al., 2010). IBDs, IED and metabolic disturbances are also linked to the PsD spectrum. Cutaneous lesions present diversity in their macroscopic clinical morphology (plaques, pustules, nail abnormalities), in their anatomical localization over the skin (trunk, limbs, scalp, folds, oral and genital mucosae), in causing nail pathology and in the extent of the surface area involved (circumscribed zones, whole-body erythroderma). Inflammation can affect the MSK apparatus by large and clinically occurs in form of arthritis (Helliwell, P. et al., 1991), enthesitis, dactylitis and spondylitis/sacro-iliitis. Although formal consensus on the definition of PsD is lacking and debate is ongoing (Ciocon and Kimball, 2007; Ritchlin, C., 2007; Chimenti et al., 2019), clinicians -mostly dermatologists and rheumatologists- commonly appreciate the value of recognising the multi-faceted clinical phenotypes of PsD under one umbrella term. Although, typically, cutaneous

manifestations are the first to present at the time of the clinical onset, later in the disease course skin and MSK manifestations tend to affect patients in a concomitant manner. As a consequence, managing cases of PsD is characteristically a pluri-dimensional and complex task, with multi-disciplinary and comprehensive approach being the most beneficial for managing the condition (Greb et al., 2016). A thorough understanding of PsD pathogenesis remains elusive (Scher et al., 2019), however, the interactions of several factors including genetic makeup, environmental triggers, exposure to chemicals (such as smoking) and dysregulated/dysfunctional inflammatory responses are all suspected to play a role in the production of the clinical phenotype.

The combination of clinical experience and a generally improved understanding of the multi-factorial mechanisms underlying PsO (Greb et al., 2016; Chimenti et al., 2019; Scher et al., 2019), have led some authors to hypothesize the concept of PsD (Scarpa et al., 2006; Scarpa et al., 2010). Following on the same theoretical thread, the definition of PsD is given as: (a) systemic –since it affects several sites of the human body, more visibly the skin and the MSK system; and (b) heterogeneous -since different clinical phenotypes may stretch across anatomical sites, while (c) both severity and clinical course present considerable variation across patients and within individuals. Although not officially accepted and validated, the definition of PsD presented above was adopted in the context of this thesis.

The relevance of PsD as a healthcare matter, whichever the disciplinary perspective taken, is notable. For example, estimates of the prevalence of cutaneous psoriatic lesions in the general population worldwide vary widely, from 0.09% to 11.4%, depending on the geographical regions studied (Michalek et al., 2016). In addition to that, the wider burden of PsD takes the form of: social stigmatization (Greb et al., 2016); underestimated disease severity and delayed diagnosis by health professionals (van de Kerkhof et al., 2015); reduced autonomy and participation in the workforce; reduced self-fulfilment and impaired QoL (van de Kerkhof et al., 2015; Greb et al., 2016).

1.2.3.2 Psoriatic Arthritis as a Condition with Potential for Structural Damage and Disability

Each clinical feature of PsA is either linked (dactylitis) to, or an indirect trigger (enthesitis) of, or a source (arthritis, spondylitis) of articular damage, eventually leading to destruction of the anatomical integrity of the joints and loss of normal MSK function. Although traditionally deemed an entity of more benign course when compared to RA (Wright, 1959), more recent appreciation -from the descriptions of longitudinal clinical series- of established and undertreated PsA

have highlighted its potential for destruction of the joints (Gladman, D.D. et al., 1987) and MSK tissues at large.

1.2.4 Treatment of Psoriatic Arthritis

The risk for permanent damage and associated disability makes the case for improving the treatment strategies currently available for PsA and for the associated conditions part of the PsD spectrum.

The drugs available for the treatment of PsA are many [the citations presented below do not include phase II clinical trials and are limited to phase III clinical trials only – as these projects provide the evidence that informs healthcare regulators and ultimately leads to drug approvals across countries and jurisdictions (Mease et al., 2000; Kaltwasser et al., 2004; Antoni et al., 2005; Mease et al., 2005; Kavanaugh et al., 2009; Lie et al., 2010; McInnes et al., 2013; Kavanaugh et al., 2014; Mease et al., 2014; Ritchlin, C. et al., 2014; McInnes et al., 2015; Gladman, D. et al., 2017; Mease et al., 2017a; Mease et al., 2017b; Deodhar et al., 2020; Mease et al., 2021; Kristensen et al., 2022; Merola et al., 2023)] and well-established in international treatment guidelines (Gossec et al., 2020; Coates, L.C. et al., 2022b; Gossec et al., 2024). Several of these pharmaceutical compounds demonstrated efficacy in clinical trials testing their effects on disease manifestations such as: peripheral arthritis; enthesitis; dactylitis.

The considerations about efficacy of drugs on axial manifestations of PsA are more derived from evidence available from Axial SpA (AxSpA) or AS studies (Poddubnyy et al., 2021; Coates, L.C. et al., 2022b). Only a limited number of studies addressed interventions for axial manifestations of PsA specifically, pointing to efficacious effects of bDMARDs [these studies were well reviewed in a recent publication (Michelena et al., 2020)].

Of particular value in the therapeutic armamentarium are those agents that exert beneficial effects on different domains -MSK or cutaneous or ocular or gastro-intestinal- of PsD. To date, the compounds that more prominently demonstrated this level of versatility are the inhibitors of the cytokine Tumor Necrosis Factor α (TNFi). However, no randomized clinical trial so far evaluated as primary endpoint the simultaneous effect of drugs on different PsA manifestations occurring contemporarily (see paragraph 1.5). One large observational study, though, reported that simultaneous beneficial effects across disease domains (namely, peripheral arthritis and skin – plus QoL) occurred in almost 25% of PsA patients following treatment (Behrens et al., 2018).

It is also important to note, however, that some classes of drugs with demonstrated efficacy on restricted PsD domains (MSK and skin) are associated

with deleterious effects on the gastro-intestinal domain (Petitpain et al., 2021; Caron et al., 2022).

Therefore, treatment for PsA is informed by the efficacy profile of available drugs and needs to be tailored as closely as possible to the phenotypic characteristics of the individual patient. The treatment should aim at covering all the relevant PsD domains affecting the individual patient, using combinations of more than one drug if necessary (Gossec et al., 2020; Coates, L.C. et al., 2022b; Gossec et al., 2024). Moreover, clinicians and patients should set shared treatment goals adopting a Treat-to-Target (T2T) strategy (or otherwise agree on means of prompt review in case of need for adjusting therapeutic goals), aiming at the attainment of Very Low Disease Activity (VLDA) status, if realistic (Coates, L.C. et al., 2019; Coates, L.C. et al., 2022b). Such personalized approach should also take into consideration the possibility of undesired effects and potential toxicity of the medications available.

Besides the use of drugs, lifestyle changes have a role in the management of PsA. Smoking status is one clinical factor associated to response to treatment (Pezzolo and Naldi, 2019), so by implication its suspension can have a beneficial impact on the effectiveness of several medications. The same applies to overweight status, a factor associated to reduced drug effectiveness (Gialouri et al., 2023). In absence of other evidence-based specific personalization factors or validated biomarkers predictive of response to therapy, clinicians agree treatment plans with their patients on the basis of pharmacokinetic properties of the compounds available (van Schie et al., 2016), on the possibility to adjust drug doses according to the subjects' bodily weight and on the convenience -or acceptability- of the different drug administration modalities.

1.2.5 Remission in Psoriatic Arthritis

There is no consensus on a definition of remission in PsA to date. Neither are validated criteria for PsA remission available in the literature.

In a review aimed at considering potential criteria for the definition of remission (Mease and Coates, 2018), a list of domains that should be part of potential remission criteria was suggested: these were peripheral arthritis, enthesitis, dactylitis, spondylitis, skin and nails. Of note, this work from Mease at al. pointed to the need for assessing activity simultaneously across the PsD disease domains, without limiting the evaluation to the MSK system features. Though no specific outcome measure was recommended to assess the domains listed above, the authors reiterated that at the core of the definition of PsA remission there should be the concept of whole, simultaneous control of inflammation in all the aspects of the condition.

Currently, no validated composite outcome measure can assess across all the domains recommended by Mease al. (Table 1). The one selected as preferred outcome measure in clinical trials of PsA by the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis network (GRAPPA) (Tillett et al., 2021b) is the Psoriatic ArthritiS Disease Activity Score [PASDAS (Helliwell, P.S. et al., 2013)], a composite index that assesses peripheral arthritis, enthesitis, dactylitis, QoL through the Physical Component Summary (PCS) of the Short Form-36 (SF-36) questionnaire (Hays et al., 1993), one serum-measured inflammatory reactant (C-Reactive Protein, abbreviated to CRP), alongside the healthcare operator's and patient's evaluation of disease activity. The PASDAS, however, does not encompass evaluation of axial involvement, skin, nails and fatigue. Moreover, its test-retest reliability is formally understudied (Tillett et al., 2021b), especially in early PsA.

Table 1 Comparison of Remission Thresholds across currently available Outcome Measures in Psoriatic Arthritis

	DAS (van der Heijde et al., 1990)	DAPSA (Schoels, M. et al., 2010)	VLDA (Coates, L.C. and Helliwell, 2016a)	CPDAI (Mumtaz et al., 2011)	PASDAS (Helliwell, P.S. et al., 2013)
Remission, near remission or very low disease activity Threshold value*	<1.6	≤4	7/7 features **	≤2 **	≤1.9 **
Domain					
Peripheral arthritis (operator's evaluation)	X	X	X	X	X
Enthesitis (operator's evaluation)	-	-	X	X	X
Axial (operator's evaluation)	-	-	-	X	-
Dactylitis (operator's evaluation)	-	-	-	X	X
Skin (operator's evaluation)	-	-	X	X	-
Nails (operator's evaluation)	-	-	-	-	-
Pain (patient's evaluation)	-	X	X	-	Bodily***
Fatigue (patient's evaluation)	-	-	-	-	-
Functional status (patient's evaluation)	-	-	X	X	X
Patient's assessment (disease activity)	X	X	X	X	X
Physician's assessment (disease activity)	-	-	-	-	X
C-reactive protein (laboratory test)	ESR	X	-	-	X
Total of domains assessed	3	4	6	7	8

DAS = Disease Activity Score; DAPSA = Disease Activity Index for Psoriatic Arthritis; VLDA = Very Low Disease Activity; CPDAI = Composite Psoriatic Disease Activity Index; PASDAS = Psoriatic ArthritiS Disease Activity Score; ESR = Erythrocyte Sedimentation Rate

* Thresholds available in published studies (Prevoo et al., 1996; Coates, L.C. and Helliwell, 2016a; Schoels, M.M. et al., 2016)
** Very low disease activity, or "near-remission" (Coates, L.C. and Helliwell, 2016a)
*** Assessment of bodily pain -not specifically of articular pain- is encompassed

One set of remission criteria proposed by Italian researchers more than a decade ago (Cantini et al., 2008) does cover -for the largest part, though not fully- the PsA disease spectrum of MSK (both articular and extra-articular) domains, thus taking into account the considerable burden that extra-articular manifestations cause, as commonly experienced by people affected by PsA. This set also encompasses Patient Reported Outcome Measures (PROMs) such as assessment of fatigue, articular pain and articular morning stiffness (Table 2). Adopting the filter of the updated PsA core domain set (Orbai et al., 2017), the remission criteria proposed by Cantini et al. seem overall more comprehensive compared to the outcome measures listed in Table 1. Therefore, Cantini's criteria offer a valuable reference for the set-up of proposals concerning the definition of remission in PsA. There are, however, limitations to the work of Cantini et al. that caution against the adoption of these remission criteria in their current form. *In primis*, there is no evidence available pointing to formal validation of Cantini's work (that is, reliability, validity, responsiveness and feasibility of the criteria were never tested). There is also scarcity of details provided on a few items listed in Table 2, namely which joint count would be better to adopt (66/68 count vs 76/78 count) or what method specifically constitutes assessment for tenosynovitis. Notably, the item named "extra-articular features" is left with a vague definition and is linked to a literature reference difficult to access. Lastly, Cantini's list does not encompass the skin/nails domain, nor health related QoL and functional status evaluation (all items that belong to the inner core of PsA domain set suggested by Orbai et al.).

Another set of PsA remission criteria from Toronto (Alharbi et al., 2020) notably overlapped with Cantini's criteria. The domains more in common between the two sets were the clinical ones: swollen and tender joints counts, tenosynovitis, inflammatory spinal pain. Alharbi and co-authors added evaluation of PsO to their selected domains, as well as evaluation of functional status plus the patient's global assessment on disease activity. These authors did not encompass, however, the assessment of fatigue or morning stiffness or dactylitis, as well as they did not add an estimation of the inflammatory burden by laboratory tests. Their threshold for patient pain evaluation (≤15) was less strict when compared to Cantini's criteria (these are presented in Table 2).

Table 2 Cantini's Remission Criteria for Psoriatic Arthritis

Remission criteria for peripheral Psoriatic Arthritis[1]. Patients to be considered in remission if all eleven items are fulfilled.

Item	Value
Patient's assessment of fatigue (Visual Analogue Scale 1-100 mm)	<10
Patient's assessment of pain (Visual Analogue Scale 1-100 mm)	<10
Articular morning stiffness (minutes)	≤15
Tender joint count	0
Swollen joint count	0
Normal Erythrocyte Sedimentation Rate (mm/h)	Women ≤30 Men ≤20
Normal C-Reactive Protein (mg/dL)	≤0.5
Dactylitis (Absent/Present)	Absent
Enthesitis[2]/tenosynovitis (absent/present)	Absent
Inflammatory spinal pain (absent/present)	Absent
Extra-articular features[3] (absent/present), except psoriasis	Absent

1) Adapted from the American College of Rheumatology remission criteria for Rheumatoid Arthritis (Pinals et al., 1981).

2) Enthesitis to be assessed according to Mander's enthesitis index (Mander et al., 1987).

3) Derived from (Gladman, D.D. et al., 1987)

1.3 Early Psoriatic Arthritis - Considerations

1.3.1 Definition of Early Psoriatic Arthritis

There are currently methodological limitations to the establishment of a definition of early PsA as a specific, finite phase within the broader course of PsA disease. Theoretically, the onset of the first, early stage of PsA should be recognizable by specific bio-markers - either in presence or absence of PsA-related symptoms reported by patients. Unfortunately, no bio-pathological marker of PsA early stage -or transition from PsO to PsA- is currently available (Wirth et al., 2022).

Advanced imaging techniques can capture inflammatory anomalies in patients affected by PsO, suggestive of an underlying developing process towards clinically apparent PsA (Zabotti et al., 2023), however, the prognostic significance of such evidence remains uncertain at present.

Further, there is not even current consensus, definition or diagnostic biomarker that characterises the end of the early PsA stage and its transition into late-stage PsA.

The few trials investigating the effectiveness of treatment strategies for early PsA (paragraph 1.5) mostly rely on operational definitions of this phase of the condition, limiting the eligibility for enrolment to those cases in whom confirmation of diagnosis of PsA succeeded yet evidence of articular damage (as evidenced clinically or, better, on imaging) was absent. One different criterion aimed at establishing the early-stage status would be the amount of time elapsed between the onset of PsA-related symptoms and the clinical diagnostic confirmation of PsA by a qualified healthcare operator. However, 27% of early PsA cases had erosions demonstrated at the time of clinical presentation in one series (Kane et al., 2003). Recent evidence points to a potential cut off value of eight months of symptoms duration prior to a formal diagnosis of PsA, beyond which structural damage became apparent on radiographs (Hen et al., 2024a). These phenomena point to the uncertainties associated with approaches based solely on elements gathered from history collection (itself an established technique in standard medical practice, that however is substantially subject to memory bias and interpretation bias).

A form of operational compromise may rely on the time-to-diagnosis criterion at the point of recruitment, imposing an arbitrary limit to participation in early PsA trials to candidates affected by the disease for too long time. In this respect, the limit of two years (Gladman, D.D., 2012) between diagnosis and enrolment into trials might represent a useful compromise. This limit, however, remain at present a sort of informal consensus among investigators who have an interest in PsA

research. No solid evidence that articular damage –on imaging- tends not to occur within two years prior to diagnostic confirmation of PsA is available at present. Indeed, one publication that this candidate co-authored (Hen et al., 2024a) indicated that anatomical damage can occur by the eight months prior to formal PsA diagnosis.

On the other hand, in the opinion of this candidate the very development of structural damage on imaging should –theoretically- mark the end of the early stage of PsA and start the transition into the late-stage of PsA.

1.3.2 Early Psoriatic Arthritis in the Broader Context of Psoriatic Disease

To add more complexity to the attempts at defining the early phase of PsA, it has to be noted that the majority of patients affected by PsA experience skin PsO well before (seven to ten years, on average) the clinical onset of the rheumatic disease (Gladman, D.D. et al., 1987; Ritchlin, C.T. et al., 2017). Therefore, in the chain of events that people affected by PsO experience throughout their life, the onset of PsA is likely not the very first pathologic event taking place. For this reason, the view of early PsA as just one of many parts of the broader PsD process would allow for putting the concatenation of pathologic events in a better and wider perspective. Namely, in such expanded context early PsA would be only one brief period within a larger timeline, where skin involvement typically initiates the processes that only later transition to MSK involvement and eventually result in structural damage of the joints. To provide the reader with an analogy, early PsA should represent one tile in the middle of -and not at the beginning of- a sort of “PsD domino” of pathologic events (Figure 3).

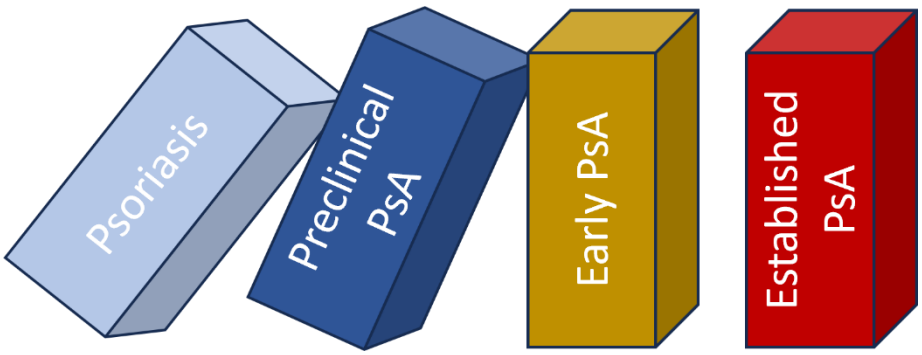

Figure 3 The "Psoriatic Disease Domino"

The concatenation of events experienced over a lifetime by patients affected by Psoriatic Arthritis (PsA) points to the possibility that early PsA is just one stage - not an isolated phenomenon- of a larger group of connected pathologies.

The "domino" concept presented here is deeply linked to the concept of Psoriatic Disease (PsD) (Scarpa et al., 2006; Scarpa et al., 2010; Scarpa et al., 2017) and partially connects to the concept of "Psoriatic March", where severe psoriasis links to cardiovascular pathologies (Boehncke et al., 2011).

Though this specific concept is only theoretical, it is the opinion of this candidate that -from a biopathological perspective- the stage corresponding to early PsA should be positioned past of -and not at the beginning of- several unknown steps that eventually cause the PsD process to spread outside the skin organ. Therefore, “early” PsA may be merely a “midway” step of the entire PsD biopathological process.

1.3.3 Does Early Psoriatic Arthritis Offer a Therapeutic Window of Opportunity?

Regardless of the position of the early PsA stage in the greater scheme of things, treating PsA as early as possible does offer advantages. The evidence gathered so far, however, focuses more on missed opportunities connected to diagnostic delays (Tillett et al., 2013; Theander et al., 2014; Haroon et al., 2015; Snoeck Henkemans et al., 2024). Even in absence of clinical trials formally comparing the efficacy of interventions applied at early versus late stage of PsA, the notion that a diagnostic delay as small as six months is associated with worse clinical outcomes demands attention (Haroon et al., 2015). Additionally, the results from the TICOPA study do suggest that the adoption of MDA as a treatment target is an achievable goal in early PsA and a T2T approach is associated to improved outcomes (Coates, L.C. et al., 2015).

1.3.4 Remission in Early Psoriatic Arthritis

As no consensus or validated definition for remission in PsA is available, the same applies to remission at the early stage of PsA. In the opinion of this candidate, the principles of whole, simultaneous control on inflammation in all the aspects of disease activity (Mease and Coates, 2018) should apply. This consideration points to the need for assessing domains of the PsD spectrum to be reflected into proposals for definition of remission in early PsA.

The medical literature provides scarce descriptions of remission in early PsA, from a handful of observational studies (Kane et al., 2003; Theander et al., 2014). In the study by Kane and co-authors published in 2003, PsA remission was described as: 1) absence of fatigue; 2) articular early morning stiffness <15 minutes of duration; 3) absence of pain in the joints (in the opinion of the candidate this was likely patient-reported, as the authors did not provide specifications related to this item); 4) complete absence of joint tenderness or swelling (including dactylitis and enthesitis) on examination; and 5) Erythrocyte Sedimentation Rate (ESR) <30 mm/h (in females) or ESR <20 mm/h (in males). Occurrence of remission (achieved by participants if five out of five of the criteria listed above were fulfilled) was recorded at one and at two years of follow-up -not

at baseline- in this observational study, with a frequency of 26% and 21%, respectively.

In a Swedish study published in 2014 (Theander et al., 2014), remission in early PsA was defined as: 1) absence of any swollen or tender joints (upon examination, not further specified); 2) ESR <20 mm/h during first hour (no sex related thresholds declared); and 3) CRP <0.5 mg/dl. In cases presenting with axial involvement, remission also required absence of signs of axial enthesitis and low-level (none or minimal) of pain in the peripheral joints and the back (no further details provided). In the authors' own words, "*owing to the mean symptom duration of 11 months before inclusion*", 3 patients (1.5%) were in spontaneous remission at the baseline time-point in this series. Five-year follow-up results showed that 35/197 patients (17.8%) were in remission later on.

Of note, all the remission criteria presented above do not assess disease activity across the wider PsD clinical spectrum, failing in part the considerations later elaborated by Mease and co-authors in regards with remission as a status that reflects simultaneous control on inflammation in all the aspects of disease activity (Mease and Coates, 2018). The view taken by both Kane et al. and Theander et al. is also heavily restricted to specific features of the MSK apparatus, so that dactylitis and enthesitis were not part of their remission criteria. Even within such limited perspective, other domains like fatigue were not represented by Theander and co-authors.

In the opinion of this candidate, given the absence of a validated definition of remission in early PsA, the same considerations presented earlier in this thesis (paragraph 1.2.5 and Table 1) should apply. Namely, no currently available composite outcome measure in PsA can assess across all the recommended domains of remission (Table 1).

The remission criteria proposed by Cantini et al., though comprehensive (as far as the MSK domains are concerned), are not validated in early PsA, are vague on the definition of "extra-articular features" and do not encompass the skin/nails domain or functional status evaluation. The remission criteria proposed by Alharbi and coworkers present the uncommon characteristic of assessing -though only in part- across the clinical spectrum of PsD, as MSK domains are listed alongside skin domains. However, the assessments of fatigue, of morning stiffness and of dactylitis, as well as an estimation of the inflammatory burden by laboratory tests, are not part of these criteria. On top of that, These criteria from the Toronto group are not validated and were tested in a cohort of cases who mostly presented with established disease [average disease duration (in years) 8.7, Standard Deviation (SD) 9.4 (Alharbi et al., 2020)].

1.3.4.1 The PASDAS Index, Specific Considerations as a Measure of Remission in Early PsA

The PASDAS score was developed by GRAPPA through one international initiative started in 2006 (Helliwell, P.S. et al., 2013). The development exercise was data-driven, it included items recommended as of core disease domains at that time (Gladman, D.D. et al., 2007) and included 503 PsA patients who experienced disease over 9.8 years on average.

The resulting composite measure assesses disease activity across the spectrum of many MSK PsA manifestations (see Table 1); is responsive to interventions and demonstrated good effect size (Helliwell, P.S. and Kavanaugh, 2014); it is recommended for use in clinical trials of PsA (Tillett et al., 2021a); and its cut-off values reflecting different levels of disease activity are established (Helliwell, P.S. et al., 2014; Helliwell, P.S. and Kavanaugh, 2014) and are also validated (Perruccio et al., 2020). The PASDAS value identified as indicative of very low disease activity -or “near remission”- is ≤1.9 (Coates, L.C. and Helliwell, 2016a).

However, the PASDAS does not encompass evaluation of features pertaining to axial PsA, skin and nails. The evaluation of pain (patient’s assessment) is indeed incorporated in PASDAS, though this item is captured generically as bodily pain (technically, not specific to articular pain). The non-MSK domain of fatigue is also not captured. Therefore, PASDAS does not assess completely across domains of PsA or PsD. The threshold for “near remission” (value of ≤1.9) remains ambiguous and it is not clear if a lower threshold would better reflect the remission status as suggested by Mease and co-authors (Mease and Coates, 2018).

The validation of PASDAS showed responsiveness to intervention in clinical trials of established PsA [average disease duration close to 7.5 years (Helliwell, P.S. and Kavanaugh, 2014)]. In early PsA (usual standard care, not in clinical trials), PASDAS demonstrated longitudinal responsiveness (Wervers et al., 2019). The evaluation of the test-retest reliability of PASDAS was formally underpowered and performed in cases of established PsA (Tillett et al., 2021a), technically limiting its validity in early PsA.

1.4 Gaps Identified in the Literature - Considerations

So far, the evidence appraised by this candidate identified some relevant gaps in the body of medical literature. The first of these gaps relates to the very definition of early PsA, that lacks biomarkers and relies on ad-hoc operational criteria that vary across clinical studies. The definition of remission in early PsA is also under-investigated, as attempts at producing criteria do not cover across MSK domains

of PsA consistently and tend not to cover the broader PsD clinical domains (for example: fatigue, skin and nails). The efficacy of different first-line treatment strategies for early PsA in treatment-naïve patients, their effectiveness across different MSK domains and their effects on broader PsD domains are also understudied. Moreover, there is a lack of formally validated composite outcome measures that assess disease activity across the clinical spectrum of PsA and PsD. Even by the non-systematic approach described by this candidate so far, the appraisal of available publications addressing the matters covered up to this point indicate relevant knowledge unmet needs.

However, the sophistication (especially the concept of looking at remission across different disease domains) and the relative novelty of the subject of this thesis demanded -in this candidate's opinion- an approach to literature appraisal as thorough as possible. Therefore, the candidate could not assume that other "niche" publications would have not been overlooked, unless one systematic review of the evidence be performed.

1.5 Treatment of Early Psoriatic Arthritis

To address the matter of appraising the literature available on the subject of this thesis (remission induction treatment strategies in early PsA), the candidate devised a broader exercise of review that encompassed as many domains as possible -within the PsA clinical spectrum as well as within the PsD spectrum- and could also be endorsed at international level. Therefore, the candidate submitted his systematic review as a project to GRAPPA network, which endorsed the project. This way, the effort would create value for the postgraduate project as well as it would add a publication of scientific value to the international research community. Following rigorous criteria of literature search and evidence appraisal design (Higgins and Cochrane Collaboration, 2020), the candidate produced one search protocol, available on PROSPERO, the International prospective register of systematic reviews maintained by the University of York [detailed description of the search protocol, with one example of the comprehensive search terms adopted, is available online (De Marco, G., et al., 2018)].

This published systematic review (De Marco, G. et al., 2020) examined seven "Patient Intervention Comparator Outcome" (PICO) research questions (detailed -alongside important considerations related to the aims of this thesis- in Appendix 1) to appraise the publications reporting on the efficacy of drugs across the clinical spectrum of PsA and PsD. Namely, the focus of the PICO questions covered: remission; peripheral arthritis; dactylitis; spondylitis/axial involvement;

enthesitis; skin; and nails. The outcomes evaluated in this exercise assessed disease domains across the range of PsD manifestations and did include composite measures. Early PsA and PsD were defined as a disease duration of ≤2 years, except for studies solely investigating outcomes restricted to the skin. Eligible references were clinical trials or well-designed prospective studies/series reporting on adult humans who were untreated for PsA and PsD as well as affected by cutaneous and/or MSK features of PsA and PsD.

Figure 4 presents the flow diagram of the candidate's systematic review. At the end of the search process, only nine references (out of 160319; publication range 1946–2019) fulfilled the eligibility criteria chosen for this exercise.

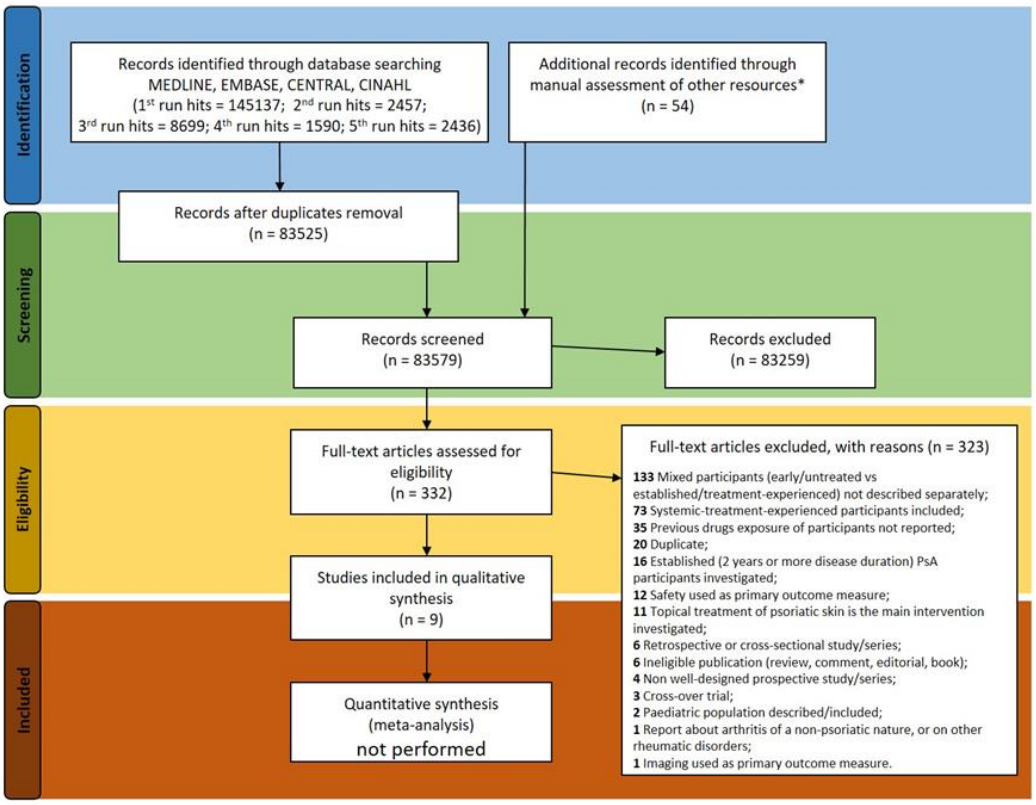

Figure 4 Flow Diagram of the Systematic Review on Treatments for Early Psoriatic Arthritis and Psoriatic Disease

The systematic approach taken by the candidate to review the evidence is presented in the diagram above. In order to make the review as robust as possible, high international standards were adhered to (Higgins and Cochrane Collaboration, 2020), also in compliance with the PRISMA statement (Moher et al., 2009).

No one of the eligible publications appraised reported on clinical studies that had adopted comprehensive (that is, assessing different PsA and PsD manifestations simultaneously – see also paragraphs 1.2.3.1 and 1.3.4) composite indices as primary outcome measures. In addition to this, no publication reported that remission was selected as primary outcome measure. Individual studies reported that apremilast and bDMARDs successfully improved outcomes [Disease Activity index for PSoriatic Arthritis (DAPSA); MDA; PASDAS; Psoriasis Area and Severity Index (PASI); Psoriatic Arthritis Response Criteria (PsARC)], though only when efficacy analyses were restricted to single manifestations of untreated PsD. In this systematic review exercise, only qualitative synthesis of evidence was possible, due to: a) data heterogeneity (disease classification criteria adopted and outcome measures reported in individual publications); b) unavailable data subsets -focused on early, untreated PsA/PsD- at single study level; c) insufficient data on the participants' exposure to treatments prior to the time of enrolment in each individual clinical study.

Effective interventions -albeit limited in scope- for early, treatment-naïve PsA and PsD were found. The appraised publications relevant to this thesis, even if not formally eligible to inclusion in the systematic review, are listed in Table 3.

No study provided evidence about the management of co-occurring cutaneous and MSK manifestations in early, treatment naïve PsA and PsD. Further, no study adopted -or proposed a definition of- comprehensive remission criteria as primary outcome measure – or even as exploratory endpoint.

The review performed by the candidate confirmed that the subject of this thesis focuses on a gap in knowledge on early PsA and PsD.

One more recent exercise of review of treatment for PsA at early stage assessed the literature produced up to 2023 (Hen et al., 2024b). The candidate participated to this exercise (roles: search strategy design, literature assessment, manuscript production). The results published by Hen and coworkers do apply to the wider MSK manifestations of PsD and confirm that, since the time of the publication of the candidate's own systematic review, no study addressed the matter of management of co-occurring cutaneous and MSK manifestations in early, treatment naïve PsA and PsD.

Table 3 Treatment of Early Psoriatic Arthritis to Remission (Systematic Review)

Reference	Primary Outcome	Results
(Scarpa et al., 2008) Randomized, open label clinical trial	Tender and swollen joint counts, PROMs	No difference between treatment arms
TICOPA (Coates, L.C. et al., 2015) Open-label, multicentre, randomised, controlled clinical trial	ACR20 response (Felson et al., 1995)	ACR20 response at 48 weeks likelier in the tight control group than in the standard care group
REMARCA (Loginova et al., 2018) Cohort study	DAPSA (Schoels, M. et al., 2010) remission	DAPSA remission achieved within 7±5 months with DMARDs
SEAM-PsA (Mease et al., 2019b) Double-blind, randomized clinical trial	ACR20 response (Felson et al., 1995)	ACR20 response rate at 24 weeks larger in the etanercept monotherapy arm
(van Mens et al., 2019) Double-blind, randomised, placebo-controlled trial	DAS remission (Prevoo et al., 1996)	DAS remission rate at week 22 larger in the TNFα-inhibitor arm
CTRI/2017/06/008888 (Unknown, 2017) Randomized, open label clinical trial	PsARC (Clegg et al., 1996a; Clegg et al., 1996b)	Not yet available, recruiting (unpublished)
SPEED (Coates, L., 2018) Randomized, single blinded clinical trial	PASDAS (Helliwell, P.S. et al., 2013)	Not yet available, recruitment completed (unpublished)

References listed in order of publication year. References related to studies not yet published on indexed journals are listed at the bottom of the table.

PROMs = Patient Reported Outcome Measures; ACR20 = American College of Rheumatology 20% response rate; DAPSA = Disease Activity index for PSoriatic Arthritis; DMARD = Disease Modifying Anti-Rheumatic Drugs; DAS = Disease Activity Score; TNFα = Tumor Necrosis Factor α; PsARC = Psoriatic Arthritis Response Criteria; PASDAS = Psoriatic ArthritiS Disease Activity Score.

1.6 Imaging in Psoriatic arthritis

The use of imaging techniques is well established in rheumatology standard practice, especially for the evaluation of common MSK disorders such as Osteoarthritis (OA) and RA (D'Agostino et al., 2016; Park and Fritz, 2023). The imaging modalities available range from Conventional Radiography (CR) to Computed Tomography (CT) -both obtained by the use of ionizing radiations- to US and MRI. Methods that require the injection of intravenous tracers emitting radiations, such as scintigraphy and Positron Emission Tomography (PET) are also available. The techniques listed above can be roughly divided in basic (such as the CR), intermediate (the CT scans) and advanced (the MRI, scintigraphy, PET scans) according to their availability as restricted by healthcare provider organizations (secondary and tertiary centres) – therefore limiting the application of advanced imaging techniques to specialists operating in large hospitals. US falls between the intermediate and the advanced category, in that scanners are widely available and affordable models (including portable ones) are widely used even in primary care organizations. However, the need for high frequency US probes (usually available with more expensive scanner models) and -above all- the specific, time-consuming training required to operate scanners at adequate standards does condition the availability of US in rheumatology – making its deployment more similar to that of an advanced imaging technique.

The use of imaging in the evaluation of PsA is extensive, at the point of both primary and secondary healthcare. The most commonly utilized method in clinical practice remains CR, followed by US in centres that have access to dedicated scanners and trained operators (Dubash, S.R. et al., 2020; Mathew et al., 2021). Historically, clinicians used CR imaging to establish the presence of PsA-related damage (erosions, joint deformities, mutilations, ankylosis) in the bones. Such procedures allowed to achieve the diagnostic confirmation of the condition as well as the assessment of the anatomical integrity of the joints imaged, at the same time (Figure 2, bottom panel and Figure 5, panel C).

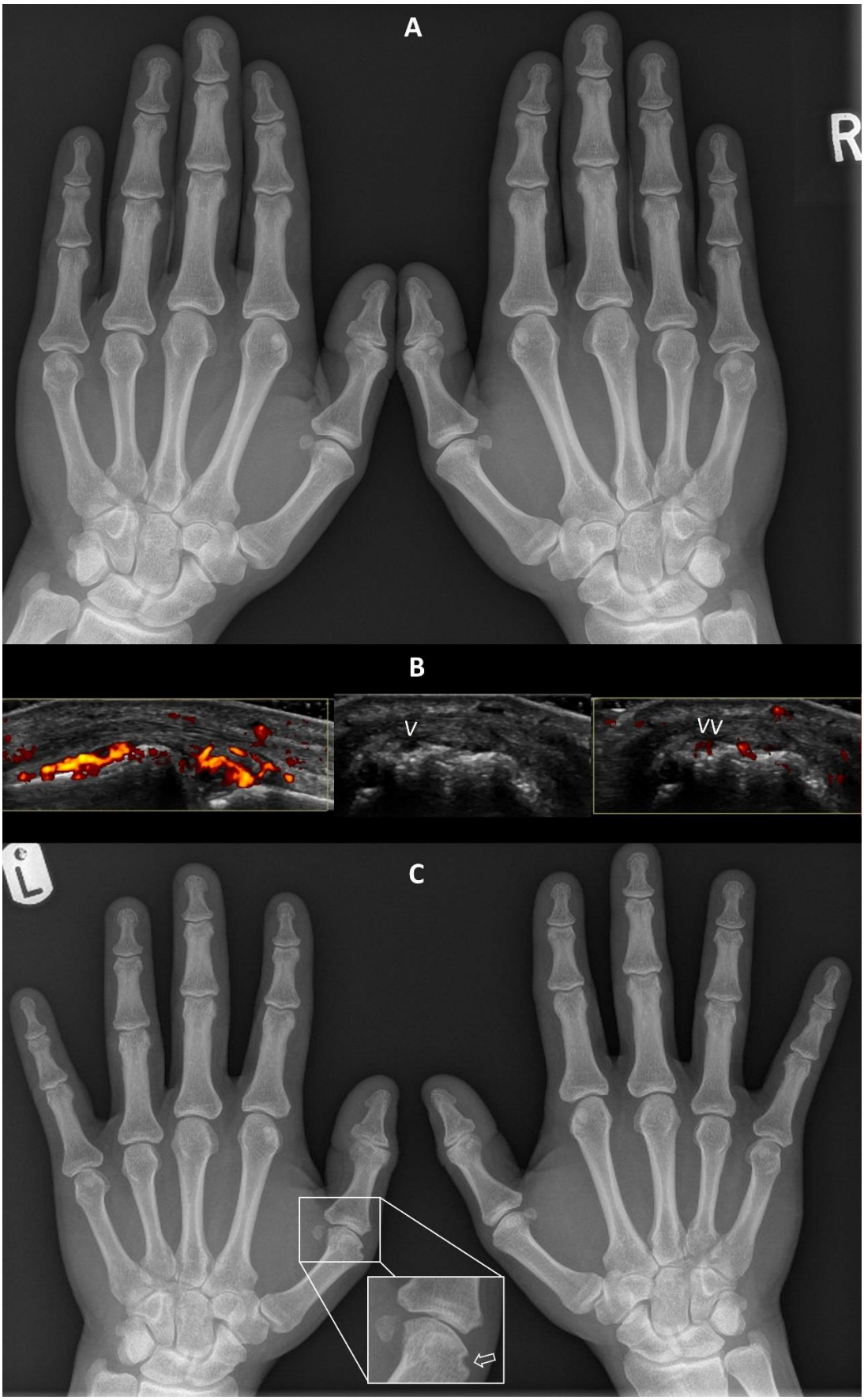

Figure 5 Conventional Radiography and Ultrasound Scan Imaging of Active Psoriatic Arthritis

(The legend of this figure is overleaf)

Panel A - X-ray image taken in December 2016 (first presentation in the Rheumatology clinic). Clinical onset of peripheral Psoriatic Arthritis six months earlier. Early stage, no erosions visible. Patient started on oral weekly MTX hastily escalated to 25 mg/week.

Panel B – Ultrasound image taken in December 2018 (same patient, follow-up visit). Active synovitis of MCPj1 (left hand): synovial hypertrophy, intra-articular effusion and intense PD signal are visible in the left-sided image. The central image (left MCPj1 again) shows erosion (hollow arrowhead) and the right-sided image shows mild-to-moderate PD signal within the same erosion (double hollow arrowhead). Some enthesitis is also visible (left-sided image). Therefore, the patient received intra-articular injection of MCPj1 (left hand) and SSZ (2000 mg/day) was added to oral weekly MTX 25 mg.

Panel C - X-ray image taken in June 2022 (same patient, further follow-up visit). Erosion at the MCPj1 (left hand) now visible on X-ray (hollow arrow in inset). The patient was lost on follow up between 2019 and 2022, that resulted in suspension of their MTX/SSZ treatment. At the beginning of 2022 they also developed acute anterior uveitis, prompting the Ophthalmologist to refer the patient back to the Rheumatology service. As a consequence, MTX was reintroduced and TNFα-inhibitor treatment was started.

Abbreviations - MTX = Methotrexate; MCPj1 = Metacarpal-Phalangeal joint 1 (thumb finger); PD = power-Doppler; SSZ = Sulphasalazine; TNFα = Tumor Necrosis Factor alpha.

Image courtesy of the author, taken with verbal consent of the patient -for educational purposes- at the Rheumatology Outpatient Clinic, Leeds Teaching Hospitals NHS Trust (UK).

The support role of CR in the differential diagnostic between PsA and other frequent MSK conditions (namely OA and calcium pyrophosphate deposition disease) is also invaluable to the rheumatologist. Despite the wide availability of CR, its relatively simple, economic technology and established standards, this imaging method presents with the significant limitation of rendering the soft tissues only with insufficient details. Such a problem is of paramount importance in the evaluation of PsA, where primary pathology affecting tendons or the non-bony parts of entheses is better visualized with different techniques (Figure 5, panel B). Recent evidence suggests that the role of CR and US in assessing and detecting PsA-related bone damage -in peripheral joints and at an early disease stage- is complementary and strongly influenced by the specific anatomical location of bone erosions (Hen et al., 2024a), leading to the impression that CR is in general able to detect more damage than US. However, data from the publication produced by Hen and co-authors highlighted that US is more sensitive than CR in detecting bone erosions at selected location (an example of US-detected erosion -not yet visible on CR- is provided in Figure 5, panel B). Moreover, CR fails to detect and characterize the hypertrophy of the synovial tissues as well as its increased vascularization, a typical imaging feature when joints are affected by active inflammation.

Lastly, the limitations of CR are also apparent in the assessment of another relevant domain within the PsA spectrum: the involvement of the axial skeleton (most frequently, sacroiliac joints, vertebras, costovertebral joints and paravertebral soft tissues). Although CR images can show extensively lesions such as erosions, bone sclerosis, ankylosis and syndesmophytes (Figure 6, panels C and D) that typically occur in the late stages of the disease, the inflammatory lesions that have not generated yet substantial amount of bone pathology are invisible on CR (Figure 7, panel A). Such pathologies are better visualized by MRI, a technique that has value in assessing the inflammatory burden present in the axial skeleton both at early and late stage of PsA (Figure 6, panels A-B and Figure 7, panels B-C).

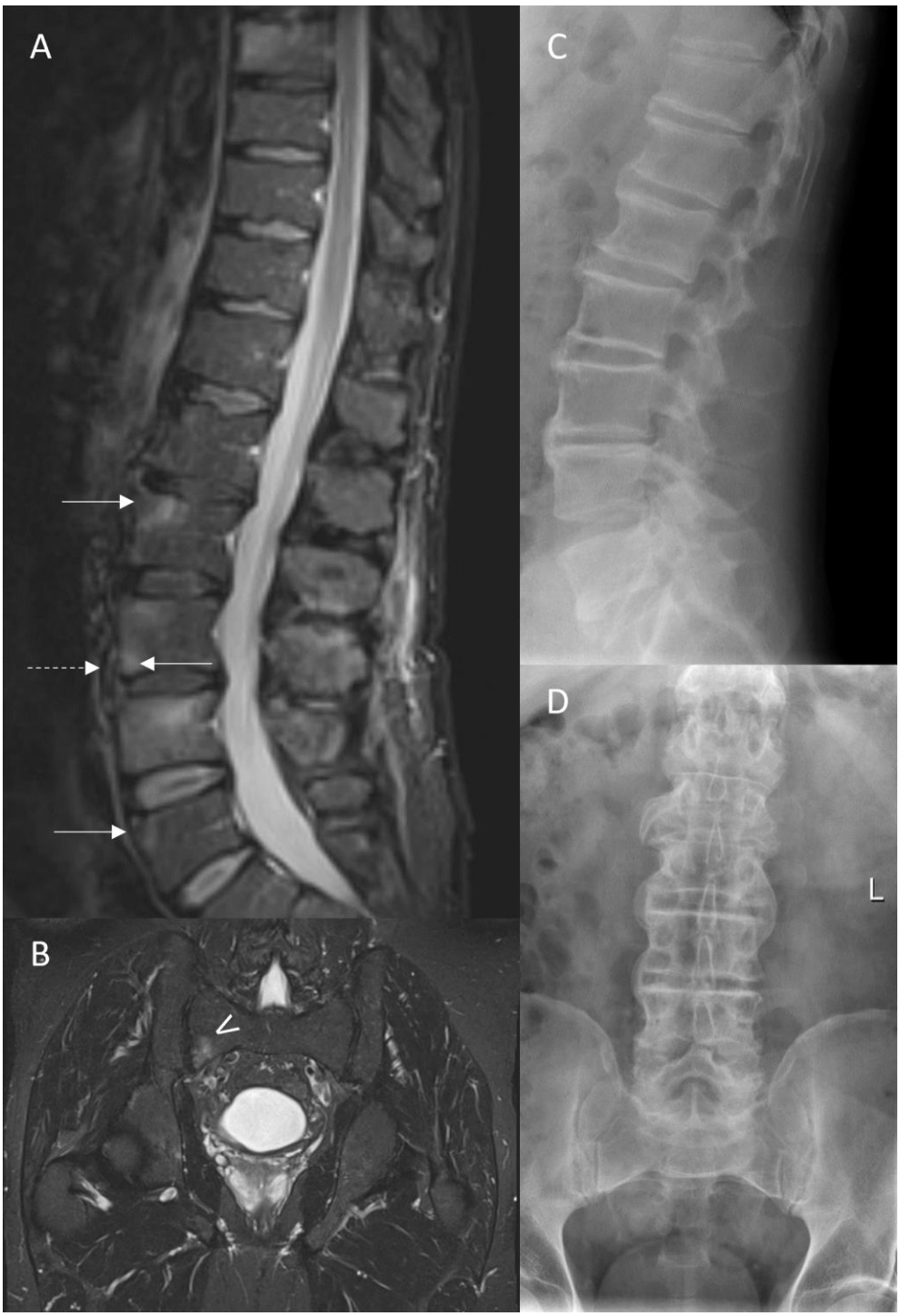

Figure 6 Psoriatic Arthritis in the Axial Skeleton – Radiographic Stage

61-year-old male, overweight. Affected by Psoriasis (without related nail dystrophy). Intense, inflammatory-sounding back pain onset when aged 56. No peripheral arthritis or dactylitis appreciated upon clinical evaluation. HLA-B27 negative, C-reactive protein normal. Diagnosis: Psoriatic Spondyloarthritis. Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) level, prior to therapy: 6/10. (continued overleaf)

Following unsuccessful treatment with two Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) and sulphasalazine, the patient started on Tumor Necrosis Factor α inhibitor (TNFi). This resulted in brilliant response on axial symptoms.

After 30 months, however, biologic treatment was switched to interleukin-17 (IL-17)-inhibitor due to secondary loss of efficacy of the TNFi agent. This change produced again beneficial effects on Spondyloarthritis-related symptoms (BASDAI score down to 2.8/10), with the additional effect of achieving clearance of the psoriatic plaques.

Panel A – Magnetic Resonance Imaging (MRI) scan of the lumbar spine, sagittal plane. Time to Echo (TE): 33 msec.; Time to Repetition (TR): 2700 msec; slice thickness 4 mm. Multiple Bone Marrow Oedema (BMO) lesions affecting the anterior corners of lumbar vertebras (white arrows). Note the hyperintense signal along the pre-vertebral soft tissues (dashed arrow), suggesting inflammation of the anterior longitudinal inter-vertebral ligament.

Panel B – MRI scan of the pelvis, coronal plane. TE: 77 msec.; TR: 4920 msec; slice thickness 4mm. BMO lesions affecting the right subchondral sacral wing (arrowhead tip).

Panels C and D – Conventional radiography showing chunky, asymmetric syndesmophytes abridging several lumbar vertebral bodies. The sacro-iliac joints are spared from ankylosis.

Image courtesy of Professor Dennis McGonagle, taken with verbal consent of the patient -for educational purposes- at the Rheumatology Outpatient Clinic, Leeds Teaching Hospitals NHS Trust (UK).

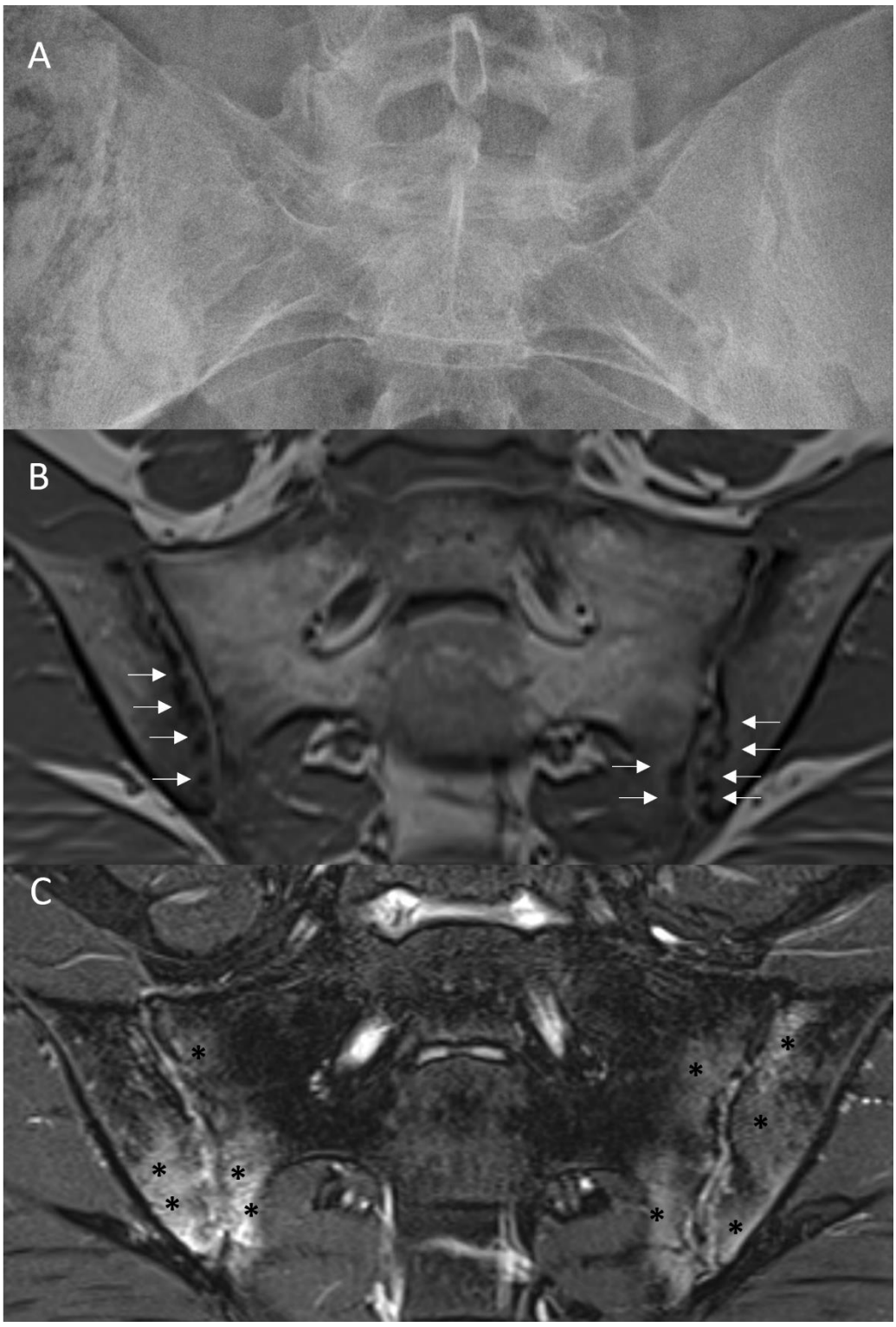

Figure 7 Psoriatic Arthritis in the Axial Skeleton – Pre-Radiographic Stage

25-year-old male, affected by plaque Psoriasis and Psoriatic Nail Dystrophy since the age of 16. Treated with topic agents and phototherapy (narrow band ultraviolets). Recent (6-9 months prior to clinical presentation) onset of inflammatory back pain (ASAS 2009 criteria fulfilled*). Absence of peripheral arthritis or dactylitis upon clinical evaluation. HLA-B27 negative. C-reactive protein 9.5 mg/L. (continued overleaf)

Panel A: conventional radiography, showing no substantial changes (no more than grade 1**) in the sacroiliac joints.

Panel B: T1 VIBE (Volumetric Interpolated Breath-hold Examination) sequence of MRI (Magnetic Resonance Imaging) scan. Time to Echo (TE) 2.46 msec.; Time to Repetition (TR) 7 msec.; slice thickness 1.5mm. The white arrows show loss of subchondral bone signal integrity and erosions (circa 1.15 mm in diameter).

Panel C: STIR (Short Tau Inversion Recovery) sequence of MRI scan. TE 68 msec.; TR 3500 msec.; slice thickness 3mm. The black asterisks show BMO (Bone Marrow Oedema) lesions.

*The Assessment of SpondyloArthritis international Society (ASAS) criteria for inflammatory back pain (Sieper et al., 2009b).

** Grading from “The Assessment of SpondyloArthritis international Society (ASAS) handbook: a guide to assess spondyloarthritis” (Sieper et al., 2009a)

Image courtesy of the author, taken with verbal consent of the patient -for educational purposes- at the Rheumatology Outpatient Clinic, Leeds Teaching Hospitals NHS Trust (UK).

Although MRI assessment of the soft tissues (in peripheral joints) can overlap to a large extent with that of US (Polachek et al., 2022), the bone cortex is impenetrable to acoustic waves. The ability to detect Bone Marrow Oedema (BMO) lesions in subchondral areas is a distinctive feature of MRI. Its advantages in detecting inflammatory bone marrow pathology in the axial skeleton -even at pre-radiographic stage, as mentioned above- are somehow mirrored by the ability of MRI (again exploiting findings of BMO) to discriminate between OA and PsA in peripheral joints (Guldberg-Moller et al., 2022). Conversely, Guldberg-Moller and co-authors reported in their study that MRI was less efficient in the detection of proliferative bone lesions -a characteristic that both US and CR were better at uncovering- while concordance about discovering erosions was high between US and MRI.

The role of imaging in PsA, it seems, further expanded in recent years. From its initial place in differential diagnostic and assessment of disease-related damage, imaging now represents a complement to clinical evaluation, in that it can characterize and quantify the inflammatory burden associated to PsA (Coates, L.C. et al., 2012), with the advantage of providing means for assessment across peripheral and axial locations within the MSK apparatus.

Another recent development is the use of imaging techniques as mean of evaluation for subclinical disease. Some authors (Dubash, S.R. et al., 2021; Felbo et al., 2022) have investigated -adopting US and MRI scanning- the significance of articular tenderness in cases of PsA where obvious clinical signs of joint swelling were not apparent, finding poor correlation between symptoms of articular pain and presence of inflammatory features on scans of the explored joints. Other authors reported that, following treatment for PsA, BMO only attenuates -though it does not resolve- and is not followed by bone damage (Poggenborg et al., 2014). Further research has more recently evaluated the discrepancy between clinical and imaging findings in PsA in one prospective study that adopted US and CR in order to investigate the propensity of developing erosions at follow-up (Gessl et al., 2023). The results published by Gessl and co-authors -in addition to highlighting the adverse prognostic value of tender joints in RA patients (a factor that was not confirmed in patients affected by PsA)- clearly point to the importance of further investigating the potential of imaging as a prognostic tool in the assessment of inflammatory arthritidies (including PsA).

However, the more intriguing data related to imaging -in regards with the subject of this thesis- are those indicating that PsA-related pathology can occur at MSK locations not affected by symptoms. There is evidence that suggests advanced imaging can reveal the presence of inflammation in MSK tissues that goes undetected upon clinical evaluation (Freeston et al., 2014). Such discrepancy

between clinical evaluation and imaging also applies to outcome measures used in clinical trials, as up to 76.2% of patients classified as in MDA presented with features of disease activity on US evaluation (Husic et al., 2014). The therapeutic implications of these findings -and especially their impact in determining if people affected by PsA do or do not achieve a state or remission following treatment- are considerable. However, this area of research is currently underinvestigated.

1.6.1 Imaging for the Evaluation of Remission in Early Psoriatic Arthritis

Though limited evidence is available in this field, communications reported at scientific congresses (Furer et al., 2020; Moly et al., 2020) did report that both US and MRI uncovered features of synovitis and tenosynovitis in PsA patients who were classified as in remission by their physicians. Interestingly, in the report from Moly et al., US inflammatory findings were associated to the presence of discrepancies in the evaluation of disease activity as judged by patients and by physicians (that is, disease judged as active by patients, but judged as in remission by physicians). Another study provided evidence that 20/54 (37%) of PsA patients classified as in remission by their assessing clinicians presented features of inflammatory activity as detected on advanced imaging (Ruta et al., 2017).

Therefore, the ability of imaging techniques to uncover inflammatory activity that is otherwise undetectable by means of clinical evaluation offers unique opportunities in the assessment of remission status in PsA patients. First, it can be argued that the different clinical remission criteria sets chosen in the literature (Husic et al., 2014; Ruta et al., 2017; Furer et al., 2020; Moly et al., 2020) may not be comprehensive enough. That is, these authors may have left behind clinically undetected residual disease activity by virtue of parameter selection bias. Second, the possibility of persistent inflammatory burden -as detected by imaging- in instances of remission that otherwise do not present with any residual signs and symptoms of PsA disease points to the existence of subgroups among patients in remission for PsA. It could be argued that, while some patients could achieve only a state of clinically detectable remission, others could achieve a state of whole -or “deep”- remission if inflammatory features were not detected on advanced imaging as well.

The latter concept is particularly intriguing -due to its potential bio-pathological implications- and leads to the subject of imaging use as prognostic tool for PsA (including cases in remission). In the study by Ruta et al., 34/54 patients (63%) who achieved remission (in their evaluating rheumatologists’ opinion) also did not present features of inflammation on advanced imaging evaluation. Out of these,

only 2/34 (5.9%) experienced a flare of PsA during the subsequent six months of study follow-up. Conversely, out of the 20 other patients recruited in this study (the very ones in clinical remission in whom advanced imaging uncovered residual features of inflammation), 13 (65%) experienced subsequent flares of PsA on further follow-up.

To date, however, no study reporting on features of residual inflammation detectable on advanced imaging was specifically designed to enrol exclusively participants affected by early PsA. Further, no such study adopting a definition of remission -both in PsA and early PsA- that is validated and assessed disease activity across the PsD clinical spectrum domains has ever been reported so far.

1.7 Rationale for Using Data from a Clinical Trial as Basis for this Thesis

In order to offer to the readers a comprehensive perspective onto this thesis, it would be beneficial to take a tiny step aside and describe the background that triggered this postgraduate project in the first place.

Before being admitted as postgraduate student by the University of Leeds in 2017, this candidate used to work as a member of staff for the Leeds Teaching Hospitals NHS Trust (LTHT), tasked with delivering clinical research sponsored or hosted by this organisation. As early as June 2015, this candidate was assigned to the GOLMePsA[1] study project, with his tasks then expanded from simple project delivery to involvement into the final stages of trial design. It was, therefore, possible to appreciate in full -and proactively direct- the potential of the clinical trial programme and push it beyond its original aims. Namely, these were: "*to assess in early diagnosed treatment naïve PsA, the clinical efficacy of a treatment strategy comprising of the combination of GOL plus MTX plus steroids versus standard care (MTX monotherapy plus steroids) using clinical and imaging outcome measures at 24 weeks.*" (De Marco, G. et al., 2017).

However, there were two orders of features that made the GOLMePsA study stand out from other trials carried out in the field of PsD. Firstly, the targeted population (that is, cases of PsA who had not ever received treatment for any manifestation of PsD – either musculoskeletal or cutaneous) would be exposed to an intense regimen of treatment [a combination of steroids, plus high-dose and rapidly escalated Methotrexate (MTX), plus Golimumab (GOL)] that would also

[1] 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.

encompass diverse modes of action. Secondly, the scope of data collection was so broad to cover the traditional rheumatic manifestations of PsD (peripheral arthritis, dactylitis, enthesitis, spondylitis, sacroiliitis) alongside with relevant clinical cutaneous domains (skin area and severity, nail involvement), as well as diverse PROMs and, in addition to all that, evaluations of inflammatory burden by two modalities of imaging acquisition (US and MRI scans).

All the characteristics briefly listed above made clear that the GOLMePsA programme had unparalleled scientific potential at that time. More importantly, it would provide a unique opportunity to investigate the elements of remission -not only disease activity amelioration- in early PsA. Therefore, the choice of the GOLMePsA trial as a platform for extended data collection -that in turn would provide the opportunity to investigate remission, beyond the original trial's aims- became the obvious one, as the potential for writing a dedicated thesis from these materials was spectacular. This order of considerations then led this candidate to apply for a PhD programme in 2017.

To provide the reader with schematics of the next five chapters, Table 4 (on next page) gives a summary of the content of this thesis.

Table 4 Thesis plan

Chapter 1	This part addresses the review of the literature pertaining to early PsA, its treatment and a few considerations about the measures of outcome currently in use in the field of PsA. This chapter includes the results of a systematic review performed by the student and published in 2019.
Chapter 2	This section presents the thesis hypotheses, its general aims and specific objectives.
Chapter 3	This part is dedicated to methodology – that is, the description of the clinical trial used as platform for the collection of data that inform this thesis, as well as the methodology used for the definition and evaluation of PsA remission.
Chapter 4	This section presents the main results of the trial (clinical and imaging) used as platform for the collection of data that inform this thesis. Results of one reliability exercise of one selected measure of outcome (the PASDAS) are also described. This part ends presenting the results related to remission analysis (clinical and imaging).
Chapter 5	This part presents a comprehensive discussion about the findings of the work underpinning this thesis.
Chapter 6	This section offers some considerations about the potential future direction of the line of work presented in this manuscript, with the conclusions of the author.

Chapter 2

2.1 Research Hypothesis

The subject of achieving remission in people affected by early PsA and treatment-naïve is understudied. There is no consensus on the definition of remission in early PsA, it is not clear which domains of the PsD spectrum should be included in any remission status and the methodology of assessment of remission -either for established or early PsA- is not validated. Treatment strategies that facilitate the achievement of remission are understudied as well.

Two research hypotheses underpin this project. It is proposed that a combination therapy consisting of steroids, high dose (25 mg/week) MTX and one TNFi (specifically, GOL) is more likely to induce remission, in patients affected by early PsA and treatment-naïve, compared to a combination of steroid and MTX (25 mg/week). It is also hypothesized that advanced imaging techniques (such as US and MRI) can detect the subclinical burden of inflammation in PsD and inform the characterization of a “deep state” of PsA remission.

The focus of this thesis is to investigate the effects of two intense therapeutic regimens administered at the early stage of PsA, their scope on the heterogeneous manifestations of the disease -as well as across different domains of PsD spectrum- and their ability to induce a state of disease remission as evaluated clinically and by advanced imaging techniques.

2.2 Aims and Objectives

2.2.1 General Aims

Three aims characterise this thesis.

1. To investigate the ability of high-dose, combination treatment (steroids, plus rapidly escalated MTX and GOL), given early in the course of PsA disease and to treatment-naïve patients, in inducing clinical amelioration of the disease after 24 weeks of intervention, as compared to non-biologic combination therapy (steroids and MTX rapidly escalated to high dose).
2. To investigate the scope of the treatment regimens described in aim 1 on the heterogeneous manifestations of PsA disease – as well as across different domains of the PsD clinical spectrum.
3. To investigate the ability of the treatment regimens described in aim 1 to induce a state of disease remission as evaluated clinically and by

advanced imaging techniques [US and MSK Whole-Body Magnetic Resonance (WB-MRI)].

2.2.2 Objectives

Six thesis objectives are set, as follows:

- To describe the effects of two intensive combination treatment regimens - after exposure to 24 weeks of intervention- on disease activity amelioration in early, treatment-naïve PsA.
- To describe the effects of two intensive combination treatment regimens across different domains of the PsD clinical spectrum in early, treatment-naïve PsA – using dedicated composite outcome measures.
- To describe the value of advanced imaging techniques (US, WB-MRI) in assessing the extent of the inflammatory burden in early PsA.
- The describe the scope for assessing the reliability of one PsA-specific composite measure of outcome (the PASDAS index) when applied solely to cases of early PsA.
- To describe the effect of intensive combination regimens on inducing remission in early, treatment-naïve PsA – using newly proposed definition sets of remission that also explore the PsD clinical spectrum.
- To describe the value of advanced imaging techniques (US, WB-MRI) in assessing the extent of the residual inflammatory burden in early PsA cases that fulfilled clinical criteria for a newly proposed definition set of remission.

Chapter 3

This chapter addresses the methodology adopted for the data acquisition of this thesis. The original data collection plan of the GOLMePsA trial was amended and expanded -reconsidering details pertaining to clinical variables, PROMs and imaging variables- in order to provide a platform for this thesis. The student had a considerable role in these operations. However, the design fundamentals and primary endpoint of the GOLMePsA trial remained unchanged.

To provide some context, the chapter first outlines the original trial set up procedures, then covers the trial design, the clinical data collection methods adopted in GOLMePsA, its imaging data acquisition methods and the statistical methods used to set up the trial. At the end of the chapter, the methods more relevant to this thesis (the PASDAS test-retest reliability exercise and the definition of PsA remission) are presented.

3.1 GOLMePsA Trial Methods

The main features of the trial protocol are available in a publication dated 2017 (De Marco, G. et al., 2017). The following two sections expand on that.

3.1.1 Trial Set Up - Registration, Ethical and Administrative Approval

The GOLMePsA trial is an investigator-initiated, single-centre study originally recorded in the European Union (EU) Clinical Trials Register in 2013 (EudraCT Number: 2013-004122-28). The UK sponsor organisation is the LTHT, which attributed to the GOLMePsA trial the following sponsor number: RR13/10782 (approval granted in December 2014).

The project's funder is Janssen Biologics BV (Leiden, The Netherlands), which also manufactures the drug GOL. Janssen had no role in the interpretation of the trial results.

The Research Ethics Committee (REC) of the Health Research Authority (HRA) (NRES Committee East Midlands – Northampton) granted a favourable ethical opinion in April 2014 (REC reference: 14/EM/0124). The Medicines & Healthcare products Regulatory Agency (MHRA) granted approval to the GOLMePsA trial in March 2015.

3.1.2 Trial design

The GOLMePsA study is a randomised (1:1 basis), double blind, placebo-controlled, two-armed, parallel group, single-centre, phase IIIb clinical trial. Figure 8 portrays the trial schematics.

The candidate assisted Professor Helena Marzo-Ortega in the trial design (especially the changes required to enable data collection for the PASDAS score test-retest exercise – please see section 3.4).

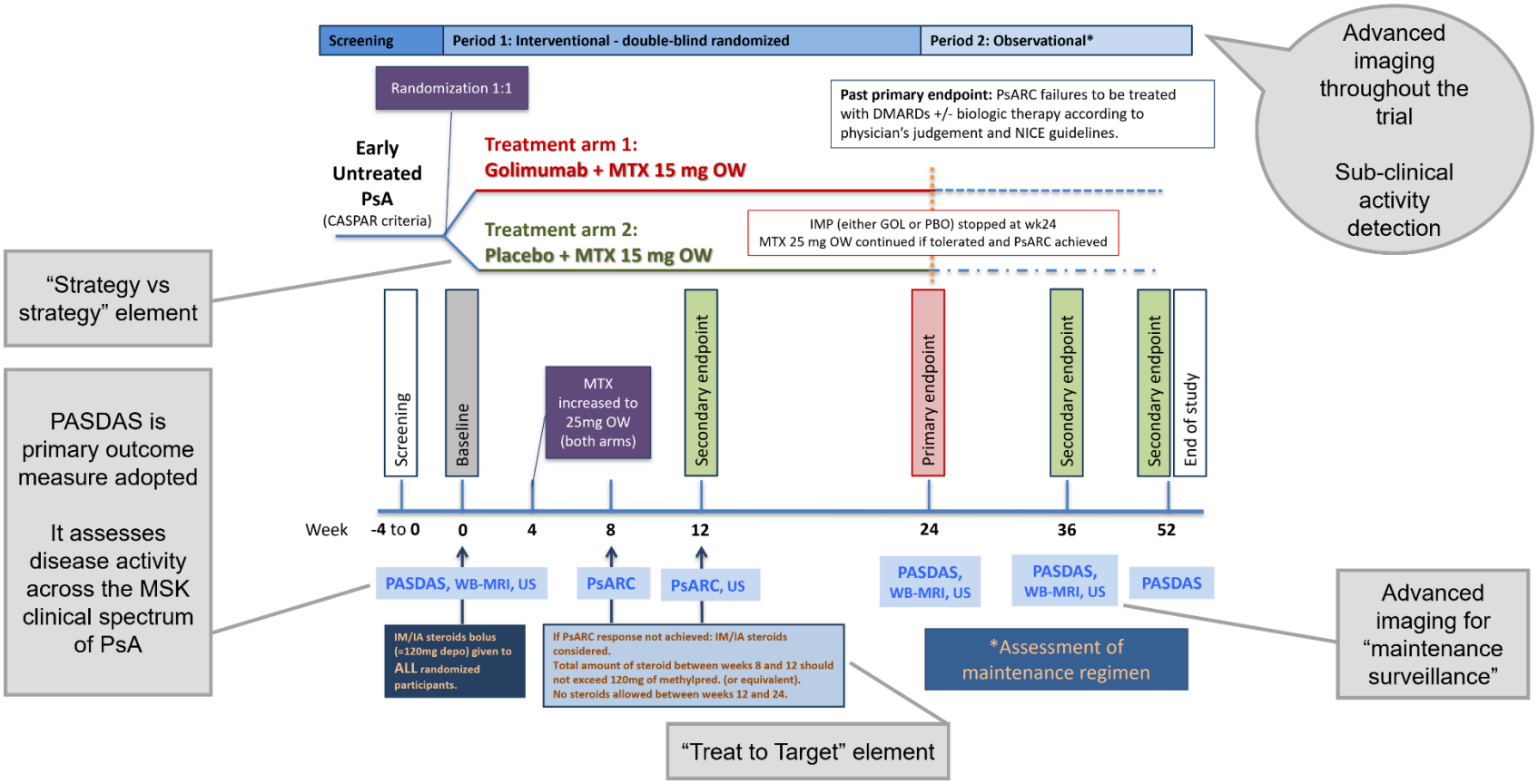

Figure 8 GOLMePsA Trial Schematic Diagram, Enhanced

PsARC = Psoriatic Arthritis Response Criteria; DMARDs = Disease-Modifying Anti-Rheumatic Drugs; NICE = National Institute for Health and Care Excellence; PsA = Psoriatic Arthritis; MTX = Methotrexate; CASPAR = ClASsification criteria for Psoriatic ARthritis; IMP = Investigational Medicinal Product; GOL = Golimumab; PBO = Placebo; PASDAS = Psoriatic ArthritiS Disease Activity Score; MSK = Musculoskeletal; WB-MRI = Whole Body Magnetic Resonance Imaging; US = Ultrasound Scan; IM = Intra-Muscular; IA = Intra-Articular

All procedures part of the GOLMePsA study took place at the Rheumatology Department and at the National Institute for Health Research (Leeds Biomedical Research Centre) -and associated research facilities- at Chapel Allerton Hospital, one site belonging to the LTHT, Leeds, UK. The design also adopted Participant Identification Centres (PICs), that sent referrals from within the wider Yorkshire region to increase the trial recruitment rate. No study-related procedures took place at PICs.

The GOLMePsA trial consisted of three parts: screening (week -4 to 0); interventional period (week 0 to 24) and observational period (week 24 to week 52). Therefore, study duration for participants completing all visits from screening to final assessment totalled fifty-two weeks, plus up to four additional weeks. The primary end-point time was week 24 (visit 8). Secondary endpoints were planned for visit 4 (week 8), visit 5 (week 12), visit 10 (week 36) and visit 11 (week 52, end of trial).

At screening (visit 1), candidates referred to GOLMePsA provided informed, written consent. They then underwent evaluations for eligibility. US and MRI scans scheduled by design to be performed prior to the trial intervention exposure could be carried out only during this period, as close as possible (ideally within ten days) to week 0 (the baseline, visit 2).

The key eligibility criteria (the reader can find the full eligibility criteria list in Appendix 2) were:

- PsA diagnosed no longer than twenty-four months prior to consent.
- Treatment-naïve PsA patients -where definition of treatment-naïve (see Appendix 2, exclusion criteria 1) encompassed previous interventions for PsO as well as for PsA- classified according to ClASsification criteria for Psoriatic ARthritis (CASPAR) criteria (Taylor et al., 2006).
- Presence of at least three swollen and three tender peripheral joints or two swollen and two tender peripheral joints in addition to one tender enthesis (either the distal Achilles' tendon insertion onto the calcaneus or proximal plantar fascia insertion onto the calcaneus).

The safety-related eligibility criteria reflected the standard rheumatology practice applying to prescription of MTX, steroids and bDMARDs (the reader is again referred to the list of GOLMePsA eligibility criteria available in Appendix 2). The list of procedures performed at screening is available in Appendix 3.

Eligibility was designed as a two-step process, requiring initial evaluation at the time of visit 1, followed by confirmation at the time of visit 2 and in any case prior to exposure to trial intervention. Only medically trained investigators could assess and confirm eligibility.

Only following the confirmation of each participant's eligibility at week 0 (visit 2, baseline time-point), the investigators could trigger the randomization process. The investigators filled in specifically designed randomization forms, then transmitted these documents -via internal communication- to the independently operated LTHT trial pharmacy randomization service. Patients were randomised -on a 1:1 basis- to receive combination therapy of GOL and MTX (GOLMTX, Arm 1) or MTX monotherapy and Placebo (PBO) (PBOMTX, Arm 2). Randomly permuted block sizes were used to generate the randomization schedule. Randomisation was stratified by the number of involved peripheral joints (oligoarticular: ≤4 joints involved / polyarticular: >4 joints involved). The investigators and the participants were kept blind to all the parts of the randomization process and were kept blind to the treatment allocation as well.

Randomization at week 0 (visit 2, baseline time-point) marked the beginning of the interventional period of the GOLMePsA trial and, as a result, participants could receive one of the two following interventions:

- Treatment arm 1 (GOLMTX): Immediate GOL (dose dependant on weight measurement recorded at the time of baseline) combined with MTX (starting at 15 mg weekly, then rapidly escalated to 25 mg weekly over twenty-eight days and continued unchanged until the end of the interventional period). The initial dose of GOL was 50 mg Subcutaneous injection (SC) four weekly (except for participants weighting 100 kg or more at baseline – in such instances the dose was 100mg). The GOL dose initially assigned by randomization to Arm 1 participants was not subsequently altered throughout the interventional period of the trial (week 0 to 24 – total of seven SC injections). The combination therapy described for treatment arm 1 was administered for a total duration of 24 weeks.
- Treatment arm 2 (PBOMTX): MTX (starting at 15 mg weekly with rapid escalation up to 25 mg over 4 weeks – as described above) plus PBO SC injection four weekly for 24 weeks in total (seven SC injections in total).

In the GOLMePsA trial, the Investigational Medicinal Products (IMPs) were defined as: GOL or PBO. Both were formulated as solution for injection in pre-filled syringes (these were identical in appearance for GOL or PBO). Within the planned trial treatment intervention, MTX constituted one of the two Non-Investigational Medicinal Products (NIMPs).

In addition to the randomly assigned treatment arm allocation (GOLMTX or PBOMTX), all participants received, at the baseline time-point, one "bolus" dose of methylprednisolone [120 mg Intra-Muscular (IM) or equivalent amount -via intra-articular injection- in case of oligo-articular, -that is, ≤4 swollen joints-

presentation]. Within the trial treatment intervention, methylprednisolone constituted the second of the two planned NIMPs.

Keeping into account that no GOLMePsA participant was ever exposed to systemic or DMARD treatment prior to enrolment, the aim of the composite, articulated interventions described above –that is, a combination of three drugs for Arm 1 and a combination of two drugs plus PBO for Arm 2- was to:

- Create an element of head-to-head intervention. That is, no treatment arm was designed to administer PBO in isolation. As a consequence, no participant avoided exposure to drugs deemed efficacious in the treatment of PsA.
- Achieve rapid ablation of inflammation, through energetic intervention administered since the baseline time-point.
- Provide all participants with the same level of steroid “bolus” exposure at baseline.
- Equalize exposure to MTX – rapidly escalated to the highest dose used in PsA- across treatment arms.

Moreover, both treatment arms encompassed an element of a T2T algorithm, involving further corticosteroid injections (IM or intra-articular, not exceeding the maximum amount of 120 mg methylprednisolone per participant) if not achieving a PsARC response (Clegg et al., 1996a) at weeks 8 or 12 (visits 4 and 5, respectively – both secondary end-points). The protocol did not allow further steroid injections (or courses of orally administered steroids) past week 12 and until week 24 (primary endpoint). Consequently, the maximum amount of methylprednisolone that participants (irrespective of treatment arm allocation) could be exposed to -between week 0 and week 24- was 240 mg.

As part of the planned data collection related to visit 5 (week 12, secondary end-point – all secondary outcomes), participants were evaluated for PsARC response, PASDAS (Helliwell, P.S. et al., 2013), MDA (as defined by Coates) (Coates, L.C. et al., 2010). Data needed for other relevant clinical outcomes, as well as the first of three follow-up US (again, all secondary outcomes) were performed at this time-point. Visit 6 and visit 7 (week 16 and 20, respectively) were planned as IMP administration events, not related to end-points or outcomes.

Beyond the week 12 time-point, any participants who presented unacceptable degrees of disease activity (as judged by the study physician by clinical assessment in conjunction with PsARC response), and who had not reached week 24 yet, would qualify for withdrawal from the trial intervention. Data scheduled for collection at the additional time-point planned in the event of

withdrawal encompassed the extensive set of variables (imaging included) used for primary and secondary endpoints. Following an instance of withdrawal, participants then could receive treatment for PsA as deemed necessary by the study physician [that is, according to standard National Health Service (NHS) clinical practice and National Institute of for Health and Care Excellence (NICE) guidance]. All participants who withdrew from the trial intervention were invited to continue to be observed for the rest of the study duration.

All participants reaching visit 8 (week 24, primary endpoint) were evaluated for PASDAS (primary outcome), MDA (as defined by Coates), PsARC and other relevant clinical outcomes. At this point they also underwent follow-up WB-MRI and US.

Participants assigned to treatment arm 1 (combination of methylprednisolone, GOL and MTX) –regardless of the PsARC response achieved at the time of visit 8 (week 24, primary endpoint) discontinued the IMP (GOL) as planned, at this point. They then continued MTX (25 mg weekly if tolerated) and attended three further data collection time-points (visit 9, 10 and 11 – all secondary endpoints, with the exception of visit 9) thereafter for the duration of the observational period of the study (that is, until visit 11 - week 52, end of trial). The planned endpoint for the last repetition of imaging was visit 10 (US, WB-MRI). In case of a PsA disease flare not occurring exactly at the time of the pre-specified endpoints described above, patients were invited to repeat clinical and imaging assessments (US and WB-MRI) via additional extra visit(s). Treatment for PsA during the observation period followed the UK standard clinical practice and relevant NICE guidance, at the investigators' discretion (that is, according to tolerance, or intervened toxicity or effectiveness of drugs). Observation and data collection continued for all participants until the end of the study, unless they wished to interrupt participation (instances of withdrawal of consent) or dropped out of the trial. The trial design did not schedule imaging data collection at week 52 time-point. Participants assigned to treatment arm 2 (combination of methylprednisolone, PBO and MTX) followed the same observation/data collection/treatment plan.

After the conclusion of their participation in the GOLMePsA trial, participants were all referred back to the NHS rheumatology clinics (in most cases, the original referring consultant) for standard treatment and follow-up of their PsA.

3.1.3 Planned Variables Collection within the GOLMePsA Trial

The list below offers details related to the data collection performed in the trial. At the operational level, the candidate performed all the clinical data collection

procedures and, in these tasks, he was assisted to the largest extent possible by the research nurses team attached to his institutions.

The variables are presented in full in the next three paragraphs, however, the reader will notice that some variables in the list are part of composite outcome measures. As such, these variables may not be presented in the results section of this thesis. Rather, composite outcome measures results will be reported.

3.1.3.1 General standard variables:

- Age (in years).
- Sex.
- Ethnic background.
- Height (cm), weight (kg) and Body Mass Index (BMI).
- PsA-related symptom duration (in months).
- Concomitant medications taken by participants (prior to baseline and up to end of trial, week 52).

3.1.3.2 Efficacy variables (Primary Outcome, Secondary Outcomes and Exploratory Outcomes):

- PASDAS (range 0-10).
- Tender Joint Count [TJC (range 0-68 out of 68; used in composite outcome measures)].
- Swollen Joint Count [SJC (range 0-66 out of 66; used in composite outcome measures)].
- Leeds Enthesitis Index [LEI (range 0-6)].
- Physician assessment of arthritis, Likert scale (range 1-5; used in composite outcome measures).
- Physician global assessment of PsD Visual Analogue Scale (VAS, range 0-100 mm; used in composite outcome measures).
- Leeds Dactylitis Index [LDI (range 0-~40)].
- PASI score (range 0-72).
- Modified Nail Psoriasis Severity Index [mNAPSI (range 0-140)].
- Composite Psoriatic Disease Activity Index [CPDAI (range 0-15)].
- MDA of PsA (achieved; yes/no).
- PsARC response (achieved; yes/no).
- ACR response (achieved; yes/no) – see also sections 3.2.2.13 and 3.2.2.14.
- Percentage (%) of Body Surface Area (BSA) affected by PsO.
- CRP concentration (in mg/L; used in composite outcome measures).
- US grey scale score [total range 0-72; 0-144 for OMERACT (Outcome Measures in Rheumatoid Arthritis Clinical Trials) definition subset].

- US power-Doppler (PD) score (total range 0-72; 0-144 for OMERACT definition subset).
- US Global OMERACT-EULAR (European Alliance of Associations for Rheumatology) Score System (GLOESS) score (total range 0-72; 0-144 for OMERACT definition subset).
- US number of entheses with grey scale abnormalities (range 0-10; 0-12 for OMERACT definition subset).
- US enthesis PD score (range 0-30; 0-36 for OMERACT definition subset).
- US total thickened entheses score (range 0-30; 0-36 for OMERACT definition subset).
- US total enthesis erosion score (range 0-30; 0-36 for OMERACT definition subset).
- US number of entheses with calcification (range 0-10).
- US number of entheses with enthesophytes (range 0-10).
- US enthesis inflammation score (range 0-70).
- US enthesis chronicity score (range 0-50).
- US remission (achieved; yes/no).
- Patient assessment of arthritis, Likert scale (range 1-5; used in composite outcome measures).
- Patient global assessment of disease activity VAS (range 0-100 mm; used in composite outcome measures).
- Patient articular pain assessment VAS (range 0-100 mm; used in composite outcome measures).
- Ankylosing Spondylitis Quality of Life (ASQoL) instrument (range 0-18; used in composite outcome measures).
- Bath Ankylosing Spondylitis Disease Activity Index [BASDAI (range 0-10; used in composite outcome measures)].
- Health Assessment Questionnaire Disability Index (HAQ-DI, range 0-3; used in composite outcome measures).
- Dermatology Life Quality Index [DLQI (range 0-30; used in outcome measures)].
- SF-36 mental and PCS scores (range 0-100; used in composite outcome measures).
- Cumulative dose of steroids administered between baseline time-point (week 0) and primary outcome time-point week 24 (in mg).
- Spondyloarthritis Research Consortium of Canada (SPARCC) (MRI imaging) spinal inflammation score (range 0-108).
- SPARCC (MRI imaging) sacroiliac joint inflammation score (range 0-72).
- Hip Inflammation MRI Scoring System (HIMRISS, MRI imaging) Bone Marrow Lesions (BML) score (range 0-100).

- HIMRISS (MRI imaging) effusion & synovitis score (range 0-30).
- Knee Inflammation MRI Scoring System (KIMRISS, MRI imaging) score (range 0-763).
- Canada-Denmark MRI Scoring System (CANDEN, MRI imaging) spine inflammation score (range 0-614).
- CANDEN (MRI imaging) spine fat score (range 0-510).
- CANDEN (MRI imaging) spine bone erosion score (range 0-208).
- CANDEN (MRI imaging) new bone formation score (range 0-460).
- Heel Enthesitis MRI Scoring (HEMRIS, MRI imaging) score (inflammation sum score 0-24; structural sum score 0-18).
- MRI Whole-Body Score for Inflammation in Peripheral Joints and Entheses in Inflammatory Arthritis (MRI-WIPE, MRI imaging) score (range 0-738).

3.1.3.3 Safety variables

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

Safety variables were assessed at each scheduled study visit (withdrawal and extra visits included).

3.2 Assessments Methods

3.2.1 Assessment of Primary Efficacy Variable

PASDAS is a composite outcome measure of disease activity in PsA. This index is a single score that provides quantitative measures of changes in disease activity based on baseline scores and changes from baseline (positive changes, that is higher score values, represent worsening of disease activity). The PASDAS demonstrated good performance in polyarticular as well as in oligoarticular PsA and assesses disease activity across MSK domains of PsA (peripheral arthritis, dactylitis, enthesitis).

Delivering the GOLMePsA trial, direct calculation of PASDAS at the bedside when assessing participants, proved to be unfeasible. The individual components

were assessed, to later 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 (SJC + 1)) + (0.048 x LN (TJC + 1)) + (0.23 x LN (LEI score + 1)) + (0.377 LN (Tender dactylitic digits count + 1)) + (0.102 x LN (CRP + 1)) +2)*1.5.

3.2.2 Assessment of Secondary Efficacy Variables

3.2.2.1 C-Reactive Protein

Standard CRP (in mg/L) was the selected acute phase reactant. The analysis of blood samples for CRP was performed locally at the central Pathology Laboratory within LTHT.

3.2.2.2 Tender Joint Count

The number of tender and painful peripheral joints was determined by examination of 78 joints (39 joints on each side of a participant's body). Joints were assessed for tenderness by pressure and joint manipulation, upon physical examination. The participants were asked for pain sensations on these manipulations and were watched for spontaneous pain reactions. Any positive response on pressure, movement, or both was then 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. Joints that were missing (due, for example, to amputation) or surgically replaced (inclusive of surgical arthrodesis) joints were identified by the investigator at the screening visit and excluded from evaluation for the remainder of the trial.

3.2.2.3 Swollen Joint Count

The number of swollen peripheral joints was determined by examination of 76 joints (38 joints on each side of the patient's body, coxofemural joints not encompassed). Joints were classified as either swollen or not swollen. Swelling was defined as palpable fluctuating deformity -compatible with synovitis- of the joint. Bony type swelling secondary to OA was assessed as not swollen unless there was unmistakable presence of fluctuation according to the investigator's clinical judgement. Where possible, the same assessor performed the TJC and SJC for a given patient -particularly during the interventional period of the trial- to minimize inter-observer variation. Joints that were missing (due, for example, to amputation) or surgically replaced (inclusive of surgical arthrodesis) joints were identified by the investigator at the screening visit and excluded from evaluation for the remainder of the trial.

3.2.2.4 Patient's Assessment of Pain (Visual Analogue Scale)

GOLMePsA participants provided an assessment of their current level of joint pain by marking a vertical line on a 100 mm, horizontal VAS, where 0 represented absence of joint pain ("excellent") and 100 represented the worst imaginable joint pain ("poor"). Whenever possible, the participants provided assessment of pain

VAS prior to the TJC and SJC examinations. Results were expressed in millimetres measured between the left end of the scale and the crossing point of the vertical line; this procedure applied to all other VAS used in the trial.

3.2.2.5 Patient's Global Assessment of Disease Activity (Visual Analogue Scale)

The participant's overall assessment of their PsA activity was recorded using the 100 mm, horizontal VAS where 0 at the left end represented "no disease activity" or "excellent" and 100 at the right end represented extremely active disease "poor". The wording proposed by Cauli et al (Cauli et al., 2011) referring specifically to PsA was used.

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

The Investigators provided an overall assessment of the severity of the participants' current PsA activity using a 100 mm, horizontal VAS, where 0 at the left end represented no disease activity ("Disease not active") and 100 at the right end represented extremely active disease ("Disease extremely active"). The investigator performing this assessment was a rheumatology trained and medically qualified operator. The same assessor should preferably perform the Physician's Global Assessment of Disease Activity VAS for a given participant -particularly during the interventional period of the trial- to minimize inter-observer variation.

3.2.2.7 Bath Ankylosing Spondylitis Disease Activity Index

The BASDAI is a patient reported outcome measure -a self-administered questionnaire- used to answer 6 questions (on a Likert scale ranging 0-10). These questions assess across the 5 major symptoms related to inflammatory axial disease 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 (Garrett et al., 1994). To give each symptom equal weighting, the mean of the 2 scores relating to morning stiffness (items 5 and 6 of BASDAI) is taken. The resulting 0 to 50 score is then divided by 5 to yield a final 0 to 10 BASDAI score.

3.2.2.8 Leeds Enthesitis Index

The LEI was developed specifically for use in PsA. It assesses entheseal tenderness at 6 anatomical locations (lateral epicondyle of the humerus, left and right; medial femoral condyle, left and right; Achilles' tendon distal insertion onto the calcaneus, left and right) (Healy and Helliwell, 2008). Each site is assigned a

score of 0 (tenderness absent) or 1 (tenderness present); the results from each site are then added to produce a total score (range 0 to 6). Only trained members of the research team administered the LEI.

3.2.2.9 Leeds Dactylitis Index

In participants presenting with dactylitis, investigators administered the LDI, one outcome measure developed to evaluate the severity of dactylitis. Once the presence of dactylitis was established in each relevant digit, the ratio of the circumference of the affected digit to the circumference of the digit on the opposite hand or foot was measured (Helliwell, P.S. et al., 2005). Digits presenting with a minimum increase of 10% in circumference over the contra-laterals qualified for dactylitis. If the same digits on each hand or foot were suspected to be involved (that is, without obvious circumference difference between contra-lateral digits), the clinical assessor referred to a table of normative values to provide comparison between expected normal circumference and observed ones. The calculated ratio was then multiplied by a tenderness score of 0 (non-tender); 1 (tender); 2 (tender and wince); or 3 (tender and withdraw). Tenderness was assessed in the area between the joints (proximal phalanx). The results of each digit are then added to produce a total score (Healy and Helliwell, 2007).

3.2.2.10 Health Assessment Questionnaire-Disability Index

The HAQ-DI is a patient-reported outcome measure, a standardized questionnaire commonly used in PsA (Coates, L., 2015) to measure disability that is associated to disease (assessment of physical function). It consists of twenty four questions referring to eight domains: dressing/grooming, arising, eating, walking, hygiene, reach, grip, and other daily activities (Fries et al., 1980).

The disability section of the questionnaire scored the participant'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 eight domains. The reported use of special aids or devices and/or the need for assistance from another person to perform these activities was also assessed. The scores for each of the functional domains were averaged to calculate the functional disability index.

3.2.2.11 Minimal Disease Activity

The MDA status, according to Coates et al (Coates, L.C. et al., 2010), was met when any participant fulfilled at least five of the seven following criteria:

Tender joint count ≤1; Swollen joint count ≤1; PASI ≤1 or Body Surface Area (BSA) ≤3; Patient pain VAS ≤15; Patient global disease activity VAS ≤20; HAQ ≤0.5; Enthesitis count ≤1.

3.2.2.12 Psoriatic Arthritis Response Criteria

The PsARC (Clegg et al., 1996a; Clegg et al., 1996b) is a composite outcome measure reported in terms of response (present vs absent) when participants achieved the following criteria:

1. At least 30% reduction in tender joints grading [grading of 68 joints; Carpal-MetaCarpal (CMC) joints and Distal Inter-Phalangeal (DIP) joints of the feet excluded).
2. At least 30% reduction in swollen joints grading (grading of 66 joints; CMC, hips and DIP of the feet excluded).
3. At least a one-point reduction in physician's assessment of articular disease (1-5 Likert scale).
4. At least a one-point reduction in patient's assessment of articular disease (1-5 Likert scale).

PsARC response –at any time-point of interest (comparison is set against baseline assessment)- occurs if improvement in two out of the four criteria listed above (one of which must be an evaluation of the peripheral joints; there must also not be worsening in any of the four criteria) is met.

3.2.2.13 American College of Rheumatology 20 Responder Index (ACR20)

ACR20 response (Felson et al., 1995) is an outcome measure that participants fulfilled when they presented with:

- ≥20% improvement in both TJC (68 joints count; CMC and DIP of the feet excluded) and SJC (66 joints count; CMC, hips and DIP of the feet excluded).

As well as:

- ≥20% improvement in at least three of the following five 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.

For the measurements performed in the GOLMePsA trial, reference of ACR20 was set at baseline visit (week 0, visit 2) values.

This composite outcome measure does not encompass assessment of dactylitis and entheseal tenderness. The cutaneous domains of PsD clinical spectrum are not part of the ACR20 items.

3.2.2.14 ACR50 and ACR70

ACR50 and ACR70 responses are composite outcome measures consisting of improvements occurring by a measure of at least 50% and of at least 70%, respectively, in the multiple disease assessment ACR criteria (as outlined in the ACR20 paragraph above). The ACR50 and ACR70 calculation is similar to the ACR20 response, as described above.

3.2.2.15 Composite Psoriatic Disease Activity Index

The CPDAI is a validated instrument intended to assess selected composite PsA activity and response to therapy (Mumtaz et al., 2011). 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 - CMC and DIP of the feet excluded) and swollen (66 joints count - CMC, hips and DIP of the feet excluded) joints; skin as assessed by the PASI and the DLQI; enthesitis as assessed by the number of sites affected by enthesitis; the HAQ; dactylitis as assessed by the number of digits affected; and spinal disease as assessed by the BASDAI and ASQoL (Doward et al., 2003). 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.

3.2.3 Measures of Cutaneous Disease Activity

3.2.3.1 Percentage of Body Surface Area

The investigator evaluated the percentage involvement generated by PsO on each participant’s BSA on a continuous scale from 0% = no involvement to 100% = full involvement, where 1% corresponds to the size of the participant’s handprint including the palm, fingers, and thumb.

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

If participants had skin affected by plaque PsO, the PASI was administered by trained research staff. The PASI combines assessments of the extent of body-

surface involvement in four 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 ranging from 0 (PsO absent) to 72 for the most severe disease activity (Fredriksson and Pettersson, 1978). Patients achieving PASI 75, 90, or 100 responses were defined as having an improvement of at least 75%, 90%, or 100%, respectively, in the PASI score compared to baseline values.

3.2.3.3 Modified Nail Psoriasis Severity Index

A modification to the NAPSI 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 is also scored for the presence or absence of splinter haemorrhages, leukonychia, red spots in the lunula and nail bed hyperkeratosis (score 1 for each if present). In GOLMePsA, assessments were planned to evaluate the oil drop dyschromia or discolouration as an independent feature (0-1). 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 (Cassell et al., 2007).

3.2.4 Quality of Life and Health Status Measures

3.2.4.1 Short Form 36

The SF-36 is a multi-purpose, short-form health survey with 36 questions (Hays et al., 1993). 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. SF-36 is one of the components of the PASDAS outcome measure (Helliwell, P.S. et al., 2013).

3.2.4.2 Ankylosing Spondylitis Quality of Life

The ASQoL instrument is a validated QoL scale originally developed to evaluate the effect of interventions in people affected by AxSpA (Doward et al., 2003). Although not validated yet in PsA, it is one component of the CPDAI outcome measure (Mumtaz et al., 2011). The ASQoL is an 18-item dichotomous (yes/no) questionnaire, filled by GOLMePsA participants at pre-specified time-points throughout the trial. The ASQoL score calculation is a sum of the individual items

(yes = 1; no = 0), ranging from 0 to 18 (where higher total score values reflect poorer QoL).

3.2.4.3 Dermatology Life Quality Index

The DLQI is a simple, patient administered, 10 question, validated, QoL questionnaire covering six 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 five-point change from baseline is considered clinically relevant (Basra et al., 2008). The DLQI is widely adopted in standard of care Dermatology practice to assess the impact of a number of cutaneous conditions –including PsO- and is a component of the CPDAI outcome measure (Mumtaz et al., 2011).

3.2.5 Assessment of Other Efficacy Variables

3.2.5.1 Ultrasound Scanning of Joints and Entheses

US images acquisition was performed by LTHT dedicated staff (part of the Leeds Biomedical Research Centre with the National Institute for Health and Care Research). The candidate had no role in image acquisition and scoring, in order to avoid breaches of the blind design of the GOLMePsA trial.

All GOLMePsA participants, regardless of the level of PsA clinical activity assessed by physical evaluation, underwent imaging assessment of prespecified sets of joints and entheses. US of joints of the hands and feet; of joints of lower and upper limbs and entheses (Achilles’ tendon distal insertion onto the heel; plantar fascia proximal insertion onto the heel; quadriceps muscle insertion onto patellar bone; patellar tendon proximal insertion onto patellar bone; patellar tendon distal insertion onto tibial bone and proximal insertions of the common extensor muscle tendon in the elbow region) were performed at prespecified time-points during the GOLMePsA trial. US were performed within ten days preceding or following the scheduled visit attendance, using a multi-planar technique with symmetrical scanning. Sonographers (blinded to the randomized treatment allocation) with specialist training in MSK US, as well as further specialism in entheses scanning, performed the investigations. Whenever possible, the same sonographer performed the scans, in dedicated rooms maximally darkened.

Joints and entheseal sites assessment evaluated the presence of Grey Scale (GS) abnormalities and PD signal at the individual joint level.

Scans of pre-defined joints assessed for the presence of synovitis and bone erosions as per established RA protocols, due to lack of currently validated procedures in PsA. After images acquisition and electronic storage in LTHT dedicated server, synovitis scoring was performed. These operations followed the EULAR-OMERACT definitions of synovitis grading adopted in RA (D'Agostino et al., 2017; Terslev et al., 2017) for the evaluation of severity of GS and PD at the individual joint level (ranges 0 to 3, where higher values reflected more severe GS and/or PD). In addition to this, a combined score –named PDUS- was performed for each joint (0 if GS=0, otherwise highest of either GS or PD score). The total sum of PDUS scores from individual joints compounds the GLOESS (D'Agostino et al., 2017; Terslev et al., 2017).

Assessment and identification of enthesopathy findings on US followed the OMERACT definitions (Wakefield et al., 2005; Terslev et al., 2014). Accordingly, enthesopathy is an "*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 evaluation applied the body of the tendon thickness for relative comparison. When scans detected PD signal at the cortical bone where tendons attach, such finding was considered entheseal. When PD signal was detected at the tendon body and/or adjacent bursitis, it was considered perientheseal and therefore not documented. Thickness and erosion assessments were scored quantitatively. Thickness findings scores ranged 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.

Quantitative scores of the maximum diameter of erosions were:

- Grade 1: >0 but <2mm.
- Grade 2: ≥2 but <3mm.
- Grade 3: ≥3mm.

Semi-quantitative values of entheseal PD were:

- Grade 1: Mild changes.
- Grade 2: Moderate changes.
- Grade 3: Severe changes.

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

Upon completion of scoring the individual findings, the cumulative totals were calculated to formulate and 'inflammation score' and a 'chronicity score'. Inflammation score: GS changes related to inflammation (entheseal hypoechogenicity and thickening) to be added to the PD scores. Chronicity score: GS changes related to chronic findings (calcifications, erosions and enthesophytes) were totalled.

US scores forming secondary endpoints included twenty-four bilateral joints [wrists; MetaCarpal-Phalangeal joints (MCPs) 2-3; hands Proximal Inter-Phalangeal joints (PIPs) 2-3; knees; MetaTarsal-Phalangeal joints (MTPs) 1-5; ankle] and ten bilateral entheses (distal quadriceps insertion onto patella; patellar ligament proximal insertion; patellar ligament distal insertion; Achilles' tendon distal insertion; proximal insertion of plantar fascia). Exploratory analysis of synovitis and enthesitis was performed in a subset of patients using scores calculated according to more recently published OMERACT definitions that include forty-eight bilateral joints (bilateral wrists; MCP1-5; hands PIP1-5; hands DIP2-5; knees; MTP1-5; tibiotalar; talonavicular and subtalar), in addition to twelve bilateral entheses (humeral lateral epicondyle; distal quadriceps insertion onto patella; patellar ligament proximal insertion; patellar ligament distal insertion; Achilles' tendon distal insertion; proximal insertion of plantar fascia) (D'Agostino et al., 2017; Terslev et al., 2017).

The definition of US remission was: GS (either in joints or entheseal hypoechogenicity) score <2 and PD score=0 for any of the joints forming part of the established scoring protocol, and for any of the planned entheses scanned. On an exploratory basis, the same definition was applied to scores calculated in the joints and entheses included in the OMERACT definitions, in the subset of patients with these scores available.

3.2.6 Assessment of Eligibility Variables (Radiographs of Hands and Feet)

X-ray images acquisition was performed by LTHT dedicated staff.

At screening, all patients who consented to enrolment had a single posterior anterior CR assessment of the left and right hand/wrist and a single dorsal plantar CR image taken of the left and right foot (unless these had already been performed within three months prior to GOLMePsA consent). Images were assessed by the study physician and/or radiologist for the presence of ill-defined ossification near joint margins (excluding osteophyte formation), solely for the purpose of verification of CASPAR criteria fulfilment (Taylor et al., 2006) – as per trial protocol (see Appendix 2).

3.2.7 Assessments for the Evaluation of Safety

3.2.7.1 Physical examination

A complete physical examination was performed, inclusive of general appearance; head; neck; thyroid; ears; nose; throat; cardiovascular apparatus; respiratory apparatus; abdomen; neurological apparatus; skin; MSK system (related and non-related to PsA).

3.2.7.2 Chest X-ray

X-ray images acquisition was performed by LTHT dedicated staff.

At screening, all patients meeting entry criteria received a single posterior-anterior CR of the chest, unless already performed within three months prior to consent. Images were evaluated by the study physician and/or authorized LTHT radiologist and assessed for the presence of findings compatible with trial exclusion criteria.

3.2.7.3 Electrocardiogram

Electrocardiogram acquisition was performed by LTHT dedicated staff.

At screening, participants received one standard 12-lead electrocardiogram. The study physician reviewed and signed off the tracing (the report was then stored in the participant's source documents). Tracings were evaluated by the study physician and assessed for the presence of findings compatible with exclusion criteria.

3.2.8 Assessment of Exploratory Variables

3.2.8.1 Whole-Body MRI (WB-MRI)

WB-MRI images acquisition was performed by LTHT dedicated staff (part of the Leeds Biomedical Research Centre with the National Institute for Health and Care Research). The candidate had no role in image acquisition and scoring, in order to avoid breaches of the blind design of the GOLMePsA trial.

WB-MRI scans were performed to assess for the presence of entheseal pathologies, BMO and synovial pathologies, of both the axial and peripheral skeleton, at screening (as close as possible to visit 2 and in any case before randomization and exposure to interventional drugs). Participants received follow-up scans at visit 8 (weeks 24) and at visit 10 (week 36), within ten days before or after the scheduled visit attendance.

Scans were performed using a commercially available 3 Tesla scanner. Fitness to undergo MRI scan was assessed during the screening process. Participants

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

3.2.8.1.1 MRI Sequences

Systematic scanning (Table 5) of the axial and peripheral skeleton was performed using the following sequences:

- T1-weighted Spin Echo (SE) before and after IV Gadolinium contrast injection.
- T2-weighted fat saturated.
- Short Tau Inversion Recovery (STIR).

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

Table 5 GOLMePsA Trial Magnetic Resonance Imaging Acquisition Protocol

Parts imaged	Coil	Sequence	FOV	Parameters (TR/TE/TI)	Resolution (mm)	Matrix	Slice gap	Time (mins)	Plane
Shoulders	Large flex coil	STIR	500 mm	4500/101/220	1.7x1.3x4.0	288x384 voxels	0.8 mm	5:39	Coronal
Spine (Cervical and thoracic)	Spine Coil	STIR T1	450 mm	4500/94/220 500/11	1.2x0.9x4.0 1.2x0.9x4.0	384x512 voxels	0.4 mm	3:02 3:01	Sagittal Sagittal
Spine (Thoracic and lumbar)	Spine Coil	STIR T1	450 mm	4500/94/220 500/11	1.2x0.9x4.0 1.2x0.9x4.0	384x512 voxels	0.4 mm	3:02 3:01	Sagittal Sagittal
Sacro-iliac joints	Spine coil	T2 FS T1	240 mm	4040/71 700/10	1.3x0.9x4.0 0.8x0.6x4.0	192x256 voxels 288x384 voxels	0.4 mm	3:44 2:17	Coronal oblique Coronal oblique
Hips	Body matrix	STIR	450 mm	4500/98/220	1.6x1.2x4.0	288x384 voxels	0.8 mm	5:39	Coronal
Hands	Body matrix	3D VIBE Dixon post Gadolinium	430 mm	6.36/2.45 & 3.7	0.8x0.8x0.8 (isotropic)	512x512 voxels	N/A	2:00	Coronal
Knees	Body matrix	3D VIBE Dixon post Gadolinium	404 mm	10/2.45 & 3.7	0.8x0.8x0.8 (isotropic)	304x512 voxels	N/A	3:28	Transverse axis
Feet and ankles*	Head coil	3D VIBE Dixon post Gd	420 mm	10/2.45 & 3.7	0.8x0.8x0.8 (isotropic)	384x512 voxels	N/A	3:07	Transverse axis

The “parts imaged” column lists the selected anatomical regions, in order of acquisition.
Midfoot joints acquired: all tarsal joints; all tarsal-metatarsal joints. Hindfoot joints acquired: all talar-calcaneal joints. Ankle joints acquired: tibial-talar and fibular-talar joints.
FOV = Field Of View; TR = Time to Repetition; TE = Time to Echo; TI = Time to Inversion; STIR = Short Tau Inversion Recovery; FS = Fat Saturated; VIBE = Volumetric Interpolated Breath-hold Examination; N/A = Not Applicable.

3.2.8.1.2 MRI Images Evaluation and Scoring

Professor Mikkel Østergaard and Professor Walter Maksymowych performed scoring of WB-MRI images. The candidate had no role in image scoring, in order to avoid breaches of the blind design of the GOLMePsA trial.

All MRI images produced by GOLMePsA data collection were assessed and scored using the following reading methods: SPARCC – Spinal Inflammation (Maksymowych et al., 2005a); SPARCC – Sacro-Iliac Joints Inflammation (Maksymowych et al., 2005b); HIMRISS (Maksymowych et al., 2014); KIMRISS (Jaremko et al., 2017); CANDEN MRI spine scoring system (Krabbe et al., 2019b); HEMRIS (Mathew et al., 2019); MRI-WIPE (Krabbe et al., 2019a).

Detailed descriptions of the MRI scoring methods listed above, strictly adherent to the content of the respective original publications, are available in Appendix 4.

3.3 GOLMePsA Trial Statistical Analysis

Doctor Elizabeth MA Hensor was tasked with the statistical analysis of the GOLMePsA trial. The candidate did contribute to several elements of the statistical analysis plan (including amendments); however, he did not directly analyse the main trial data in order to preserve the blind design of the trial. The candidate had a main role in data and results interpretation alongside Professor Helena Marzo-Ortega.

On a similar note, the data management of the GOLMePsA trial was tasked with dedicated LTHT staff. A notable role in these activities was performed by Doctor Onorina Guerra. The candidate had a prominent role in producing the data management plan (and related amendments). He also coordinated and performed many tasks in the data management activities (including the production of data capturing systems, case report forms, management of data queries and data cleaning).

3.3.1 Sample Size Determination

Using in-house unpublished data, it was estimated that the minimum clinically important difference would be 0.7 units on the PASDAS. This estimate is similar to a published value for smallest detectable difference of 0.8 units (Helliwell, P.S. et al., 2014). The aim of the GOLMePsA trial analysis was to detect a difference of at least 1 unit between the two treatment arms. The SD of PASDAS in the TICOPA MTX rapid escalation arm (Coates, L.C. et al., 2015; Coates, L.C. and Helliwell, 2016b) at 24 weeks (restricted to patients who remained on MTX throughout) was 1.57. Assuming $\delta=1$, $\sigma=1.57$, at alpha=0.05 and 1-Beta=0.8, the

sample size calculation exercise produced the enrolment target of 78 patients (39/treatment arm). Originally, the sample size for the GOLMePsA trial was adjusted to account for 10% drop-out, requiring a total of 88 (44 per group). However, because recruitment proved to be slower than anticipated -in part due to the Severe Acute Respiratory Syndrome CoronaVirus 2 (SARS-CoV-2) pandemic- drop-out was reassessed once 76 participants had the opportunity to reach the primary endpoint. Only 4 (5%) withdrew from follow-up prior to that point. Therefore, the total required sample size was revised down to 84 (42 per treatment arm) - 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 treatment group should be included (Whitehead et al., 2016). The GOLMePsA trial research staff aimed at recruiting patients into the WB-MRI subset until there were at least 30 patients (15 per group) with scans available at both baseline and week 24, at which point WB-MRI ceased to be performed in the remaining patients (explanation provided in the results chapter, paragraph 4.1.3.2).

3.3.2 Methods for Withdrawals, Missing Data, and Outliers

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

Visits which fell outside ±14 days of the scheduled date were considered missing for analysis purposes.

For participants who withdrew early, in the primary analysis data from the withdrawal visit were imputed for subsequent visits for continuous outcomes, and non-response were imputed for binary outcomes.

Multiple imputation by chained equations was used to address the remainder of the missing data for primary and secondary outcomes. The number of imputed datasets was determined by the Monte Carlo (MC) error rate of the resulting combined estimates. A minimum of 20 datasets was imputed; where MC errors calculated for the coefficient and standard error for the treatment group term were more than 10% of the estimated standard error, the number of imputations were increased in increments of 5 until the MC error was <10% of the standard error. Continuous interval, count or ordinal outcomes were imputed using predictive mean matching to 10 nearest neighbours; categorical outcomes were 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) were computed passively following imputation of the underlying score or components, provided that the sample size was sufficient for the imputation models to converge. If the number of parameters

to be estimated exceeded the number of patients, these variables were directly imputed.

All imputation models included: 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 was missing. Only values from the main primary and secondary endpoints (12, 24, 36, 52 weeks) were included in imputation models. If imputation models continued to fail, mixed modelling were explored as an alternative.

Sensitivity analyses relating to missing data included: 1) restricting analysis of the data to the observed values only; and 2) 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.

Outliers, defined as values lying more than three times the inter-quartile range from the nearest quartile, were identified during the blind data review. Those confirmed to be due to data entry errors were corrected in the database. In all other cases outliers were included in the main analysis, though sensitivity analyses were performed to assess whether the exclusion of these data points would affect study conclusions. The same approach was 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 exceeded an absolute value of 2.5).

Analysis of exploratory WB-MRI outcomes was performed on data of the available cases only.

3.3.3 Data Transformations

Data transformations was used with the exception of transformations required for calculation of composite measures; any severely skewed variables were compared between groups using non-parametric quantile regression.

3.3.4 Planned Subgroups, Interactions, and Covariates

All analyses controlled for the stratification factor and baseline values of the outcome. Where the aim was to relate clinical or imaging responses to baseline joint counts or to symptom duration, these variables were added to the relevant models as covariates after the initial estimate of the treatment effect was obtained. Interactions between each variable and treatment were assessed and considered substantive if found to be significant at the 10% level. Planned

exploratory subgroup analyses investigated differences in treatment response at week 24 according to oligo/polyarthritis status and symptom duration at baseline. The total amount of steroids received by week 12, as a post-randomisation variable, was not adjusted for in the analysis but was instead compared between groups.

3.3.5 Statistical Considerations on Study Participants

3.3.5.1 Disposition of Participants and Withdrawals

All participants who provided informed consent had to be accounted for in the GOLMePsA study. The frequency and percentage of participants in each treatment arm, the study withdrawals, subgroups, and major protocol violations had also to be presented. As per standard in clinical trial reporting (Begg et al., 1996), the following elements of disposition will be presented (the reader could find the extensive reported totals in the results chapter, Figure 10):

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

3.3.5.2 Protocol Violations and Deviations

The following were considered major protocol violations and patients meeting any of the criteria listed below were excluded from the per-protocol set. Decisions as to which patients met these criteria were 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 (that is, persons included in the trial in error):
    - Inclusion:
        - Patients with a diagnosis of PsA as per the CASPAR criteria confirmed up to 24 months prior to screening.
        - Patients 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.

        - Patients who, at the time of screening and baseline, were treatment naïve to DMARDs.
    - Exclusion:
        - Patients who received previous treatment with any DMARDs at therapeutic dose.
        - Patients who received previous treatment with GOL or other TNFi or other biologic drugs.
        - Any chronic inflammatory arthritis diagnosed before the age of 16 years.
        - Patients who had received any systemic/intraarticular corticosteroids within 4 weeks prior to screening. Topical preparations with steroids for cutaneous use, or inhalers for the treatment of asthma were not considered systemic/intra-articular corticosteroids.
- Patients who missed >20% or 2 or more consecutive doses of GOL.
- Patients whose MTX 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 the steroid bolus at baseline).
- Patients who attended more than one study visit (up to week 24) outside the pre-specified seven-day window.
- Patients who withdrew from study treatment for any reason.
- Patients without primary endpoint data available.

3.3.6 Demographics and Other Baseline Characteristics

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

3.3.6.1 Demographics

Age, sex and ethnicity were reported. Descriptive data were presented as appropriate to the data type, mean and SD for age, absolute and relative frequencies for sex and ethnicity.

3.3.6.2 Baseline and Screening Conditions

3.3.6.2.1 Baseline Medical History

The following were 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).

3.3.6.2.2 Baseline Physical Exam

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

- BMI (kg/m2).
- Abnormalities:
    - Cardiovascular.
    - Respiratory.
    - Abdomen.
    - Neurological.
    - Dermatological.

3.3.6.2.3 PsA Specific Baseline and Screening History

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

- Percentage of body surface area affected by PsO (%).
- PASI score.
- mNAPSI.
- CPDAI.
- PASDAS.
- LEI.
- Imaging scores.
- Patient VAS global disease activity.
- DLQI score.
- SF-36 PCS.
- SF-36 Mental Component Score (MCS).

3.3.6.3 Measurement of Treatment Compliance

A participant was considered overall compliant for each study period if they missed no more than 20% of the expected doses and not missing 2 consecutive doses of IMP. GOL was directly administered by the study team and was fully reported; MTX compliance was monitored verbally at each visit.

3.3.7 Efficacy Analyses

3.3.7.1 Primary Efficacy Variable Analysis

The primary endpoint was assessed in the full analysis set, with participants assigned to the study arms to which they were originally randomised to (intention-to-treat analysis). Full descriptive data was provided for the PASDAS score at week 24. Unadjusted and adjusted estimates of the treatment effect were obtained; the unadjusted estimate was considered supplementary to the primary adjusted estimate. The difference between treatment group means was presented alongside the related 95% Confidence Interval (CI) around the difference. Analysis of covariance by multiple linear regression was used to compare PASDAS between the two treatment groups at week 24, controlling for the values at baseline, as well as whether the participants presented clinical polyarthritis status at baseline (stratification factor). In the primary analysis the actual stratification status was used. In a sensitivity analysis the stratification status used at randomisation (irrespective of actual status) was used if this differed from the actual status. If visual inspection of model residuals indicated that the data violated the assumptions of linear regression, heteroscedasticity-robust standard errors were specified.

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

H0: $\mu 1 = \mu 2$

The alternative hypothesis was:

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

Where $\mu 1$ and $\mu 2$ represent the covariate-adjusted average in treatment arm 1 and treatment arm 2, respectively.

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

3.3.7.2 Secondary Efficacy Variable Analysis

Full descriptive data were provided for all secondary endpoints. Adjusted estimates of effect size were provided for binary secondary endpoints using multiple binary logistic regression and odds ratios with 95% CIs were presented. This applied to MDA, PsARC response, ACR 20/50/70, PASI75, US remission, steroid therapy required up to week 12 (Y/N).

The analysis of continuous interval outcomes used the technique multiple linear regression; differences between treatment group means and 95% CIs were

presented. This applied to PASDAS, CPDAI, patient global VAS, SF36 PCS and MCS, US outcomes.

Count outcomes were analysed using an appropriate generalised linear model (see Table 6); incident rate ratios and 95% CIs were presented. If negative binomial regression was used, the mean dispersion parameter was applied. In the case of missing scores for individual digits, the exposure was amended to indicate the number of digits/entheses assessed. This applied to the LEI, the LDI and the mNAPSI.

Severely skewed outcomes for which an appropriate generalised linear model could not be identified were analysed using quantile (median) regression; differences between medians and 95% CIs were presented. If the median was 0 in both groups, then alternative point of comparison was attempted in the following sequence until model convergence was achieved (75th percentile, 90th percentile, 95th percentile). This applied to PASI and to DLQI.

All analyses were controlled for the stratification factor and baseline values of the outcome where relevant. Two-sided significance at $p<0.05$ was the criterion applied to all secondary outcomes. In case the primary outcome analyses did not produce statistically significant results, then all secondary outcomes would be downgraded and considered exploratory.

Table 6: Models Used for Analysis of Secondary Outcomes

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

The appropriateness of these models was determined following initial blind review of the data. In the event that, once allocation was known, the specified model failed to converge, an alternative model was used.

If multiple imputation models failed to converge due to the level of attrition and/or the complexity of the models relative to the number of participants, mixed modelling was explored as an alternative. For each outcome, a mixed effects model was specified, mirroring the planned generalised linear or logistic model specified above. The mixed models included 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 were included. In the primary analysis, an interaction between treatment group and time was specified. For planned subgroup analyses, a three-way interaction was specified between treatment group, time, and oligo/polyarthritis status or symptom duration at baseline. The covariate-adjusted treatment effect was estimated at each visit via marginal means.

3.3.7.3 Other Efficacy Variable Analyses

A number of sensitivity analyses was conducted. In addition to sensitivity analyses relating to missing data or outliers (see section 3.3.2) and stratification status (see section 3.3.7.1), a per-protocol analysis was performed, repeating the primary endpoint analysis in the per-protocol set. In addition, comparisons were made between PsARC response status calculated using the 68/66 tender/swollen assessments originally specified by the criteria and response status calculated using the extended 78/76 joint assessments. The McNemar's test was used to compare response status according to the reduced and expanded joint assessments sets. This analysis was performed in the observed data (i.e.: without imputation).

In a subset of patients, total synovitis and enthesitis scores calculated in expanded sets of joints defined in the more recently published OMERACT definitions were compared between groups according to the same methods as for secondary outcomes. This analysis was conducted in the subset of participants for whom the expanded joint scores were collected at screening. In addition, for patients in the WB-MRI subset, the WB-MRI lesion scores were compared between groups on an exploratory basis using the same methods as for secondary outcomes. However, the focus was on quantifying the potential treatment effect. A range of CIs (75%, 85%, 95%) around the difference between the treatment arms was calculated, to indicate the level of confidence with which it could be said that there was potential for a substantive difference between groups.

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

Pearson's product-moment correlation or Spearman's rank correlation, according to data type, were used to quantify the extent of association between TJC, SJC and total PDUS (US GLOESS) at screening. In specific joints for which both clinical examination and US were performed, sensitivity and specificity of tenderness, swelling and both tenderness and swelling for detecting joints scoring more than GS<2 and PD=0 were calculated, together with associated 95% CIs 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, was performed on 24-week MDA versus 24-week US remission.

3.3.7.4 Additional Unplanned Analysis

After breaking the blind, the candidate requested other members of the GOLMePsA research team (specifically, the trial statistician and the chief investigator) to perform further unplanned analysis. Namely, it was decided to report additional data on PASDAS status and response variables that were published since the inception of the trial (Helliwell, P.S. et al., 2014; Coates, L.C. and Helliwell, 2016a; Mulder et al., 2022). These were PASDAS very low disease activity, PASDAS moderate or good response, and PASDAS meaningful change value for improvement achieved (Y/N). These were analysed according to the same methods indicated for the binary response variables (i.e.: adjusted estimates of effect size were provided for binary secondary endpoints using multiple binary logistic regression; odds ratios and 95% CIs were presented). All analyses controlled for the stratification factor and baseline values of the outcome where relevant. Two-sided significance at $p<0.05$ was the criterion applied to indicate potential differences between treatment arms; however, as these comparisons were unplanned, they were considered exploratory.

In addition to these unplanned additional endpoints, unplanned additional descriptive summaries of total US-GS and US-PD were 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 tender dactylitis count and 'any' dactylitis count were presented to give further context to the LDI results, which only counted tender dactylitis.

3.4 PASDAS Score Test-Retest Methods

Historically, outcome measures in PsA trials focused on the articular manifestations of disease, with a recent emphasis in composite tools. The PASDAS is a composite measure with defined cut-offs levels indicative of disease severity (Helliwell, P.S. et al., 2014) and excellent responsiveness when compared with other PsA-specific and non-specific composite measures. Although PASDAS is one of the recommended GRAPPA measures for research trials (Tillett et al., 2021a), data on its test-retest reliability are limited particularly in PsA of short disease duration.

Aims and Objectives - To assess the test-retest reliability of the PASDAS composite index in a cohort of early, untreated PsA patients.

Sample Size Determination - To estimate the Intra-Class Correlation Coefficient (ICC) between two repeated readings -and prior to treatment exposure- (maximum 4 weeks apart, by protocol) of the PASDAS composite index with a CI of width 0.2, 31 patients -assuming that the ICC is 0.85- would be needed. For the patient's global assessment of disease activity VAS, which provides the greatest loading on the PASDAS score, ICC = 0.87 (Helliwell, P.S. and Kavanaugh, 2014). This analysis element was added in an amendment to the GOLMePsA research protocol posterior to recruitment inception. Data were collected from a subset of participants recruited to the GOLMePsA clinical trial, after the protocol amendment enabled additional data collection at the screening visit. Therefore, data were not available for all participants recruited. The aim was to obtain data from at least 31 patients.

Statistical analysis - An assessment of the test-retest reliability of the PASDAS was performed, by calculating the $ICC_{(3,1)}$ between PASDAS measurements collected at screening and at baseline (maximum 4 weeks apart, by protocol); a 95% CI was constructed.

3.5 Psoriatic Arthritis Remission Methods

3.5.1 Definitions of Novel Remission Sets

As discussed in chapter 1 (paragraphs 1.2.5 and 1.3.4), there is no consensus definition on remission in PsA (covering neither the early stage or the established disease stage). Many limitations were highlighted in that part of this thesis, above all the lack of scope of currently used outcome measures.

Therefore, for the purposes of this thesis, novel sets of remission criteria for PsA were needed. Domains relevant to estimate disease activity '*tout court*' –either

related to joints, or to extra-articular MSK manifestations or to skin or to PROMs or to imaging- were chosen, in order to generate remission criteria sets that would assess disease activity across different domains simultaneously and to the largest extent possible. Taking into account international guidance on relevant domain in research on PsA disease (Orbai et al., 2017) and reviewing past proposals available in the literature (Cantini et al., 2012; Mease and Coates, 2018; Alharbi et al., 2020), the newly generated remission criteria for PsA used in this thesis are listed in Table 7. In total, three sets were generated. Set A (composed by eleven items, remission fulfilled if 11/11 items met) encompasses clinical MSK domains of PsA (articular and extra-articular) as well as PROMs. Set B (composed by thirteen items, remission fulfilled if 13/13 items met) expands the items of set A adding skin and nail disease domains. Set C (composed by fifteen items, remission fulfilled if 15/15 items met) further expands the domains items, including evaluation of inflammatory burden by advanced imaging techniques.

Table 7 New Proposed Remission Criteria for PsA

Remission item	Item category	Item definition	Set A	Set B	Set C
Fatigue	PROM	Q1 BASDAI ≤1	YES	YES	YES
Articular pain (peripheral joints)	PROM	VAS pain ≤10 mm	YES	YES	YES
Articular morning stiffness (peripheral joints)	PROM	≤15 minutes	YES	YES	YES
Patient's global assessment of disease activity	PROM	VAS Global ≤10 mm	YES	YES	YES
Patient's assessment of spinal symptoms	PROM	Q2 BASDAI ≤1	YES	YES	YES
Physician's global assessment of disease activity	Clinician's evaluation	PhVAS Global = 0 mm	YES	YES	YES
C-reactive protein	Laboratory Test	≤5 mg/L	YES	YES	YES
Tender joint count (TJC)	Clinician's evaluation	TJC = 0/78	YES	YES	YES
Swollen joint count (SJC)	Clinician's evaluation	SJC = 0/76	YES	YES	YES
Dactylitis	Clinician's evaluation	Dactylitic digits count = 0/20	YES	YES	YES
Enthesitis (1)	Clinician's evaluation	LEI = 0/6	YES	YES	YES
Skin psoriasis	Clinician's evaluation	PASI score = 0	NO	YES	YES
Psoriatic nail dystrophy	Clinician's evaluation	mNAPSI = 0	NO	YES	YES
Ultrasound Scan (US)	Imaging	US Score = Remission (2)	NO	NO	YES
Magnetic Resonance Imaging (MRI)	Imaging	MRI scored 0 (3)	NO	NO	YES

DEFINITIONS OF REMISSION ACCORDING TO EACH SET

Set A (basic)- Remission state achieved if 11/11 items were met (YES); Set B (extended to skin domains)- Remission state achieved if 13/13 items were met (YES); Set C (global, inclusive of imaging)- Remission state achieved if 15/15 items were met (YES).

NOTES: (1) As assessed by Leeds Enthesitis Index; (2) Definition of US remission as per GOLMePsA Statistical Analysis Plan; (3) Definition of MRI remission: MRI-WIPE score = 0 plus SPARCC sacroiliac joints score = 0 plus SPARCC spine score or CANDEN BMO score = 0.

ABBREVIATIONS NOT EXPLAINED IN TABLE: PROM = Patient Reported Outcome Measure; Q1 = Question 1; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; VAS = Visual Analogue Scale; Q2 = Question 2; PhVAS = Physician's VAS; LEI = Leeds Enthesitis Index; PASI = Psoriasis Area and Severity Index; mNAPSI = modified Nail Psoriasis Severity Index. MRI- WIPE = MRI Whole-Body Score for Inflammation in Peripheral Joints and Entheses in Inflammatory Arthritis; SPARCC = Canadian Spondyloarthritis Research Consortium; CANDEN = Canada-Denmark MRI scoring system; BMO = Bone Marrow Oedema.

All sets proposed cover multiple domains relevant to PsA disease and to PsD. No calculation coefficients are linked to any single item and no formulas are thereby required. GOLMePsA participants fulfilled remission status if all relevant criteria by set were satisfied.

3.5.2 Early Psoriatic Arthritis Remission – Statistical Analysis

This analysis is one of the major focuses of this thesis. However, the reader is invited to consider that all data were extracted from the GOLMePsA programme. Particular attention should be given to the fact that the primary endpoint of the trial does not coincide with the analysis carried out for this thesis. Specifically, the statistical work on remission in early PsA performed by the candidate was an unplanned, post-hoc analysis of the GOLMePsA programme. As such, it has to be considered exploratory and it would be appropriate to mention that statistical analysis on early PsA remission is not part of the approved statistical analysis plan of the GOLMePsA trial.

This candidate, however, faced interesting considerations when setting up the statistical methodology that underpins this thesis. Namely, against the background of relative novelty of the matter of remission in PsD -an outcome per se uncommonly chosen as primary measure in earlier studies- the review of the medical literature (summarized in section 1.5) offered more obstacles than hard data when the candidate looked for a rational basis for the sample size calculations. There is considerable heterogeneity occurring across different clinical trials, the most relevant factors compounding it being made by participants recruitment (especially the duration of PsD they experienced prior to consent), as well as previous exposure to medications (either for the purposes of treating PsA or PsO-related manifestations), or the choice of outcome measures selected in clinical trials of PsA/PsD.

Ideally, outcomes from the SEAM-PsA trial (Mease et al., 2019b) -specifically, those related to the treatment arm comprising MTX and etanercept given to treatment-naïve participants- would be ideal to set up the sample size calculations specific for the purposes of this thesis. Unfortunately, informal requests to the SEAM-PsA trial authors did not lead to the provision of the data of interest.

In the remission study by Cantini and colleagues (Cantini et al., 2008), 24.1% of PsA patients achieved remission at least once. A sample size calculation exercise based on this estimate of remission following treatment and on the figure of 1.5% provided by Theander and colleagues about spontaneous remission in absence of treatment (Theander et al., 2014), at alpha=0.05 and 1-Beta=0.8, would yield a result of 66 persons as enrolment target. However, it is important to underline

that Cantini and colleagues presented remission results only on PsA cases requiring second-line drugs (that is, participants described in their cohort failed to respond to anti-inflammatories and local infiltrative therapies). Further, Treatments in their cohort were miscellaneous, including MTX, ciclosporin and TNFi agents administered according to the opinion of the treating clinicians (and not according to a pre-specified treatment protocol). Lastly, remission was defined by Cantini without taking into account axial manifestations of PsA or skin-related domains of the PsD clinical spectrum.

To provide an alternative estimate using a different outcome measure, the prevalence of remission in PsA was derived from one post-hoc analysis performed on trials of ixekizumab in PsA (Coates, L.C. et al., 2022a). In this study, up to 12% of participants (biologic-naïve) achieved PASDAS very low disease activity after exposure to ixekizumab. Therefore, assuming the prevalence of remission was 12% in participants exposed to treatment and 1% in participants on placebo at alpha=0.05 and 1-Beta=0.8, the sample size calculation exercise would yield 156 persons.

Being the statistical analysis presented in this thesis a post-hoc one, none of the estimates mentioned above could have influenced the original sample size calculation used when planning the GOLMePsA trial and the resulting enrolment target (paragraph 3.3.1).

Full descriptive data (contingency tables) of remission occurrence among GOLMePsA participants are provided in the results chapter, without adjustment for baseline covariates. The three remission sets (A, B, C) defined above (Table 7) were applied to the GOLMePsA dataset (observed data, no imputation), as well as Coates VLDA criteria (Coates, L.C. and Helliwell, 2016a), PASDAS near remission criteria and CPDAI remission (Helliwell, P.S. et al., 2014; Coates, L.C. and Helliwell, 2016a; Mulder et al., 2022).

To test the difference in occurrence of remission in the two treatment arms of the GOLMePsA trial, the Fisher’s exact test was used.

Chapter 4

This chapter presents the data collected from the GOLMePsA trial and the related analysis. It also offers the results of the work on the reliability exercise performed on the PASDAS composite outcome measure, as well as the work performed by the candidate on remission in early PsA – a post-hoc analysis of the GOLMePsA data.

4.1 Results

4.1.1 GOLMePsA Trial Recruitment Activities

Recruitment activities began on late October 2015, following notification of the authorization to start by the trial sponsor, LTHT (the reader is referred to paragraph 3.1.1).

Overall, recruitment spanned between October 2015 and February 2022 (total of 75 months) – as presented in Figure 9. Two-hundred-nineteen referrals were received over that period, mainly from the Leeds area (49/219 persons -22.4%- were referred from the PICs located in the wider Yorkshire region). The most relevant factor that determined the considerable length of the recruitment period was reluctance to join the trial, as 66/219 (30.1%) candidates declined participation (only 35 persons –or 16% of the candidates- did not fulfil eligibility assessment prior to consent stage). Other substantial factors contributing to the lengthy enrolment time were: one period of recruitment suspension mandated by the trial sponsor (LTHT) between March 2018 and April 2019 [requested following sponsor audit activity aimed at implementing International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidance updates across its research portfolio, in anticipation of one MHRA inspection planned for late 2018]; and the SARS-CoV2 pandemic (30 January 2020 – 5 May 2023). These two major factors, however, only partially influenced the rate of referral or -more intriguingly when related to the pandemic event- the rate of declined participation by candidates referred for enrolment consideration.

A total of 84 participants were enrolled, meeting the revised recruitment target of the GOLMePsA trial (section 3.3.1). Overall, screening procedures were performed in 106 individuals (rate of successful recruitment: 84/106 - 79.2%). Among screening failures, no clear lack-of-eligibility pattern emerged.

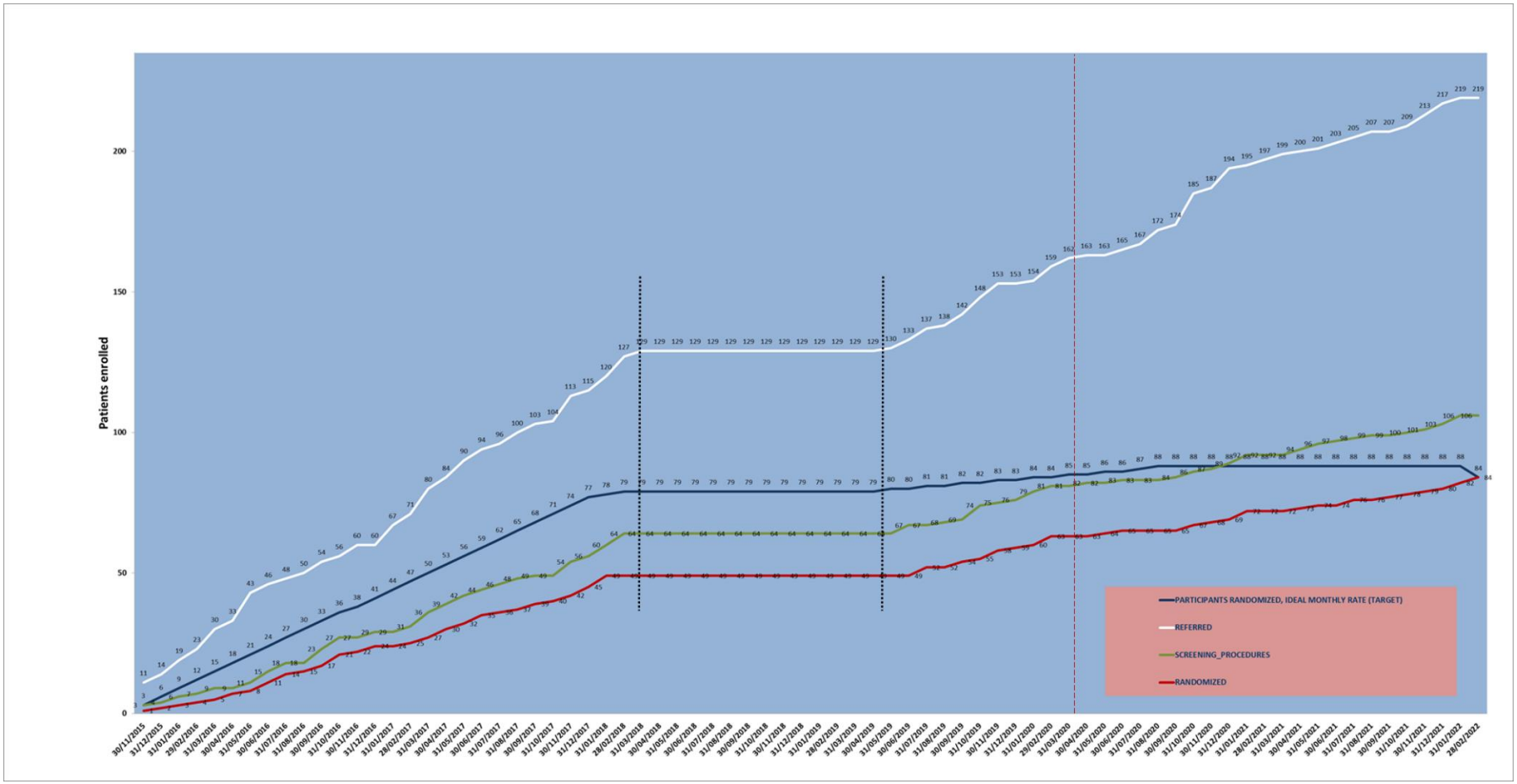

Figure 9 GOLMePsA Trial, Enrolment Diagram

The period between the two black dotted lines represents the sponsor-mandated pause in recruitment (March 2018 to April 2019). The red, dashed line marks the start of SARS-CoV2 Pandemic lockdown in the UK (which in addition caused one temporary sponsor-mandated pause in recruitment).

4.1.2 GOLMePsA Trial Clinical Results

4.1.2.1 Participants' Disposition

As mentioned in chapter 3 (paragraph 3.3.5.1), The GOLMePsA trial statistical plan mandated that all participants who had provided written informed consent had to be accounted in full – in order to adhere to reporting standards (Begg et al., 1996).

The diagram depicted in Figure 10 represents the participants' flow during their time in the trial. Of note, the retention rate throughout the trial (that is, until week 52) was high -that is, 77/84, or 91.7% of recruited patients- and above the originally hypothesized drop-out rate.

Four participants withdrew from treatment (before week 24), 3 in the GOLMTX (Arm 1) group and 1 in the PBOMTX (Arm 2) group. Reasons for withdrawal were inadequate compliance to the intervention (3 cases overall, 2 in Arm 1); and one instance of suspected neurological adverse reaction (in Arm 1).

In addition to the four participants who were withdrawn, 3 more persons were associated with major protocol deviations [2 received more than one Non-Steroidal Anti-Inflammatory Drug (NSAID) at a time, 1 attended more than one visit out of window before the measurement of the primary endpoint of 24 weeks]. All three of these participants were allocated to Arm 1.

As a result, the per-protocol-set of participants recorded at the time-point of primary endpoint (week 24) was 77 persons (37 allocated to Arm 1 and 40 allocated to Arm 2).

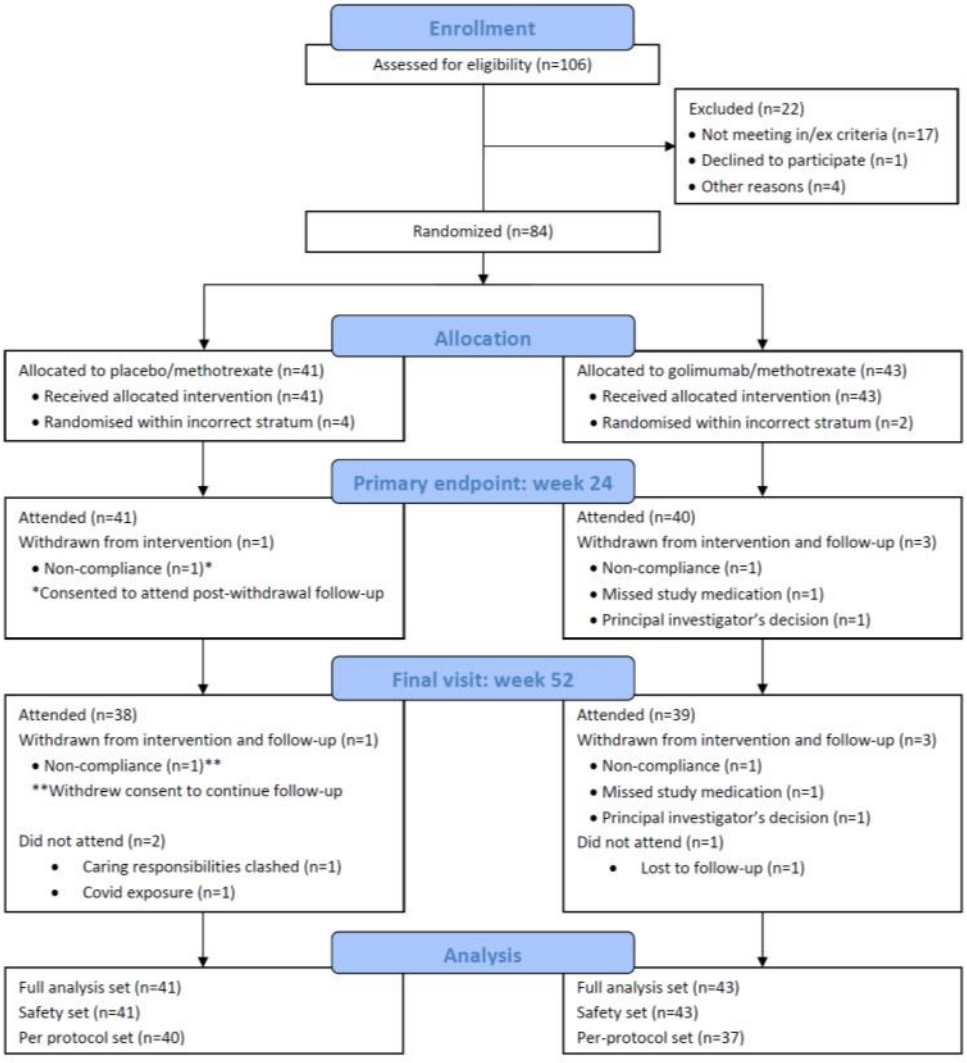

Figure 10 GOLMePsA Trial Participants' Disposition

This diagram is the CONSORT (Begg et al., 1996) flow of the GOLMePsA trial. It summarizes screening, treatment allocation and rates of attendance from visit 1 (consent) through week 0 (visit 2, baseline; the time-point of randomization) to week 52 (end of trial). Allocation to golimumab/methotrexate was Arm 1 (GOLMTX); placebo/methotrexate was arm 2 (PBOMTX). In/ex criteria = inclusion criteria / exclusion criteria.

Six participants (Arm 1 n=4; Arm 2 n=2) were randomised within the incorrect stratum - that is, the randomisation process assigned them within the oligoarthritis list when they in fact presented with clinical polyarthritis (three occurrences) or vice versa (another three occurrences). As a result, this issue needed discussion between the investigators and the trial statistician. In their opinion, the matter did not warrant exclusion from the per-protocol population. In an update to the statistical analysis plan of the GOLMePsA trial, it was pre-specified that the main analysis of the primary endpoint would adjust for the actual stratification status of these participants, whilst a sensitivity analysis would repeat this adjustment for the status used during randomisation (the reader can refer to section 3.3.2).

4.1.2.2 Demographic and Other Baseline Characteristics

Table 8 summarizes the participants' demographics as recorded before the inception of exposure to the trial intervention. The variables are presented by treatment allocation (Arm 1, GOLMTX; Arm 2, PBOMTX) and in total. Smoking status is presented at the bottom of the table.

Overall, the variables presented in this section were well balanced across the treatment arms. Interestingly, all participants reporting a family history of AS were assigned to Arm 2, whilst a greater proportion of participants in Arm 1 reported a family history of PsA (19% vs 7%).

Considerable amounts of participants were smokers –or had quit smoking- at the time of data collection.

Table 8 GOLMePsA Trial - Demographic and Other Baseline Characteristics

Variable	Allocation		
	Arm 1 GOLMTX (N=43)	Arm 2 PBOMTX (N=41)	Total N=84
Age, in years	42.1 (12.5)	42.9 (12.5)	42.5 (12.4)
	23.0 to 73.0, n=43	18.0 to 65.0, n=41	18.0 to 73.0, n=84
Sex			
Male	24 (55.8%)	22 (53.7%)	46 (54.8%)
Female	19 (44.2%)	19 (46.3%)	38 (45.2%)
Ethnicity group			
White	29 (67.4%)	32 (78.0%)	61 (72.6%)
Asian	3 (7.0%)	2 (4.9%)	5 (6.0%)
Other	1 (2.3%)	1 (2.4%)	2 (2.4%)
Not stated	10 (23.3%)	6 (14.6%)	16 (19.0%)
Family history of RA			
No	32 (74.4%)	28 (68.3%)	60 (71.4%)
Yes	10 (23.3%)	13 (31.7%)	23 (27.4%)
Not Known	1 (2.3%)	0 (0.0%)	1 (1.2%)
Family history of AS			
No	42 (97.7%)	36 (87.8%)	78 (92.9%)
Yes	0 (0.0%)	4 (9.8%)	4 (4.8%)
Not Known	1 (2.3%)	1 (2.4%)	2 (2.4%)
Family history of PsO			
No	24 (55.8%)	19 (46.3%)	43 (51.2%)
Yes	18 (41.9%)	22 (53.7%)	40 (47.6%)
Not Known	1 (2.3%)	0 (0.0%)	1 (1.2%)
Family history of PsA			
No	34 (79.1%)	37 (90.2%)	71 (84.5%)
Yes	8 (18.6%)	3 (7.3%)	11 (13.1%)
Not Known	1 (2.3%)	1 (2.4%)	2 (2.4%)
Family history of IBD			
No	40 (93.0%)	35 (85.4%)	75 (89.3%)
Yes	2 (4.7%)	5 (12.2%)	7 (8.3%)
Not Known	1 (2.3%)	1 (2.4%)	2 (2.4%)
Family history of CVD			
No	24 (55.8%)	26 (63.4%)	50 (59.5%)
Yes	18 (41.9%)	14 (34.1%)	32 (38.1%)
Not Known	1 (2.3%)	1 (2.4%)	2 (2.4%)
Smoker status			
Current	11 (25.6%)	5 (12.2%)	16 (19.0%)
Previous	14 (32.6%)	11 (26.8%)	25 (29.8%)
Never	18 (41.9%)	25 (61.0%)	43 (51.2%)
Pack years smoking	1.0 (IQR 0.0, 7.5)	0.0 (IQR 0.0, 2.4)	0.0 (IQR 0.0, 5.6)
	0.0 to 41.2, n=41	0.0 to 38.0, n=41	0.0 to 41.2, n=82

Categorical variables presented as n (%); continuous variables presented as Mean (Standard Deviation, SD) or Median (Inter-Quartile Range, IQR; first quartile to third quartile range); absolute range, n.

GOLMTX = combination of golimumab and methotrexate; PBOMTX = combination of placebo and methotrexate; RA = Rheumatoid Arthritis; AS = Ankylosing Spondylitis; PsO = Psoriasis; PsA = Psoriatic Arthritis; IBD = Inflammatory Bowel Diseases; CVD = Cardio-Vascular Diseases.

4.1.2.3 Variables Related to Disease Severity and Composite Outcome Measures at Baseline

Physical observations and clinical features indicative of PsD activity –either articular, extra-articular or cutaneous- as collected at the time of baseline, are listed in Table 9. The variables are presented by treatment allocation (Arm 1, GOLMTX; Arm 2, PBOMTX) and in total.

Participants who were overweight represented a considerable proportion of recruits (15/84; 17.9%) in the GOLMePsA trial, as reflected by the mean BMI.

Most of the cases enrolled experienced the onset of PsA-related symptoms within twenty-one months prior to enrolment. It is interesting to note the recorded prevalence of cases of polyarthritis (that is, ≥4 joints considered affected by clinically active PsA in the opinion of the assessors) at baseline: 61/84 (72.6%) recruits.

Arguably, the levels of PsA severity among the persons successfully enrolled could be in connection with the proportion of candidates who declined participation in the trial prior to consent. Assuming that the proportion of polyarthritis were similar in the candidates who declined participation in GOLMePsA, it could be hypothesized that persons more severely affected by PsA would also be more reluctant in taking part in the clinical trial. It is unfortunate to report that, due to a combination of regulations and trial design (candidates who declined participation had not -by definition- signed the informed consent), it was not possible to perform statistical tests – aiming at exploring this matter further.

However, the observation of a large prevalence of polyarthritis hints to selection bias by PsA disease severity (that is: despite the hypothesized general reluctance to join research, the more severe cases referred for eligibility consideration may also have presented with an increased propensity to be recruited).

In the opinion of this candidate, however, cases of oligoarthritis were substantially well represented at baseline (23/84 – 27.4% of recruits). This observation should have a relevant impact on the generalizability of the results and conclusions. Of note, 7.3% (3/41) of participants in Arm 2 and 2.3% (1/43) in Arm 1 fulfilled criteria for MDA status (Coates, L.C. et al., 2010) at baseline.

The majority of participants (63/84; 75%) presented with peripheral joint synovitis, in non-symmetric fashion. Clinically obvious cases of axial PsA were not common (3/84; 3.6%), however, this variable was reliant only on the clinical judgement of the investigators. The presence of inflammatory involvement of the DIP joints of the hands (3/84; 3.6%) and feet is only partially reflected by the figures presented in Table 9. The use of the definition “predominant” was based on clinical

judgement and the design of data collection did not provide for capturing in a specific variable the burden of small distal joints in the hands or feet – or the associated, if observed, psoriatic nail dystrophy. In the opinion of this candidate, the proportion of 3.6% underrepresents such clinical feature.

The MSK extra-articular manifestations of PsD were well represented among recruits. Overall, presence of signs of dactylitis (56/84; 66.7%) or of entheseal tenderness (52/84; 61.9%) were frequent among the GOLMePsA participants. It is important to note that the presence of dactylitis is one of the clinical criteria needed to fulfil the CASPAR classification criteria (Taylor et al., 2006) for PsA.

Laboratory tests of autoimmunity did not result in uncovering instances of clinical connective tissue diseases [Anti-Nuclear Auto-antibodies (ANA) were positive in 4/84 recruits; 4.8%]. On a similar matter, it was reassuring to record -by the time of the trial conclusion- that the exposure to the trial intervention (GOL administered to participants randomised to Arm 1) did not lead to the development of conditions within the lupus spectrum (itself a potential side effect of exposure to TNFi). The proportions of RF (6/84; 7.1%) and anti-Cyclic Citrullinated Peptides (anti-CCP) positivity (6/84; 7.1%) among GOLMePsA participants was as expected for people affected by PsA (Boyd et al., 2022). These laboratory findings were not related to any instance of misdiagnosed RA, as reported in Table 9 (all GOLMePsA participants fulfilled the CASPAR classification criteria – which are inclusive of radiographic evaluation). Eighteen participants were HLA-B27 positive (the prevalence was 21.4%). Ten participants were unable to receive the test; hence, the prevalence of HLA-B27 in tested persons (18/74) was 24.3%.

When present, PsO usually preceded the onset of PsA (median of seven years). Only 10/84 participants (11.9%) did not present with PsO lesions obviously apparent upon clinical evaluation. On the other hand, about one quarter of the participants presented with a BSA considerably (that is, equal or above 3%) affected by manifestations of PsO. Since the PASI is mainly an outcome measure, related figures are presented in Table 10. However, the symptoms attributable to PsO lesions were prevalent among the GOLMePsA participants (itching in 59/84, 70.2%; soreness in 34/84, 40.5%), with some recruits even experiencing pain in the areas affected by PsO. Fingernails evaluation was performed in all baselined participants. The number of instances in which examination of the fingernails failed was negligible, and in all cases (two in total) due to nail varnishing at the time of the baseline assessment.

Baseline values of the major composite outcome measures and PROMs evaluated in the GOLMePsA trial are listed in Table 10. Indices such as PASDAS, CPDAI and disease activity VAS reflected the average high level of disease

activity that participants experienced at the time of trial entry. Overall, at baseline no considerable imbalance of the variables (listed in Table 9 and Table 10) emerged across the allocated groups of trial treatment.

Table 9 Clinical Features, Including Immunology Status, at Baseline

Variable	Allocation		
	Arm 1 GOLMTX N=43	Arm 2 PBOMTX N=41	Total N=84
CASPAR criteria met			
Yes	43 (100.0%)	41 (100.0%)	84 (100.0%)
BMI (kg/m^2)	29.9 (5.4) 21.3 to 43.0, n=43	29.7 (5.8) 19.1 to 46.7, n=41	29.8 (5.6) 19.1 to 46.7, n=84
Weight ≥ 100kg			
No	36 (83.7%)	33 (80.5%)	69 (82.1%)
Yes	7 (16.3%)	8 (19.5%)	15 (17.9%)
Joint symptoms duration, in months	10.1 (IQR 5.3, 24.1); 1.8 to 61.5, n=43	10.2 (IQR 5.2, 18.1); 1.7 to 197.7, n=41	10.2 (IQR 5.3, 21.6); 1.7 to 197.7, n=84
PsA disease duration, in months	0.5 (0.2, 2.5); 0.0 to 7.7, n=43	0.5 (0.2, 1.3); 0.1 to 7.3, n=41	0.5 (0.2, 1.9); 0.0 to 7.7, n=84
Oligo/polyarthritis status (actual)			
Oligoarthritis	12 (27.9%)	11 (26.8%)	23 (27.4%)
Polyarthritis	31 (72.1%)	30 (73.2%)	61 (72.6%)
Oligo/polyarthritis status (as randomized)			
Oligoarthritis	12 (27.9%)	11 (26.8%)	23 (27.4%)
Polyarthritis	31 (72.1%)	30 (73.2%)	61 (72.6%)
Axial disease			
No	41 (95.3%)	40 (97.6%)	81 (96.4%)
Yes	2 (4.7%)	1 (2.4%)	3 (3.6%)
Predominant DIP (hands) disease			
No	41 (95.3%)	40 (97.6%)	81 (96.4%)
Yes	2 (4.7%)	1 (2.4%)	3 (3.6%)
Symmetrical arthritis			
No	34 (79.1%)	29 (70.7%)	63 (75.0%)
Yes	9 (20.9%)	12 (29.3%)	21 (25.0%)
Dactylitis			
Current	30 (69.8%)	26 (63.4%)	56 (66.7%)
None	11 (25.6%)	13 (31.7%)	24 (28.6%)
Previous History	2 (4.7%)	2 (4.9%)	4 (4.8%)
Entheseal tenderness			
Absent	14 (32.6%)	18 (43.9%)	32 (38.1%)
Present	29 (67.4%)	23 (56.1%)	52 (61.9%)
Anti-CCP status			
Negative	40 (93.0%)	36 (87.8%)	76 (90.5%)
Positive	2 (4.7%)	4 (9.8%)	6 (7.1%)
Missing	1 (2.3%)	1 (2.4%)	2 (2.4%)
RF status			
Negative	41 (95.3%)	36 (87.8%)	77 (91.7%)
Positive	2 (4.7%)	4 (9.8%)	6 (7.1%)
Missing	0 (0.0%)	1 (2.4%)	1 (1.2%)

Variable	Allocation		
	Arm 1 GOLMTX N=43	Arm 2 PBOMTX N=41	Total N=84
ANA status			
Negative	41 (95.3%)	37 (90.2%)	78 (92.9%)
Positive	1 (2.3%)	3 (7.3%)	4 (4.8%)
Missing	1 (2.3%)	1 (2.4%)	2 (2.4%)
dsDNA status			
Negative	41 (95.3%)	39 (95.1%)	80 (95.2%)
Positive	0 (0.0%)	1 (2.4%)	1 (1.2%)
Missing	2 (4.7%)	1 (2.4%)	3 (3.6%)
Evidence of PsO			
Current	29 (67.4%)	25 (61.0%)	54 (64.3%)
Current and FH	8 (18.6%)	12 (29.3%)	20 (23.8%)
FH	3 (7.0%)	1 (2.4%)	4 (4.8%)
None	1 (2.3%)	1 (2.4%)	2 (2.4%)
Previous and FH	1 (2.3%)	2 (4.9%)	3 (3.6%)
Previous	1 (2.3%)	0 (0.0%)	1 (1.2%)
PsO symptom duration, in months	130.7 (IQR 54.1, 217.3); 10.1 to 547.8, n=38	123.9 (IQR18.3, 338.8); 0.7 to 552.1, n=39	128.4 (IQR 49.3, 270.7); 0.7 to 552.1, n=77
PsO disease duration, in months	85.6 (IQR 9.7, 181.2); 0.3 to 547.8, n=38	79.9 (IQR 6.1, 287.0); 0.2 to 552.1, n=38	83.3 (IQR 8.9, 238.5); 0.2 to 552.1, n=76
BSA affected by PsO (total %)	1.0 (IQR 0.3, 4.0); 0.0 to 48.0, n=43	0.9 (IQR 0.3, 2.5); 0.0 to 20.0, n=41	1.0 (IQR 0.3, 2.9); 0.0 to 48.0, n=84
PsO severity, by BSA			
<3%	30 (69.8%)	33 (80.5%)	63 (75.0%)
≥3%	13 (30.2%)	8 (19.5%)	21 (25.0%)
PsO nail dystrophy			
Not assessed	1 (2.3%)	1 (2.4%)	2 (2.4%)
No	17 (39.5%)	15 (36.6%)	32 (38.1%)
Yes	25 (58.1%)	25 (61.0%)	50 (59.5%)
PsO symptoms, pain			
No	36 (83.7%)	37 (90.2%)	73 (86.9%)
Yes	7 (16.3%)	4 (9.8%)	11 (13.1%)
PsO symptoms, itching			
No	12 (27.9%)	13 (31.7%)	25 (29.8%)
Yes	31 (72.1%)	28 (68.3%)	59 (70.2%)
PsO symptoms, soreness			
No	23 (53.5%)	27 (65.9%)	50 (59.5%)
Yes	20 (46.5%)	14 (34.1%)	34 (40.5%)

Categorical variables presented as n (%); continuous variables presented as median (Inter-Quartile Range, IQR; first to third quartile range); absolute range, n.

GOLMTX = combination of golimumab and methotrexate; PBOMTX = combination of placebo and methotrexate; BMI = Body Mass Index; ANA = Anti-Nuclear Autoantibody; CCP = Cyclic Citrullinated Peptide Antibody; DIP = Distal Interphalangeal Joints of the hands; dsDNA = double stranded DeoxyriboNucleic Acid; PsA = Psoriatic Arthritis; PsO = Psoriasis; FH = Family History

Table 10 Baseline Values of Primary and Secondary Outcomes (Composite Outcome Measures and Patient-Reported Outcome Measures)

Variable	Allocation		
	Arm 1 GOLMTX N=43	Arm 2 PBOMTX N=41	Total N=84
PASDAS	5.9 (1.3); 2.6 to 8.7, n=43	5.6 (1.1); 3.3 to 7.7, n=40	5.7 (1.2); 2.6 to 8.7, n=83
Leeds Enthesitis Index (LEI)	1.0 (IQR 0.0, 2.0); 0.0 to 6.0, n=43	1.0 (IQR 0.0, 2.0); 0.0 to 6.0, n=41	1.0 (IQR 0.0, 2.0); 0.0 to 6.0, n=84
Leeds Dactylitis Index (LDI)	12.9 (IQR 0.0, 64.8); 0.0 to 202.9, n=43	15.6 (IQR 0.0, 54.7); 0.0 to 109.8, n=41	14.1 (IQR 0.0, 55.5); 0.0 to 202.9, n=84
PASI (Psoriasis Area and Severity Index) score	3.4 (IQR 0.5, 6.9); 0.0 to 34.8, n=43	2.6 (IQR 0.9, 5.1); 0.0 to 15.4, n=40	2.7 (IQR 0.6, 6.0); 0.0 to 34.8, n=83
mNAPSI	2.5 (IQR 0.0, 16.0); 0.0 to 73.0, n=42	3.0 (IQR 0.0, 10.0); 0.0 to 54.0, n=40	3.0 (IQR 0.0, 12.0); 0.0 to 73.0, n=82
Minimal Disease Activity (MDA)	1/43 (2.3%)	3/41 (7.3%)	4/84 (4.8%)
CPDAI	7.0 (2.6); 3.0 to 13.0, n=43	6.4 (2.7); 3.0 to 12.0, n=40	6.7 (2.6); 3.0 to 13.0, n=83
Participant DA-VAS	59.1 (21.4); 0.0 to 95.0, n=43	52.1 (25.2); 7.0 to 95.0, n=41	55.7 (23.5); 0.0 to 95.0, n=84
DLQI	5.0 (IQR 1.0, 9.0); 0.0 to 26.0, n=43	3.0 (IQR 1.0, 7.0); 0.0 to 25.0, n=41	3.5 (IQR 1.0, 8.5); 0.0 to 26.0, n=84
SF-36 PCS	32.5 (10.0); 9.1 to 53.5, n=43	37.5 (9.9); 21.0 to 56.0, n=40	34.9 (10.2); 9.1 to 56.0, n=83
SF-36 MCS	46.7 (10.7); 22.2 to 64.4, n=43	46.6 (12.5); 11.0 to 62.2, n=40	46.7 (11.5); 11.0 to 64.4, n=83

Continuous variables presented as Mean (Standard Deviation, SD) or Median (Inter-Quartile Range, IQR; first to third quartile range); absolute range, n (observations available); Categorical variables presented as n (%). GOLMTX = combination of golimumab and methotrexate; PBOMTX = combination of placebo and methotrexate; PASDAS = Psoriatic ArthritiS Disease Activity Score; CPDAI = Composite Psoriatic Disease Activity Index; DA-VAS = disease activity visual analogue scale; DLQI = Dermatology life Quality Index; SF-36 = Short Form 36; PCS = Physical Component Summary; MCS = Mental Component Summary.

4.1.2.4 Primary Efficacy Endpoint of the GOLMePsA Trial: PASDAS at Week 24

Results of the main analysis of the primary outcome -PASDAS at 24 weeks- are presented in Table 11 and Figure 11. In both treatment arms, the primary outcome measure values decreased –as compared to baseline values- indicating amelioration of the disease activity. The difference between the two treatment arms at week 24, once missing data, baseline PASDAS values and poly/oligoarthritis status were accounted for, was -0.55 (CI -1.12 to 0.03; p=0.064). The difference between the treatment arms was smaller than the pre-specified target difference of 1 unit – a value chosen after having considered the published smallest detectable difference between groups of 0.8 units (Helliwell, P.S. et al., 2014). Therefore, the null hypothesis that there was no clinically meaningful difference between the treatment arms, was accepted.

The required pre-specified statistical power was achieved. The target sample size was revised downwards towards the end of the trial (see section 3.3.1), in light of slow recruitment and better-than-anticipated retention. Regardless, the observed pooled SD -at week 24- was smaller than that assumed in the sample size calculation (1.35 vs 1.57, respectively). In addition, there were at least 39 participants in each treatment arm with data available at week 24. The actual power achieved to detect a difference of 1 unit of PASDAS -with SD 1.35 and sample sizes of 41 and 43 per arm- was 92%.

Several sensitivity analyses were conducted to assess the impact of:

- adjustment for baseline PASDAS values and the stratification variable (polyarthritis status vs oligoarthritis status).
- stratification status supplied at the time of randomisation instead of the actual status, where these differed.
- different approaches to handling missing data.
- reanalysing the data in the per-protocol efficacy set.

None of the sensitivity analyses yielded a clinically or statistically significant difference between the treatment arms.

As illustrated in Table 9, the median duration of PsA-related symptoms at baseline was 10.2 months. The analysis of PASDAS changes at week 24 by disease duration (<12 months vs >12 months) subgroups did not result in statistically significant differences between treatment arms.

Among participants, in general, the improvements observed in PASDAS score were maintained over time (depicted in Figure 12).

Table 11 GOLMePsA Trial, Main Analysis for The Primary Outcome, PASDAS at 24 Weeks

	Arm 1 GOLMTX			Arm 2 PBOMTX			Adjusted Difference	95% CI	t	p-value	Nimp
	Mean	SD	N	Mean	SD	N					
PASDAS BSL	5.91	(1.30)	43	5.56	(1.12)	40					
PASDAS WK24	2.70	(1.38)	43	3.09	(1.32)	41	-0.55	(-1.12,0.03)	-1.88	0.064	84

Population: Full analysis set. Mean, Standard Deviation (SD) and Number (N) of participants with data available pre-imputation are presented -for the observed values- at Baseline (BSL) and week 24 (WK24) time-points.

The calculation of the difference between the two treatment arms at week 24 was performed using the statistic multiple linear regression. This analysis was performed after withdrawal visit data were carried forward and then using multiple imputation to address any remaining missing data. The estimation obtained by this analysis was adjusted for baseline PASDAS values, as well as for the stratification variable poly/oligoarthritis status (using the participant's actual status).

The adjusted difference of the means of the two treatment arms (with the related 95% Confidence Interval, CI) is presented. The total number of participants included in analysis following imputation (Nimp) is also presented.

The pooled SD of the observed values at 24 weeks, for comparison to the value of 1.57 used in the sample size calculation, was 1.35.

GOLMTX = combination of golimumab and methotrexate; PBOMTX = combination of placebo and methotrexate; PASDAS = Psoriatic ArthritiS Disease Activity Score

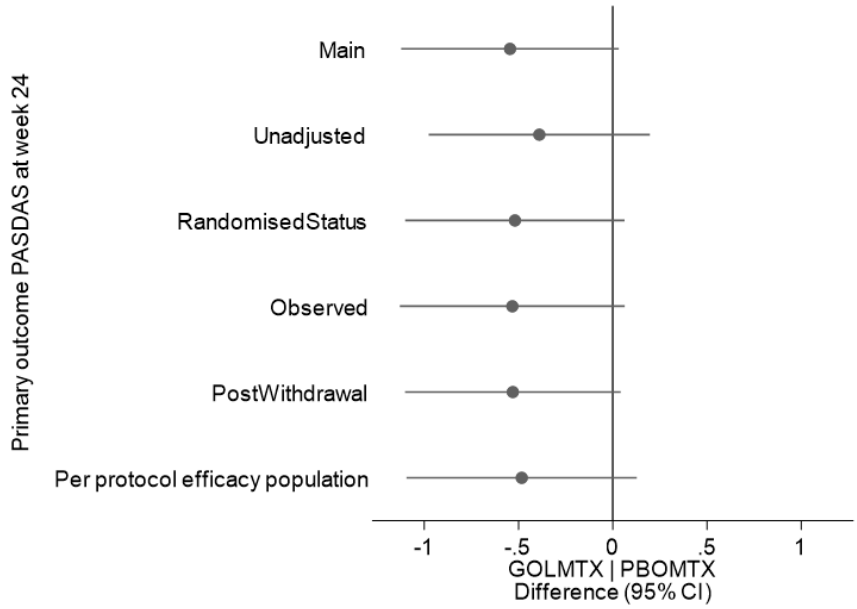

Figure 11 Forest Plot of Primary Outcome Analysis

Population: Full analysis set. Mean between-arm differences and 95% Confidence Intervals (CI) were plotted for the main, supplementary and sensitivity analyses of the primary outcome. GOLMTX = combination of golimumab and methotrexate (Arm 1); PBOMTX = combination of placebo and methotrexate (Arm 2).

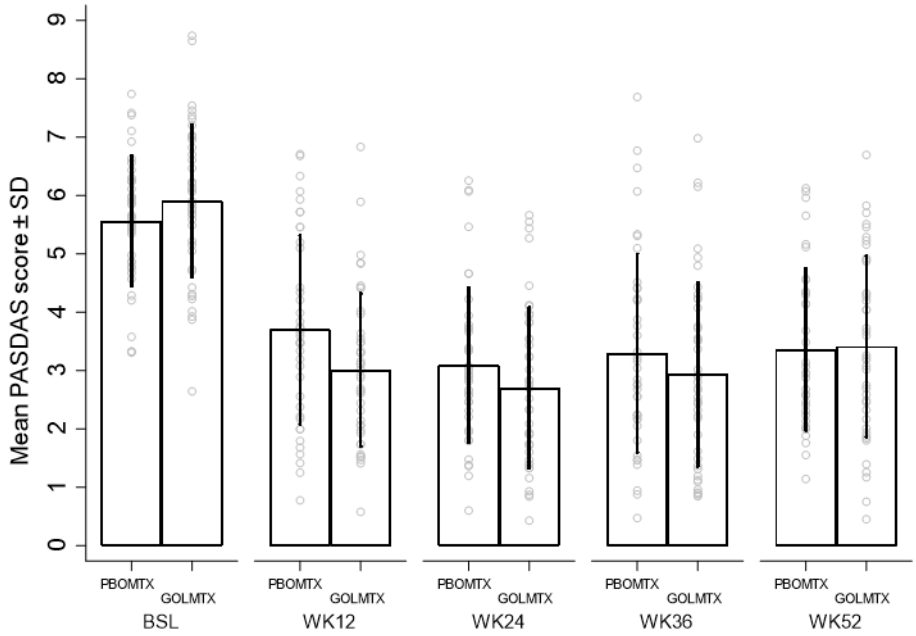

Figure 12 PASDAS Score, Mean by Time-Point

Population: Full analysis set. Graphical summary of descriptive data for PASDAS score over time, by treatment arm [GOLMTX = combination of golimumab and methotrexate (Arm 1); PBOMTX = combination of placebo and methotrexate (Arm 2)]. Observed data were plotted; withdrawal visit data were carried forward for participants who withdrew from the intervention early. SD = Standard Deviation.

Time-points

BSL = Baseline visit (week 0); WK12 = week 12 visit; WK24 = week 24 visit; WK36 = week 36 visit; WK52 = week 52 visit.

4.1.2.5 Secondary Outcomes of The GOLMePsA Trial

As a consequence of the lack of a clinically or statistically significant difference in the primary outcome between treatment arms, all secondary outcome analyses were downgraded and considered exploratory (see paragraph 3.3.7.2).

4.1.2.5.1 Musculoskeletal Domains and Related Patient-Reported Outcome Measures (Continuous Variables)

Results of linear regression analyses comparing continuous secondary outcomes across treatment arms are presented in Table 12, Figure 13, Figure 14 and Figure 15. All of these analyses were adjusted for baseline values of the outcome and for the stratification variable.

Although the CPDAI composite outcome measure encompasses skin (though not the nails) assessment, the related results are presented in this paragraph – as the majority of domains measured by this index (six out of seven) reflects MSK disease activity.

For both the clinical outcomes and the PROMs, the exploratory results achieved suggested the possibility of a beneficial effect of the combination treatment used in Arm 1 (GOLMTX) over the regimen used in Arm 2 (PBOMTX). Such effect was detected -as soon as at 12 weeks- for PASDAS [mean difference (95% CI) -0.86 (-1.48 to -0.24); p=0.007] and CPDAI [-0.96 (CI -1.88 to -0.04); p=0.041]. However, these differences were not maintained to week 24 or beyond, and there were no substantive or statistically significant differences in participant global disease activity VAS, SF-36 PCS or MCS. However, all these variables improved -and to a clinically relevant extent- in both arms over time and with similar magnitude. In both arms, maximal improvement was generally observed at weeks 12-24 and was largely sustained beyond that, with a slight worsening by the end of the observational period of the trial (week 52).

Table 12 GOLMePsA Trial, Musculoskeletal Domains (Secondary Outcomes), Continuous Variables

	Arm 1 GOLMTX			Arm 2 PBOMTX			Difference	95% CI	t	p-value	Nimp
	Mean	SD	N	Mean	SD	N					
PASDAS baseline	5.91	(1.30)	43	5.56	(1.12)	40					
PASDAS week 12	3.01	(1.31)	43	3.70	(1.62)	40	-0.86	(-1.48,-0.24)	-2.76	0.007	84
PASDAS week 36	2.93	(1.57)	43	3.30	(1.70)	40	-0.58	(-1.26,0.11)	-1.68	0.096	84
PASDAS week 52	3.42	(1.55)	42	3.36	(1.39)	36	-0.07	(-0.72,0.59)	-0.20	0.844	84
CPDAI baseline	7.00	(2.56)	43	6.42	(2.67)	40					
CPDAI week 12	3.49	(2.41)	41	4.10	(2.76)	41	-0.96	(-1.88,-0.04)	-2.07	0.041	84
CPDAI week 24	3.12	(2.45)	40	3.24	(2.58)	41	-0.44	(-1.41,0.54)	-0.89	0.375	84
CPDAI week 36	3.17	(2.80)	40	2.97	(2.69)	39	-0.44	(-1.46,0.58)	-0.86	0.392	84
CPDAI week 52	3.49	(2.75)	39	3.03	(2.71)	36	-0.32	(-1.34,0.71)	-0.61	0.541	84
Participant DA-VAS baseline	59.07	(21.35)	43	52.12	(25.24)	41					
Participant DA-VAS week 24	27.72	(23.42)	43	27.56	(23.54)	41	-2.35	(-12.14,7.43)	-0.48	0.633	84
Participant DA-VAS week 52	36.57	(26.06)	42	32.73	(25.62)	37	1.24	(-9.95,12.43)	0.22	0.826	84
SF36 PCS baseline	32.46	(10.02)	43	37.47	(9.93)	40					
SF36 PCS week 24	46.10	(9.32)	43	45.62	(9.45)	41	2.24	(-1.76,6.25)	1.12	0.268	84
SF36 PCS week 52	42.80	(10.38)	42	44.44	(10.25)	37	1.21	(-3.42,5.83)	0.52	0.605	84
SF36 MCS baseline	46.70	(10.70)	43	46.60	(12.48)	40					
SF36 MCS week 24	51.27	(8.84)	43	52.11	(9.34)	41	-0.85	(-4.23,2.54)	-0.50	0.620	84
SF36 MCS week 52	51.65	(9.75)	42	52.44	(10.03)	37	-1.39	(-5.02,2.24)	-0.76	0.449	84

Population: Full analysis set. This table presents results for continuous secondary outcomes. Mean, Standard Deviation (SD) and Number (N) of participants with data available pre-imputation are presented for the observed values at screening (or baseline) and weeks 12, 24, 36, and 52, with the exception of DA-VAS and SF36 component summaries which are presented at weeks 24 and 52. The difference between the treatment arms was calculated using multiple linear regression, following carrying forward withdrawal visit data and then using multiple imputation to address any remaining missing data. Each estimate was adjusted for baseline values of the outcome and the stratification variable poly/oligoarthritis status (using the participant's actual status). The total number of participants included in analysis following imputation (Nimp) is also presented.

GOLMTX = combination of golimumab and methotrexate; PBOMTX = combination of placebo and methotrexate; PASDAS = Psoriatic ArthritiS Disease Activity Score; CPDAI = Composite Psoriatic Disease Activity Index; DA-VAS = Disease Activity Visual Analogue Scale; SF-36 = Short Form 36; PCS = Physical Component Summary; MCS = Mental Component Summary.

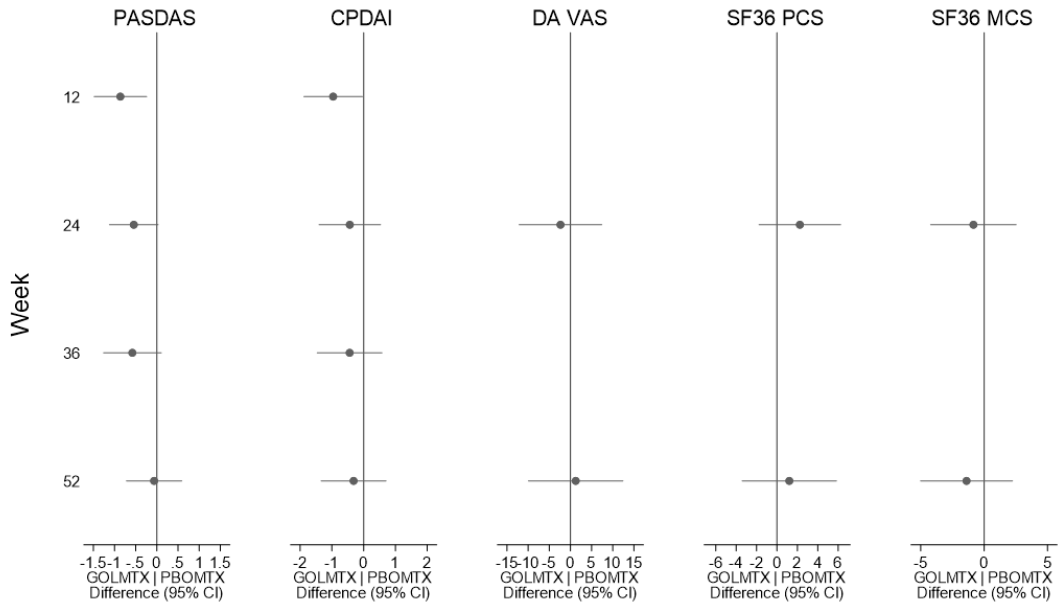

Figure 13 Forest Plots of Musculoskeletal Domains (Secondary Outcomes), Continuous Variables

Population: Full analysis set

Mean between-arms [GOLMTX = combination of golimumab and methotrexate (Arm 1); PBOMTX = combination of placebo and methotrexate (Arm 2)], differences and 95% Confidence Intervals (CI) plotted for the analyses of continuous composite outcome measures and of participant-reported outcomes (secondary outcomes).

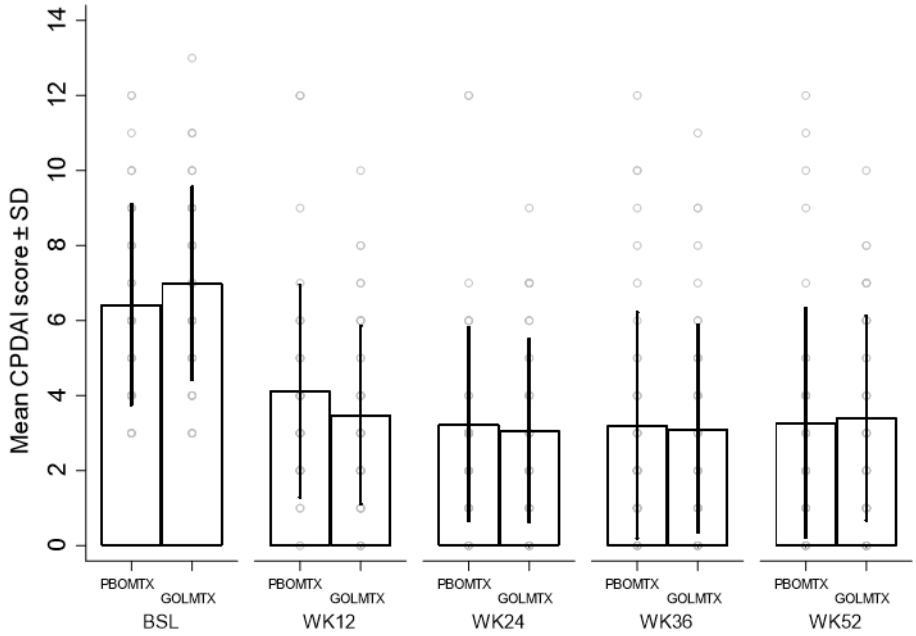

Figure 14 Plot of Musculoskeletal Domains (Secondary Outcomes) - CPDAI Score, by Treatment Arm (Observed Data)

Population: Full analysis set. Graphical summary of descriptive data for CPDAI (Composite Psoriatic Disease Activity Index) score over time, by treatment arm [GOLMTX = combination of golimumab and methotrexate (Arm 1); PBOMTX = combination of placebo and methotrexate (Arm 2)]. Observed data were plotted; withdrawal visit data were carried forward for participants who withdrew from the intervention early. SD = standard deviation.

Time-points

BSL = Baseline visit (week 0); WK12 = week 12 visit; WK24 = week 24 visit; WK36 = week 36 visit; WK52 = week 52 visit.

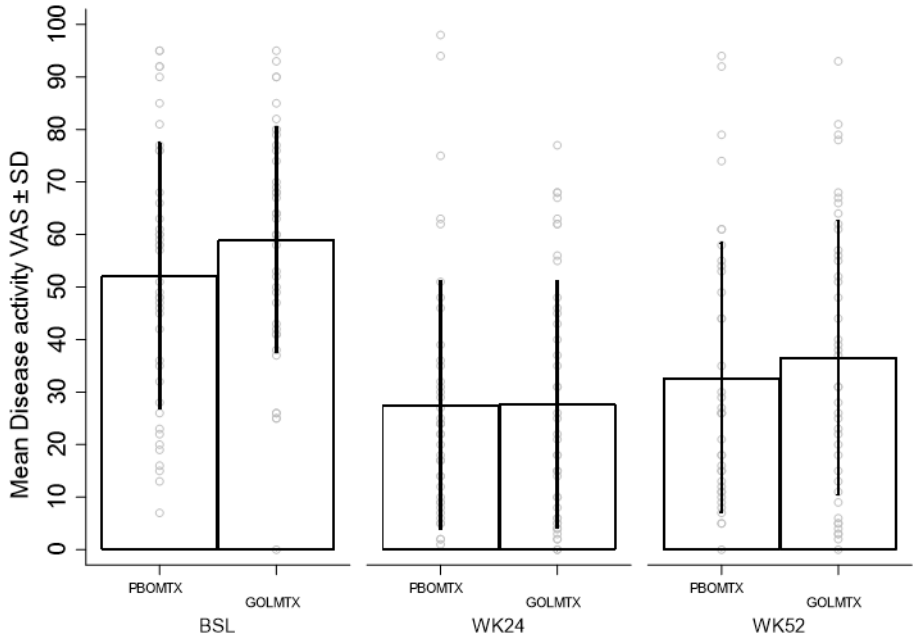

Figure 15 Plot of Musculoskeletal Domains (Secondary Outcomes) - Disease Activity VAS, by Treatment Arm (Observed Data)

Population: Full analysis set. Graphical summary of descriptive data for Disease Activity Visual Analogue Scale (VAS) over time, by treatment arm [GOLMTX = combination of golimumab and methotrexate (Arm 1); PBOMTX = combination of placebo and methotrexate (Arm 2)]. Observed data were plotted; withdrawal visit data were carried forward for participants who withdrew from the intervention early.

Time-points

BSL = Baseline visit (week 0); WK24 = week 24 visit; WK52 = week 52 visit.

4.1.2.5.2 Musculoskeletal Domains (Binary Variables)

Results of logistic regression analyses comparing binary secondary outcomes between the treatment arms are presented in Table 13 and Figure 16. All of these analyses were adjusted for the stratification variable.

This candidate is well aware of the effect that administration of steroids can have across the domains (MSK as well as cutaneous) of the PsD clinical manifestations. The choice of presenting these data specifically in this paragraph is only related to the preponderance of MSK domains results presented throughout the thesis in general.

Amongst the response outcomes, there were no statistically or clinically meaningful differences across treatment groups in MDA status [at week 24, 24/43 (55.8%) in treatment arm 1 and 24/41 (58.5%) in treatment arm 2; Odds Ratio (OR) 0.90 (95% CI 0.38-2.13); p-value 0.802] or in prevalence of ACR20 response [at week 24, 28/43 (65.1%) in treatment arm 1 and 27/41 (65.9%) in treatment arm 2; OR 0.97 (95% CI 0.39-2.38); p-value 0.939] or in prevalence of ACR50 response [21/43 (48.8%) in treatment arm 1 and 15/41 (36.6%) in treatment arm 2; OR 1.67 (95% CI 0.70-4.02); p-value 0.251].

The results suggested that a greater proportion of participants randomized to Arm 1 achieved ACR70 response [15/43 (34.9%) vs.6/40 (15.0%); OR 3.12 (95% CI 1.07-9.10); p-value 0.037] and PsARC responses [37/43 (86.0%) vs. 26/41 (63.4%); OR 3.70 (95% CI 1.25-10.97); p-value 0.018] at week 12, although the gap was closing by week 24 and closed further by weeks 36 and 52. Interestingly, for MDA, ACR20 and PsARC response, the point estimate of the adjusted OR was below 1 –that is, numerically in favour of Arm 2- at week 52.

A larger proportion of participants randomized to Arm 2 received additional IM steroid at week 8 or 12 [48.78% vs 20.93%; adjusted OR 0.28 (95% CI 0.11-0.72), p=0.009].

Table 13 GOLMePsA Trial, Musculoskeletal Domains (Secondary Outcomes), Binary Variables

	Arm 1 GOLMTX			Arm 2 PBOMTX			OR	95% CI	t	p-value	Nimp
	n	N	%	n	N	%					
Minimal disease activity week12	20	/43	(46.5)	18	/40	(45.0)	1.08	(0.45,2.60)	0.17	0.869	84
Minimal disease activity week 24	24	/43	(55.8)	24	/41	(58.5)	0.90	(0.38,2.13)	-0.25	0.802	84
Minimal disease activity week 36	25	/43	(58.1)	22	/40	(55.0)	1.14	(0.48,2.72)	0.30	0.767	84
Minimal disease activity week 52	17	/42	(40.5)	20	/37	(54.1)	0.63	(0.26,1.55)	-1.00	0.315	84
ACR20 response week 12	28	/43	(65.1)	23	/40	(57.5)	1.34	(0.55,3.27)	0.65	0.516	84
ACR20 response week 24	28	/43	(65.1)	27	/41	(65.9)	0.97	(0.39,2.38)	-0.08	0.939	84
ACR20 response week 36	27	/43	(62.8)	24	/40	(60.0)	1.19	(0.48,2.94)	0.38	0.701	84
ACR20 response week 52	23	/42	(54.8)	28	/37	(75.7)	0.48	(0.19,1.22)	-1.54	0.124	84
ACR50 response week 12	20	/43	(46.5)	12	/40	(30.0)	1.89	(0.78,4.63)	1.40	0.161	84
ACR50 response week 24	21	/43	(48.8)	15	/41	(36.6)	1.67	(0.70,4.02)	1.15	0.251	84
ACR50 response week 36	21	/43	(48.8)	16	/40	(40.0)	1.50	(0.63,3.60)	0.91	0.363	84
ACR50 response week 52	16	/42	(38.1)	15	/37	(40.5)	0.99	(0.40,2.46)	-0.01	0.991	84
ACR70 response week 12	15	/43	(34.9)	6	/40	(15.0)	3.12	(1.07,9.10)	2.09	0.037	84
ACR70 response week 24	19	/43	(44.2)	10	/41	(24.4)	2.50	(0.98,6.40)	1.91	0.056	84
ACR70 response week 36	14	/43	(32.6)	9	/40	(22.5)	1.72	(0.65,4.57)	1.09	0.277	84
ACR70 response week 52	11	/42	(26.2)	8	/37	(21.6)	1.38	(0.48,3.92)	0.60	0.548	84
PsARC response week 8	34	/43	(79.1)	31	/41	(75.6)	1.22	(0.44,3.39)	0.38	0.706	84
PsARC response week 12	37	/43	(86.0)	26	/41	(63.4)	3.70	(1.25,10.97)	2.36	0.018	84
PsARC response week 24	38	/43	(88.4)	36	/41	(87.8)	1.06	(0.28,4.02)	0.09	0.926	84
PsARC response week 36	38	/43	(88.4)	33	/40	(82.5)	1.73	(0.50,5.94)	0.87	0.385	84
PsARC response week 52	28	/42	(66.7)	27	/37	(73.0)	0.82	(0.32,2.12)	-0.41	0.684	84
Steroid received before week 24	9	/43	(20.9)	20	/41	(48.8)	0.28	(0.11,0.72)	-2.62	0.009	84

Population: Full analysis set. Descriptive data [n /N (%)] are presented for the observed values at baseline and weeks 12, 24, 36, and 52, and (additional) steroid received before week 24. The difference between the treatment arms was calculated using binary logistic regression, assuming non-response for anyone who withdrew from protocol treatment and then using multiple imputation to address any remaining missing data. Each estimate was adjusted for the stratification variable poly/oligoarthritis status (using the participant's actual status). The total number of participants included in analysis following imputation (Nimp) is also presented.
GOLMTX = combination of golimumab and methotrexate; PBOMTX = combination of placebo and methotrexate; ACR20 = American College of Rheumatology 20 Responder Index; ACR50 = American College of Rheumatology 50 Responder Index; ACR70 = American College of Rheumatology 70 Responder Index; PsARC = Psoriatic Arthritis Response Criteria.

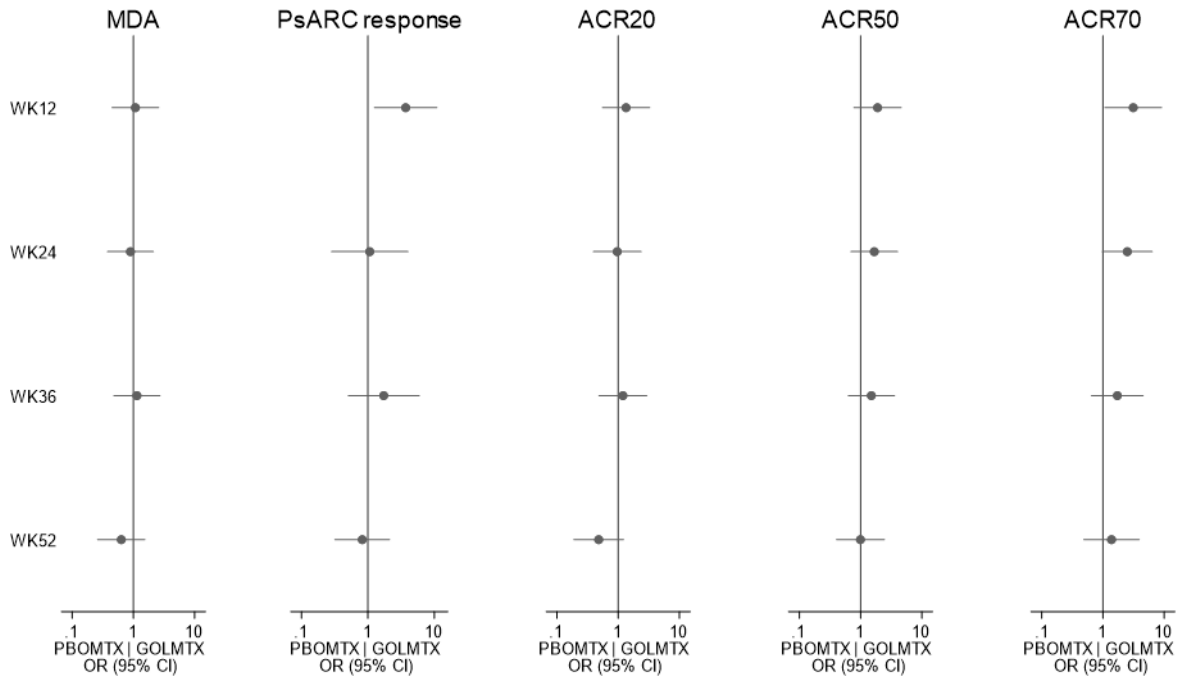

Figure 16 Forest Plots of Musculoskeletal Domains (Secondary Outcomes), Binary Variables

Population: Full analysis set. Between-arm Odds Ratios (OR) and 95% Confidence Intervals (CI) were plotted for the analyses of binary secondary outcomes. MDA = Minimal Disease Activity; PsARC = Psoriatic Arthritis Response Criteria; ACR20 = American College of Rheumatology 20 Responder Index; ACR50 = American College of Rheumatology 50 Responder Index; ACR70 = American College of Rheumatology 70 Responder Index. GOLMTX = combination of golimumab and methotrexate (Arm 1); PBOMTX = combination of placebo and methotrexate (Arm 2)

4.1.2.5.3 Musculoskeletal Domains (Count-Type Distributed Variables)

Results of negative binomial regression analyses comparing count-distributed secondary outcomes between the treatment arms are presented in Table 14 and Figure 17. All of these analyses were adjusted for baseline values of the outcome and for the stratification variable.

There were no statistically significant differences between treatment arms in the count-distributed outcome LEI, at any of the trial time-points. Mean LEI was approximately 60% lower at week 24 compared to baseline in both arms. There were considerable improvements in LDI in both arms from week 12 onwards, with the descriptive data consistent with an earlier improvement in Arm 1. Although incident rate ratios for the differences between arms were low at all time points, CIs were wide. Only at week 52 did the data suggest a difference in favour of the Arm 1 intervention on an exploratory basis: Incidence-Rate Ratio (IRR) = 0.06 (95% CI: 0.00,0.84), p=0.037. The driver of improvement in LDI -in both arms- seemed to be the amelioration of tenderness, as the LDI includes the tender dactylitis count. Both the median and 75th percentile for tender dactylitis count were 0, in both arms, from week 12 onwards. However, counting digits with any dactylitis the 75th percentile was 1 in both groups at week 12 and then remained at 1 throughout for Arm 2, compared to 0 from week 24 onward in Arm 1 (Figure 18).

Table 14 GOLMePsA Trial, Musculoskeletal Domains (Secondary Outcomes), Count-Type Distributions Variables

	Arm 1 GOLMTX			Arm 2 PBOMTX			IRR	95% CI	t	p-value	Nimp
	Mean	SD	N	Mean	SD	N					
Leeds enthesitis index baseline	1.37	1.48	43	1.51	1.76	41					
Leeds enthesitis index week 12	0.74	1.35	43	0.95	1.76	41	1.01	(0.48,2.14)	0.04	0.971	84
Leeds enthesitis index week 24	0.53	0.98	43	0.61	1.34	41	1.10	(0.49,2.46)	0.23	0.817	84
Leeds enthesitis index week36	0.74	1.43	43	0.65	1.37	40	1.35	(0.63,2.93)	0.77	0.441	84
Leeds enthesitis index week 52	0.50	0.97	42	0.43	1.09	37	1.29	(0.55,3.03)	0.58	0.563	84
Leeds dactylitis index baseline	38.04	50.84	43	26.60	30.56	41					
Leeds dactylitis index week 12	2.22	7.92	43	11.46	19.88	41	0.17	(0.02,1.26)	-1.73	0.083	84
Leeds dactylitis index week 24	0.48	2.52	43	5.04	17.10	41	0.26	(0.01,7.64)	-0.79	0.432	84
Leeds dactylitis index week 36	3.36	15.15	43	4.38	11.31	40	0.11	(0.01,1.21)	-1.80	0.071	84
Leeds dactylitis index week 52	3.45	14.76	42	6.58	14.89	37	0.06	(0.00,0.84)	-2.09	0.037	84

Mean, Standard Deviation (SD) and Number (N) of participants with data available pre-imputation are presented for the observed values at baseline and weeks 12, 24, 36, and 52. The Incidence-Rate Ratio (IRR) between the treatment arms has been calculated using negative binomial regression, following carrying forward withdrawal visit data and then using multiple imputation to address any remaining missing data. Each estimate was adjusted for baseline values of the outcome and the stratification variable poly/oligoarthritis status (using the participant's actual status). The total number of participants included in analysis following imputation (Nimp) is also presented.

GOLMTX = combination of golimumab and methotrexate; PBOMTX = combination of placebo and methotrexate; mNAPSI = modified Nail Psoriasis Severity Index.

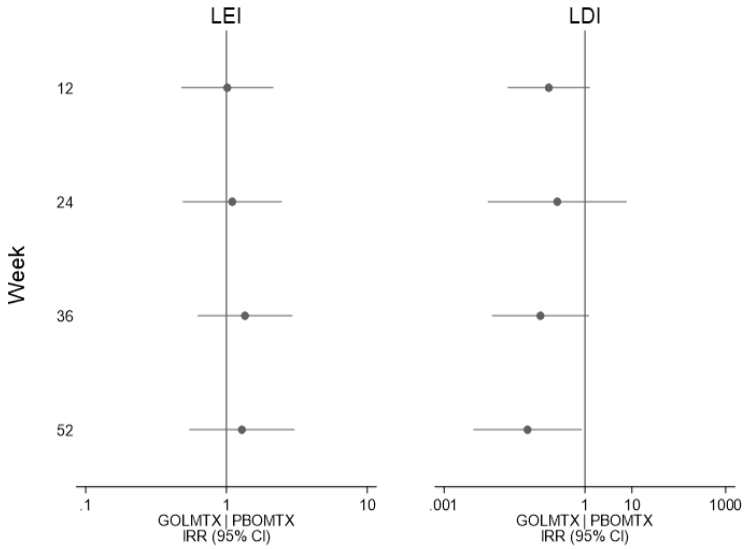

Figure 17 Forest Plots of Musculoskeletal Domains (Secondary Outcomes), Count-Type Distributed Variables

Population: Full analysis set. Between-arm Incident Rate Ratios (IRR) and 95% Confidence Intervals (CI) were plotted for the analyses of count-distributed secondary outcomes. GOLMTX = combination of golimumab and methotrexate (Arm 1); PBOMTX = combination of placebo and methotrexate (Arm 2).

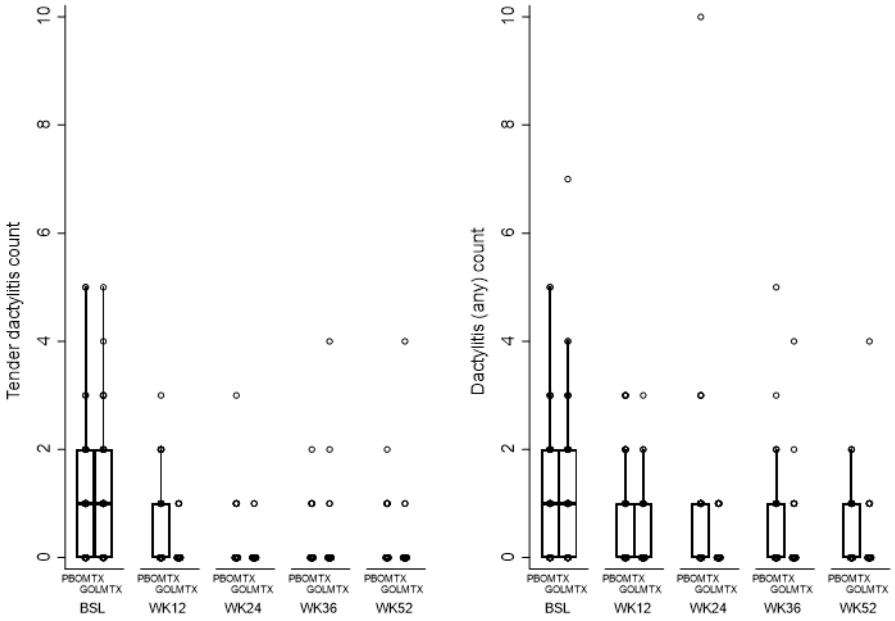

Figure 18 Box Plots of Musculoskeletal Domains (Secondary Outcomes) Tender and Any Dactylitis Counts, by Treatment Arm

Population: Full analysis set (observed data only). Graphical summary of descriptive data for dactylitis counts over time, by treatment arm. Observed data were plotted; withdrawal visit data were carried forward for participants who withdrew from the intervention early. GOLMTX = combination of golimumab and methotrexate (Arm 1); PBOMTX = combination of placebo and methotrexate (Arm 2).

Time-points

BSL = Baseline visit (week 0); WK12 = week 12 visit; WK24 = week 24 visit; WK36 = week 36 visit; WK52 = week 52 visit.

4.1.2.5.4 Cutaneous Domains and Related Patient-Reported Outcomes (Skewed Variables)

Results of quantile regression analyses comparing skewed secondary outcomes between the treatment arms are presented in Table 15 and Figure 19. All of these analyses were adjusted for baseline values of the outcomes and for the stratification variable. Note that for PASI score at 24 weeks, the arms were compared at the 75th percentile rather than the median, as stipulated in the statistical analysis plan under circumstances in which the median regression models failed to converge.

There were no statistically significant differences between treatment arms in the skewed outcomes PASI score (observed reduction in Arm 1: 3.40 at baseline to 0.00 at week 24; observed reduction in Arm 2: 2.60 at baseline to 0.60 at week 24) and DLQI, at any of the time points. Both PASI score and DLQI improved in each treatment arm. Maximal improvement was at around 24 weeks in both arms.

Table 15 GOLMePsA Trial, Cutaneous Domains (Secondary Outcomes), Skewed Variables

	Arm 1 GOLMTX				Arm 2 PBOMTX				Difference	95% CI	t	p-value	Nimp
	Median	1st Q	3rd Q	N	Median	1st Q	3rd Q	N					
PASI score baseline	3.40	(0.50,	6.90)	43	2.60	(0.85,	5.10)	40					
PASI score week12	0.20	(0.00,	1.20)	43	1.00	(0.00,	2.10)	41	-0.38	(-1.53,0.77)	-0.66	0.512	84
PASI score week 24	0.00	(0.00,	0.70)	43	0.60	(0.00,	1.60)	41	-0.44	(-1.33,0.44)	-1.00	0.320	84
PASI score week 36	0.00	(0.00,	0.60)	43	0.70	(0.00,	1.75)	40	-0.47	(-1.22,0.28)	-1.24	0.220	84
PASI score week 52	0.55	(0.00,	1.80)	42	0.40	(0.00,	1.60)	37	0.05	(-0.85,0.95)	0.11	0.912	84
DLQI baseline	5.00	(1.00,	9.00)	43	3.00	(1.00,	7.00)	41					
DLQI week 24	1.00	(0.00,	1.00)	43	1.00	(0.00,	2.00)	41	-0.50	(-1.42,0.42)	-1.09	0.281	84
DLQI week 52	1.00	(0.00,	4.00)	42	1.00	(0.00,	2.00)	37	0.01	(-1.44,1.47)	0.02	0.985	84

Population: Full analysis set. Descriptive data [median, first and third quartile (1st Q, 3rd Q), Number (N) of participants with data available] are presented for the observed values at baseline and weeks 12, 24, 36, and 52 for PASI score, and weeks 24 and 52 for DLQI. The difference in medians between the treatment arms was calculated using quantile (median) regression, following carrying forward withdrawal visit data and then using multiple imputation to address any remaining missing data. Each estimate was adjusted for baseline values of the outcome and the stratification variable poly/oligoarthritis status (using the participant's actual status). The total number of participants included in analysis following imputation (Nimp) is also presented.

GOLMTX = combination of golimumab and methotrexate; PBOMTX = combination of placebo and methotrexate; PASI = Psoriasis Area and Severity Index; DLQI = Dermatology Life Quality Index.

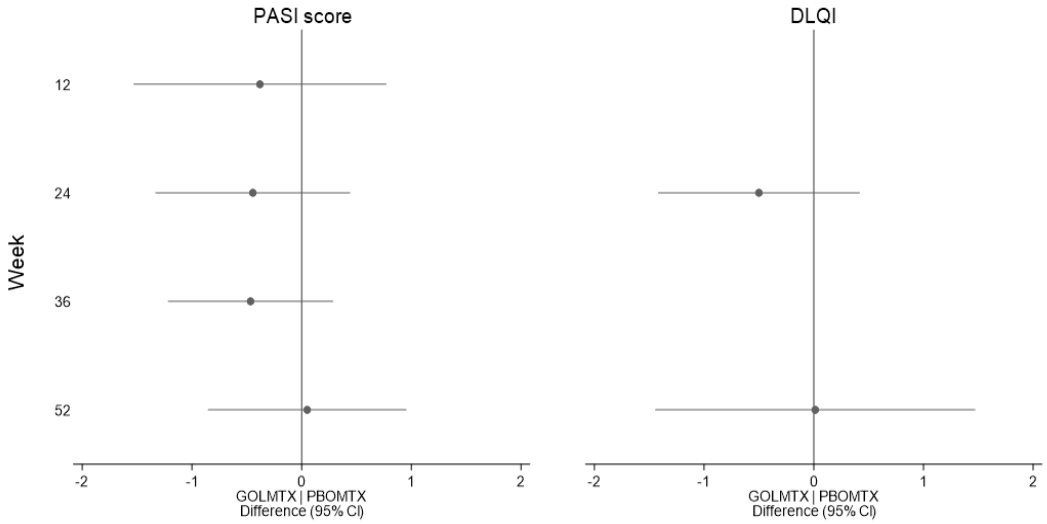

Figure 19 Forest Plots of Cutaneous Domains (Secondary Outcomes), Skewed Variables

Population: Full analysis set. Differences and 95% Confidence Intervals (CI) were plotted for the analyses of skewed secondary outcomes. PASI = Psoriasis Area and Severity Index; DLQI = Dermatology Life Quality Index. GOLMTX = combination of golimumab and methotrexate (Arm 1); PBOMTX = combination of placebo and methotrexate (Arm 2).

Note that, at week 24, PASI score was compared between the arms at the 75th percentile instead of the median.

4.1.2.5.5 Cutaneous Domains (Binary Variables)

Results of logistic regression analyses comparing binary secondary outcomes between the treatment arms are presented in Table 16 and Figure 20. All of these analyses were adjusted for the stratification variable.

Firth's penalised maximum likelihood logistic regression (unplanned analysis) was used for PASI75 response at 12 weeks due to data sparsity which caused the standard maximum likelihood model to separate.

The proportion of participants achieving PASI75 response appeared substantively larger in Arm 1 (GOLMTX) at all time-points. However, due to the substantially restricted sample size of 21/84 (25%) participants with >=3% of BSA affected by PsO at baseline, the data were only suggestive of a significant difference on an exploratory basis at week 24.

The same considerations apply to participants who presented with PASI score equal to zero, across time-points and irrespective of the treatment group allocation. Overall, a few patients presented at baseline with skin not affected by PsO lesions (10/83; 12% - PASI data missing in 1 participant at baseline). At week 12, PASI score of zero was recorded in 29/84 (34.5% of total cohort; 17/43 in Arm 1 and 12/41 in Arm 2). At week 24, PASI score of zero was recorded in 38/84 (45.2% of total cohort; 22/43 in Arm 1 and 16/41 in Arm 2). At week 36, PASI score of zero was recorded in 38/83 (45.8% of participants with data available; 24/43 in Arm 1 and 14/40 in Arm 2). At week 52, PASI score of zero was recorded in 29/79 (36.7% of participants with data available; 16/42 in Arm 1 and 13/37 in Arm 2). No difference between treatment groups -at any time-point- was found.

Table 16 GOLMePsA Trial, Cutaneous Domains (Secondary Outcomes), Binary Variables

	Arm 1 GOLMTX			Arm 2 PBOMTX			OR	95% CI	t	p-value	Nimp
	n	N	%	n	N	%					
PASI 75 response week12	7	/13	(53.8)	0	/8	(0.0)	16.72	(0.86,326.19)	1.86	0.063	21
PASI 75 response week 24	11	/13	(84.6)	3	/8	(37.5)	8.9	(1.09,72.42)	2.04	0.04	21
PASI 75 response week 36	9	/13	(69.2)	2	/8	(25.0)	6.71	(0.86,52.14)	1.82	0.069	21
PASI 75 response week 52	6	/13	(46.2)	2	/7	(28.6)	2.34	(0.33,16.66)	0.85	0.397	21

Population: Full analysis set. Descriptive data [n /N (%)] are presented for the observed values at baseline and weeks 12, 24, 36, and 52. The difference between the treatment arms was calculated using binary logistic regression, assuming non-response for anyone who withdrew from protocol treatment and then using multiple imputation to address any remaining missing data. Each estimate was adjusted for the stratification variable poly/oligoarthritis status (using the participant's actual status). The total number of participants included in analysis following imputation (Nimp) is also presented.
GOLMTX = combination of golimumab and methotrexate; PBOMTX = combination of placebo and methotrexate; PASI75 = reduction of PASI (Psoriasis Area and Severity Index) of at least 75%, as compared to baseline levels.

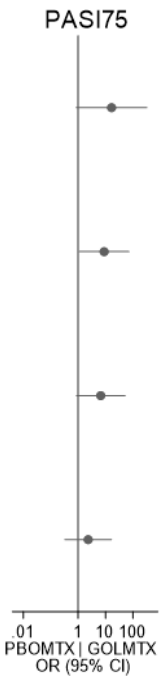

Figure 20 Forest Plot of Cutaneous Domain PASI75 (Secondary Outcomes), Binary Variables

Population: Full analysis set. Between-arm Odds Ratios (OR) and 95% Confidence Intervals (CI) were plotted for the analyses of binary secondary outcomes. PASI75 = reduction of PASI (Psoriasis Area and Severity Index) of at least 75%, as compared to baseline levels. GOLMTX = combination of golimumab and methotrexate (Arm 1); PBOMTX = combination of placebo and methotrexate (Arm 2)

4.1.2.5.6 Cutaneous Domains (Count-Distributed Secondary Outcomes)

Results of negative binomial regression analyses comparing count-distributed secondary outcomes (cutaneous domains) between the treatment arms are presented in Table 17 and Figure 21. All of these analyses were adjusted for baseline values of the outcome and for the stratification variable.

There were no statistically significant differences between treatment arms in the count-distributed outcome mNAPSI, at any of the time points. The largest difference in mNAPSI was seen at week 24 [adjusted IRR 0.51 (CI 0.23-1.09)] but this was not statistically significant (p=0.081). Maximal improvement was at around 24-36 weeks, in both arms.

Table 17 GOLMePsA Trial, Cutaneous Domains (Secondary Outcomes), Count-Type Distributions Variables

	Arm 1 GOLMTX			Arm 2 PBOMTX			IRR	95% CI	t	p-value	Nimp
	Mean	SD	N	Mean	SD	N					
mNAPSI baseline	11.36	18.15	42	7.25	11.26	40					
mNAPSI week 12	6.37	10.66	43	4.78	8.73	41	0.68	(0.32,1.41)	-1.05	0.296	84
mNAPSI week 24	3.12	6.88	43	4.02	6.41	41	0.51	(0.23,1.09)	-1.74	0.081	84
mNAPSI week36	5.50	11.16	42	4.47	7.73	40	0.75	(0.36,1.59)	-0.74	0.458	84
mNAPSI week 52	7.72	12.27	40	3.91	7.32	34	1.12	(0.46,2.72)	0.26	0.798	84

Mean, Standard Deviation (SD) and Number (N) of participants with data available pre-imputation are presented for the observed values at baseline and weeks 12, 24, 36, and 52. The Incidence-Rate Ratio (IRR) between the treatment arms has been calculated using negative binomial regression, following carrying forward withdrawal visit data and then using multiple imputation to address any remaining missing data. Each estimate was adjusted for baseline values of the outcome and the stratification variable poly/oligoarthritis status (using the participant's actual status). The total number of participants included in analysis following imputation (Nimp) is also presented.

GOLMTX = combination of golimumab and methotrexate; PBOMTX = combination of placebo and methotrexate; mNAPSI = modified Nail Psoriasis Severity Index.

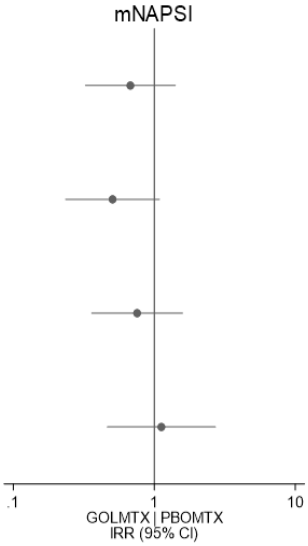

Figure 21 Forest Plot of Cutaneous Domain mNAPSI (Secondary Outcomes), Count-Distributed

Population: Full analysis set. Between-arm Incident Rate Ratios (IRR) and 95% Confidence Intervals (CI) were plotted for the analyses of count-distributed secondary outcomes. GOLMTX = combination of golimumab and methotrexate (Arm 1); PBOMTX = combination of placebo and methotrexate (Arm 2).

4.1.3 GOLMePsA Trial Imaging Results

All imaging data were originally collected as secondary outcomes or exploratory outcomes. As reported in paragraph 4.1.2.4, the analyses on the GOLMePsA trial primary endpoint did not produce statistically significant differences between treatment groups. Consequently, all analyses on any imaging data were downgraded to exploratory (see paragraph 3.3.7.2).

4.1.3.1 Ultrasound Scanning Imaging (Secondary Outcomes) Results

At first glance, data from the basal (baseline) US scores showed on average moderate levels of pathologies (Table 18). The results firstly reported in this section describe findings pertaining to the peripheral joints. In particular, the averages of global US GLOESS index were 24.8 (Arm 1 participants) and 21.6 (Arm 2 participants) –against a theoretical maximum of 72- in participants scanned at baseline. Among the participants who had an extended set of joints scanned (theoretical maximum score 144), the baseline average levels of global US GLOESS were 45.0 (Arm 1 participants) and 37.1 (Arm 2 participants).

However, breaking down the components of GLOESS -that is, GS abnormalities and PD findings- it was interesting to note one relevant discrepancy between the two components of GLOESS. The data portrayed in Figure 22 clearly point to the fact that the main contributor making up the global US GLOESS (top left panel) was in fact the GS total score (top right panel). This meant that GS abnormalities were indeed moderate in magnitude, on average, prior to exposure to the treatment interventions. However, the total PD articular score level at baseline was just of mild magnitude (below 5 – maximum scores possible were 72 or 144 if extended set of joints was scanned) across treatment groups (Figure 22, left bottom panel).

Basal findings in the entheses differed in magnitude to those related to US evaluation of the joints. Namely, the average baseline PD entheseal scores (regardless of whether the subset of entheses scanned were extended or not) were low in magnitude as compared to the theoretical maximum (all participants scanned subset - 5.4 among Arm 1 participants and 4.6 among Arm 2 participants, with theoretical maximum 30; extended entheses scanned subset - 7.1 among Arm 1 participants and 5.8 among Arm 2 participants, with theoretical maximum 36). The chronicity scores at baseline were also low or very low in magnitude, regardless of the subset (restricted or extended) of entheses scanned (Table 18).

Table 18 Ultrasound Scanning Imaging (Secondary Outcomes), Continuous Variables

	Arm 1 GOLMTX			Arm 2 PBOMTX			Difference	95% CI	t	p-value	Nimp
Score	Mean	SD	Nn	Mean	SD	Nn					
US GLOESS BSL	24.78	(13.02)	41	21.59	(11.19)	41					
US GLOESS WK12	23.07	(11.74)	40	18.74	(10.12)	39	1.72	(-2.04,5.48)	0.91	0.364	84
US GLOESS WK24	22.44	(10.26)	41	20.63	(10.06)	38	0.51	(-3.60,4.61)	0.25	0.806	84
US GLOESS WK36	24.20	(7.96)	41	22.46	(9.83)	39	1.05	(-2.79,4.89)	0.54	0.588	84
US GLOESS (extended subset) BSL	45.00	(19.67)	30	37.07	(14.95)	30					
US GLOESS (extended subset) WK12	38.07	(17.42)	30	31.14	(15.08)	28	2.59	(-5.14,10.32)	0.67	0.505	60
US GLOESS (extended subset) WK24	33.43	(16.16)	30	31.32	(17.65)	28	0.53	(-8.73,9.78)	0.11	0.910	60
US GLOESS (extended subset) WK36	33.40	(12.51)	30	31.79	(12.09)	28	1.38	(-5.22,7.99)	0.42	0.676	60
US enthes. INFL score BSL	5.37	(3.89)	38	4.25	(3.74)	36					
US enthes. INFL score WK12	4.68	(4.28)	38	4.86	(4.80)	36	-0.76	(-2.45,0.93)	-0.90	0.372	84
US enthes. INFL score WK24	4.90	(3.92)	39	4.89	(4.49)	37	-0.25	(-2.05,1.55)	-0.28	0.781	84
US enthes. INFL WK36	4.14	(3.45)	37	6.17	(6.49)	35	-2.26	(-4.39,-0.14)	-2.12	0.037	84
US enthes. INFL sc. (ext. subset) BSL	7.07	(4.84)	30	5.83	(4.38)	30					
US enthes. INFL sc. (ext. subset) WK12	6.25	(4.44)	28	5.22	(4.80)	27	0.57	(-1.63,2.77)	0.52	0.606	60
US enthes. INFL sc. (ext. subset) WK24	6.66	(6.19)	29	5.18	(4.47)	28	0.99	(-1.79,3.78)	0.72	0.478	60
US enthes. INFL sc. (ext. subset) WK36	4.66	(4.05)	29	7.04	(7.34)	26	-2.28	(-5.24,0.67)	-1.55	0.127	60
US enthes. CHRON sc. BSL	3.47	(3.03)	30	3.00	(3.10)	30					
US enthes. CHRON sc. WK12	2.50	(2.79)	34	3.17	(2.38)	29	-0.95	(-1.93,0.03)	-1.95	0.058	84
US enthes. CHRON sc. WK24	2.53	(2.21)	38	2.85	(2.31)	34	-0.60	(-1.54,0.35)	-1.26	0.213	84
US enthes. CHRON sc. WK36	2.97	(2.66)	37	2.79	(2.64)	33	0.31	(-0.88,1.50)	0.52	0.606	84
US enthes. CHRON sc. (ext. subset) BSL	4.17	(3.36)	30	3.87	(3.50)	30					
US enthes. CHRON sc. (ext. subset) WK12	3.31	(3.31)	29	3.62	(2.80)	26	-0.64	(-1.72,0.44)	-1.18	0.242	60
US enthes. CHRON sc. (ext. subset) WK24	2.93	(2.64)	29	3.52	(2.79)	27	-0.75	(-1.96,0.46)	-1.24	0.220	60
US enthes. CHRON sc. (ext. subset) WK36	3.59	(3.19)	29	2.38	(1.98)	26	1.03	(-0.23,2.29)	1.65	0.107	60

Population: Full analysis set. Results for imaging (continuous) secondary outcomes are presented. Mean, Standard Deviation (SD) and Number (N) of participants with data available pre-imputation are presented for the observed values at baseline (BSL) and weeks 12, 24 and 36 (WK12, WK24 and WK36). The difference between the treatment arms was calculated using multiple linear regression, following carrying forward withdrawal visit data and then using multiple imputation to address any remaining missing data. Each estimate was adjusted for baseline values of the outcome and the stratification variable poly/oligoarthritis status (using the participant's actual status). The total number of participants included in analysis following imputation, Nimp, is also presented. US = Ultrasound Scan; GLOESS = Global OMERACT-EULAR Scoring System; INFL = Inflammatory; CHRON = Chronicity

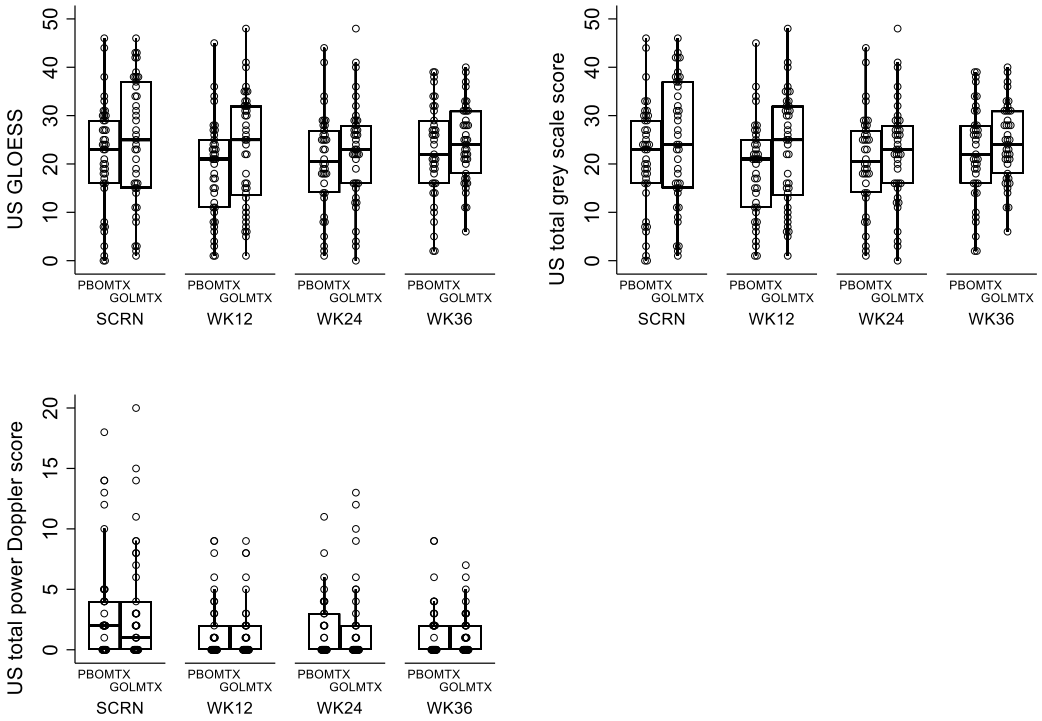

Figure 22 Box Plots of Ultrasound Scanning Imaging (Secondary Outcomes), GLOESS score, total Grey Scale and Power-Doppler, by Treatment Arm

Population: Full analysis set (observed data only). Graphical summary of descriptive data for continuous US variables over time, by treatment arm. Observed data were plotted; withdrawal visit data were carried forward for participants who withdrew from the intervention early.

US = Ultrasound Scan; GLOESS = Global OMERACT-EULAR Scoring System; GOLMTX = combination of golimumab and methotrexate (Arm 1); PBOMTX = combination of placebo and methotrexate (Arm 2); SCRN = Basal (baseline) scan; WK12 = Week 12; WK24 = Week 24; WK36 = Week 36

The analysis of follow-up US data showed that changes in ultrasound-detected pathologies were modest in magnitude, in both arms (Table 18). There were not clinically or statistically significant differences in US GLOESS score at any of the time-points, whether assessing the set of joints scanned in all participants or the expanded set of joints evaluated in a subset of participants (Figure 23). The (unplanned) descriptive summaries of total US GS and PD scores suggested that the US GLOESS score -at any time-point- primarily reflected the amount of findings captured by the GS scores; these did not show relevant fluctuation over time, whichever the treatment arm analysed (Figure 22). The same descriptive analysis showed that US GLOESS PD scores were low in magnitude -whichever the time-point considered- though it is important to note that these PD sub-indices showed a trend to improvement from baseline levels in both groups at weeks 12-36 (again, the differences were not statistically significant).

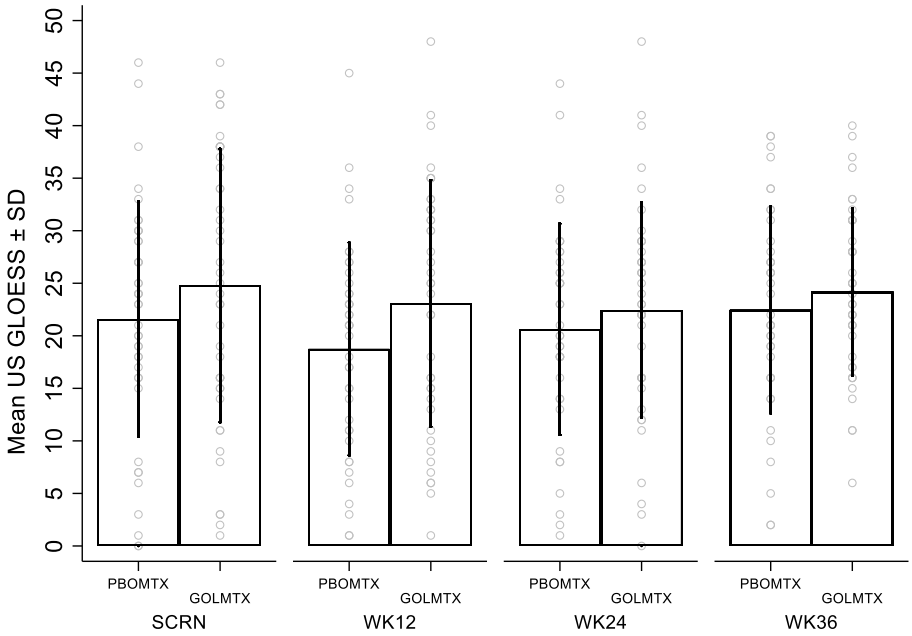

Figure 23 Plot of Ultrasound Scanning Imaging (Secondary Outcomes), GLOESS Score by Treatment Arm (Observed Data)

Population: Full analysis set. Graphical summary of descriptive data for US GLOESS over time, by treatment arm. Observed data were plotted; withdrawal visit data were carried forward for participants who withdrew from the intervention early.

US = Ultrasound Scan; GLOESS = Global OMERACT-EULAR Scoring System; SD = Standard Deviation; GOLMTX = combination of golimumab and methotrexate (Arm 1); PBOMTX = combination of placebo and methotrexate (Arm 2); SCRN = Basal (baseline) scan; WK12 = Week 12; WK24 = Week 24; WK36 = Week 36

The follow-up entheseal inflammatory score at weeks 12 or 24 did not differ across treatment groups -either using the main or expanded sets of entheses scanned. At 36 weeks, the data suggested (Figure 24, Figure 25) a benefit of the Arm 1 intervention regimen (GOLMTX) over that of Arm 2 (PBOMTX) [main set difference -2.26 (CI -4.39 to -0.14); p=0.037]. However, this appeared to be largely due to one participant in the PBOMTX arm with an extremely high score of 34 at this one visit, compared to the next highest score at this visit of 17. This participant was scanned by a different sonographer operator at each visit. Excluding this participant from an unplanned ad-hoc sensitivity analysis yielded a more modest estimate of the difference, which was not statistically significant [-1.52 (CI -3.18 to 0.13); p=0.071]. In addition, the mean chronicity score at week 36 was numerically lower in the PBOMTX arm, despite having shown some exploratory evidence of a difference in favour of GOLMTX at week 12 (Table 18, Figure 26).

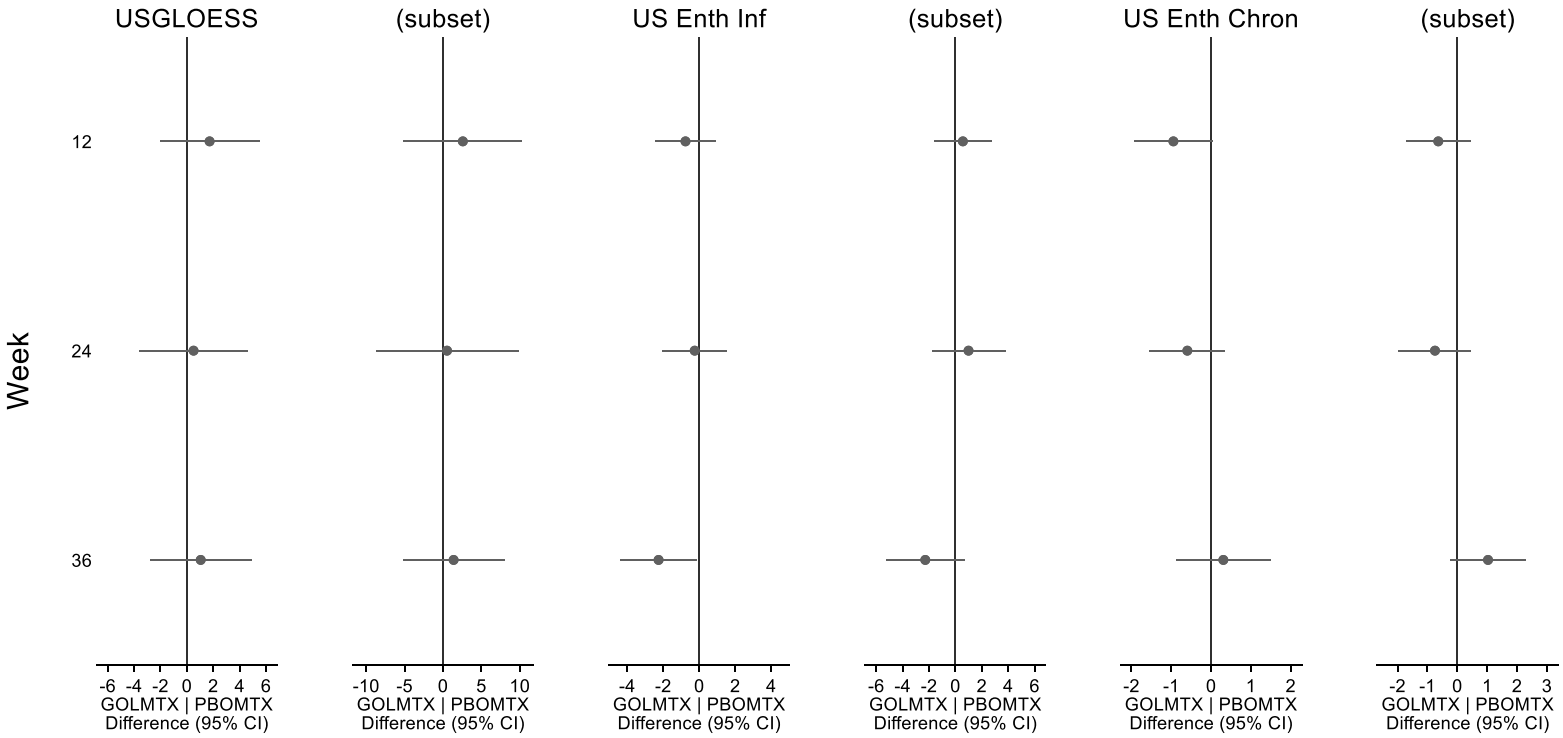

Figure 24 Forest Plots of Ultrasound Scanning Imaging (Secondary Outcomes), Continuous Variables

Population: Full analysis set. Mean between-arm differences and 95% Confidence Intervals (CI) were plotted for the analyses of continuous ultrasound secondary outcomes. US = Ultrasound Scan; GLOESS = Global OMERACT-EULAR Scoring System; Enth Inf = Entheseal Inflammatory; Enth Chron = Entheseal Chronicity; GOLMTX = combination of golimumab and methotrexate (Arm 1); PBOMTX = combination of placebo and methotrexate (Arm 2)

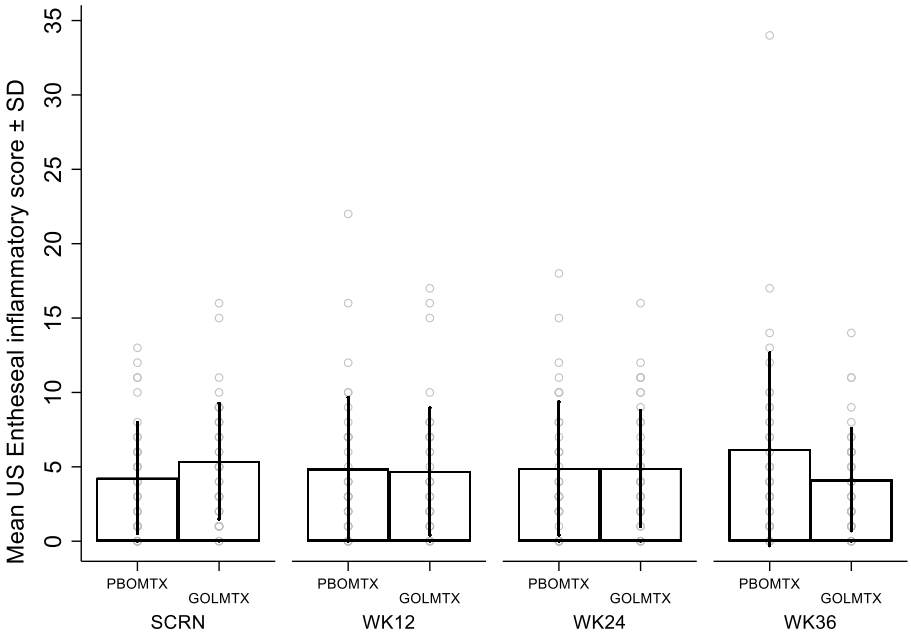

Figure 25 Plot of Ultrasound Scanning Imaging (Secondary Outcomes), Entheseal Inflammatory Score by Treatment Arm (Observed Data)

Population: Full analysis set. Graphical summary of descriptive data for US Entheseal inflammatory score over time, by treatment arm. Observed data were plotted; withdrawal visit data were carried forward for participants who withdrew from the intervention early.

US = Ultrasound Scan; SD = Standard Deviation; GOLMTX = combination of golimumab and methotrexate (Arm 1); PBOMTX = combination of placebo and methotrexate (Arm 2); SCRN = Basal (baseline) scan; WK12 = Week 12; WK24 = Week 24; WK36 = Week 36

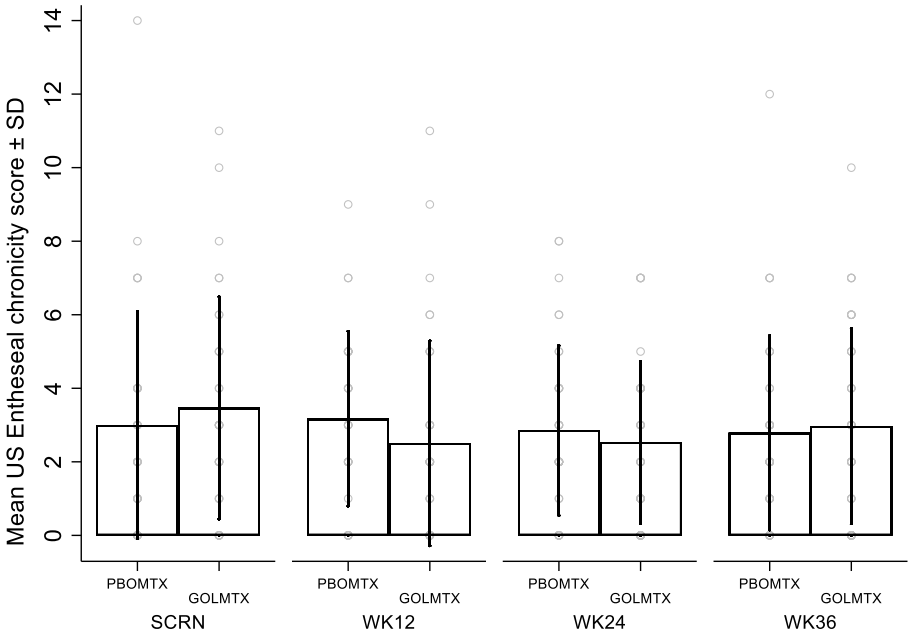

Figure 26 Plot of Ultrasound Scanning Imaging (Secondary Outcomes), Entheseal Chronicity Score by Treatment Arm (Observed Data)

Population: Full analysis set. Graphical summary of descriptive data for US Entheseal chronicity score over time, by treatment arm. Observed data were plotted; withdrawal visit data were carried forward for participants who withdrew from the intervention early.

US = Ultrasound Scan; SD = Standard Deviation; GOLMTX = combination of golimumab and methotrexate (Arm 1); PBOMTX = combination of placebo and methotrexate (Arm 2); SCRN = Basal (baseline) scan; WK12 = Week 12; WK24 = Week 24; WK36 = Week 36

No participant was in US remission at the time of the basal scan preceding the exposure to trial interventions. Only a minority of participants achieved US remission (<10% in each allocation group, at each visit) and there were no statistically significant differences between the treatment arms (Table 19, Figure 27, Figure 28). The remission criteria for both articular and entheseal pathology were GS<2 and PD=0 (paragraph 3.2.5.1).

One illustrating image of successful course of treatment as assessed by US is provided in Figure 29.

Table 19 Ultrasound Scanning Imaging (Secondary Outcomes), Binary Variables

	Arm 1 GOLMTX			Arm 2 PBOMTX			OR	95% CI	t	p-value	Nimp
	n	N	%	n	N	%					
US imaging remission WK12	1	/43	(2.3)	4	/41	(9.8)	0.33	(0.04,2.83)	-1.02	0.309	84
US imaging remission WK24	3	/43	(7.0)	3	/41	(7.3)	0.87	(0.17,4.60)	-0.16	0.871	84
US imaging remission WK36	1	/43	(2.3)	2	/41	(4.9)	0.48	(0.04,5.52)	-0.59	0.555	84

Population: Full analysis set. This table presents results for imaging binary secondary outcomes. Descriptive data [n /N (%)] are presented for the observed values at weeks 12, 24 and 36 (WK12, WK24 and WK36). The difference between the treatment arms was calculated using binary logistic regression, assuming non-response for anyone who withdrew from protocol treatment. Multiple imputation was then used to address any remaining missing data. Each estimate was adjusted for the stratification variable poly/oligoarthritis status (using the participant's actual status). The total number of participants included in analysis following imputation, Nimp, is also presented.

US = Ultrasound Scan

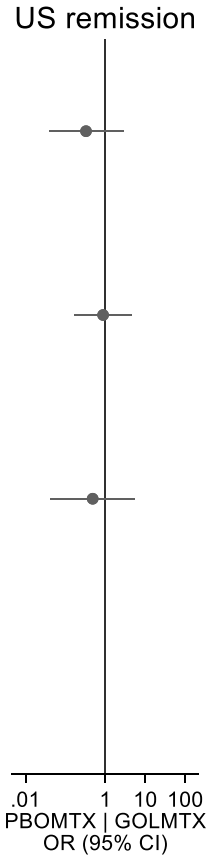

Figure 27 Forest Plot of Ultrasound Scanning Imaging - Remission (Secondary Outcomes), Binary Variables

Population: Full analysis set

Between-arm Odds Ratios (OR) and 95% Confidence Intervals (CI) were plotted for the analyses of imaging secondary outcomes (binary).

US = Ultrasound Scan; GOLMTX = combination of golimumab and methotrexate (Arm 1); PBOMTX = combination of placebo and methotrexate (Arm 2)

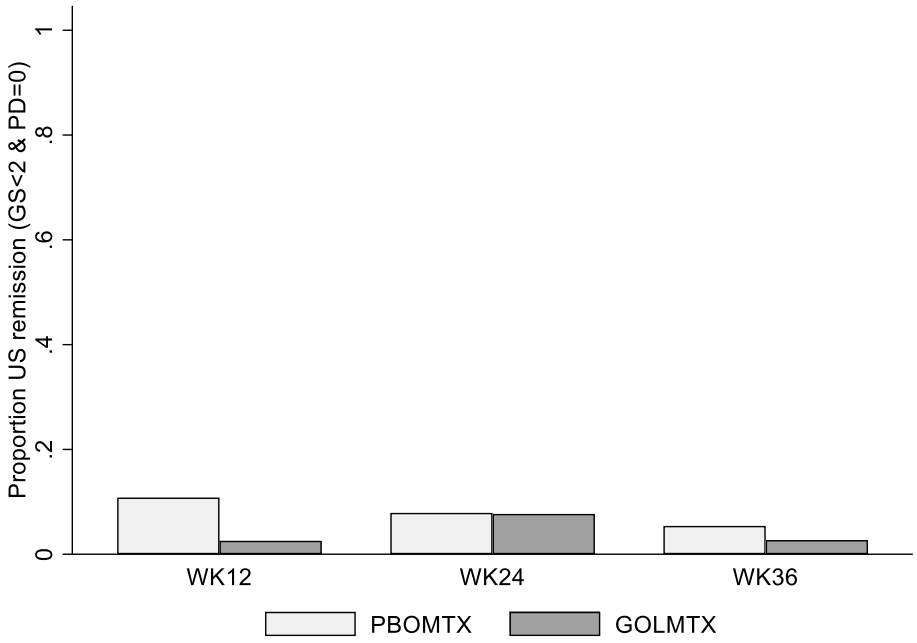

Figure 28 Plot of Ultrasound Scanning Imaging (Secondary Outcomes), Remission (GS<2 & PD=0) by Treatment Arm (Observed Data)

Population: Full analysis set. Graphical summary of descriptive data for US remission (GS<2 & PD=0) over time, by treatment arm. Observed data were plotted; non-response was assumed for participants who withdrew from the intervention early.

US = Ultrasound Scan; SD = Standard Deviation; GOLMTX = combination of golimumab and methotrexate (Arm 1); PBOMTX = combination of placebo and methotrexate (Arm 2); WK12 = Week 12; WK24 = Week 24; WK36 = Week 36

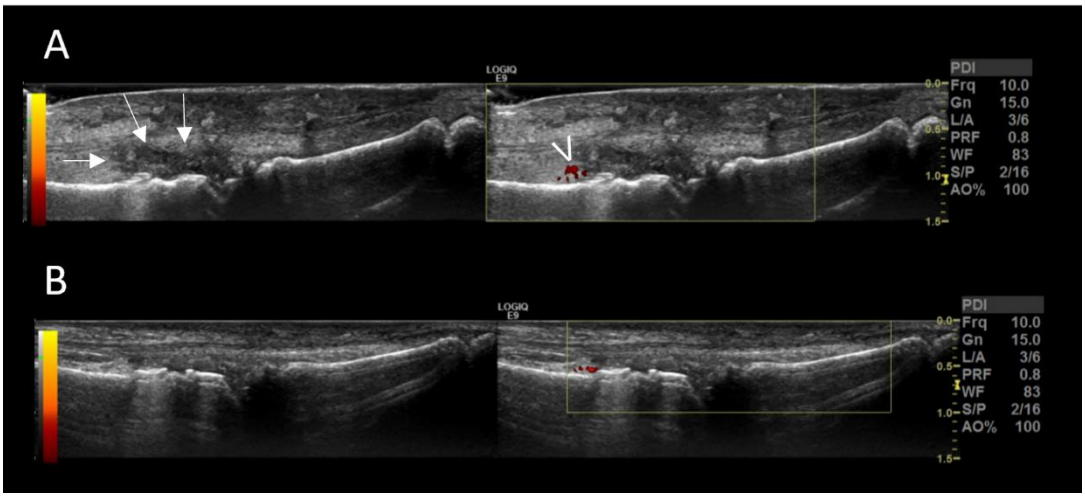

Figure 29 Example of Successful Treatment as Assessed by US Scan

Female, 40-year-old at the time of enrolment in GOLMePsA. Clinical polyarthritis associated with dactylitis. Cutaneous domains were involved, with minimal plaque psoriasis and psoriatic nail dystrophy.

HLA-B27 negative, C-Reactive protein at baseline 36 mg/L.

Allocated to Arm 1 (combination of golimumab and methotrexate).

C-Reactive protein at week 24 (primary outcome endpoint) normalized.

The images depict metatarsal-phalangeal joint number two of the left foot.

Panel A: Moderate synovial hypertrophy (arrows, image on the top left side) and mild power-Doppler signal (arrowhead, top right-sided image) found at the time of baseline, preceding exposure to trial intervention. Increased thickness of the subcutaneous tissues (oedema), due to dactylitis, is also visible.

Panel B (bottom images): Full resolution of the synovial hypertrophy and substantial reduction of the subcutaneous oedema. Minimal residual power-Doppler signal, at the proximal articular capsule attachment onto the metatarsal bone (right-sided bottom image, red spot). Images taken at the time of trial intervention conclusion (week 24).

Image -captured with consent by the participant- courtesy of Dr. Di Matteo, scan performed at the National Institute for Health Research, Leeds Biomedical Research Centre, Chapel Allerton Hospital (Leeds Teaching Hospitals NHS Trust).

4.1.3.2 Magnetic Resonance Imaging (Exploratory Outcomes) Results

Between November 2015 and January 2018, 37 persons who consented to take part in the GOLMePsA programme underwent the scheduled MRI scans that preceded exposure to IMP. Of these patients, 2 (2/37; 5.4%) failed the trial screening procedures and concluded participation in the study prior to exposure to the IMP.

In total, 35 GOLMePsA participants -who subsequently received the IMP at least once- also underwent basal MRI scans. Overall, 35 out of the 84 participants recruited (41.7%) had the basal MRI scan.

It would be useful to mention that in 2018 the MRI scanner originally used at the time of GOLMePsA inception was decommissioned. At that time, the study recruitment was underperforming and in addition recruitment activities were paused by the trial sponsor (LTHT) due to auditing processes. The decommissioning of the original scanner -itself needed in order to replace the machine with a more recent model- would have determined subsequent relevant differences in the quality of new images acquired with the new system. This would have in turn created a substantial lack of homogeneity between the GOLMePsA participants who were enrolled up to 2018 and those who were enrolled thence until the conclusion of recruitment (in 2023). In consideration of the impact on the scientific integrity of the data collection that such an event would have generated, the GOLMePsA investigators took the decision to terminate MRI data acquisition in 2018 -allowing for the last participant scanned to reach the last time-point of planned imaging acquisition (week 36)- and to downgrade the MRI data from secondary to exploratory endpoint.

By 2018, Participants enrolled and baselined in the trial were 49. At that time, therefore, 71.4% (35/49) successfully attended the basal MRI scan. The 14 participants unable to undergo the MRI scan presented with contraindications to the procedure (mainly allergic statuses that contra-indicated the injection of gadolinium-based contrast agents).

Out of 35 patients who underwent basal MRI scans, 31 (88.6%) were able to attend planned follow-up scans at week 24 and at week 36. The instances of failed attendance were all due to unforeseen circumstances, so no rectification was possible despite the best organizational efforts produced by the GOLMePsA staff.

Data from the basal (baseline) scores showed fairly low levels of inflammatory pathology (Table 20), as expected in cases of PsA at early stage. The data, regardless of the score considered, were skewed in distribution.

Table 20 Magnetic Resonance Imaging (Exploratory Outcomes) Total Scores at Baseline

Variable	Allocation		
	Arm 1 (GOLMTX) N=14	Arm 2 (PBOMTX) N=17	Total N=31
Peripheral			
MRI-WIPE	29.0 (14.0-40.0); 12.0 to 84.0, n=13	42.0 (27.0-63.0); 5.0 to 116.0, n=16	37.0 (19.0-55.0); 5.0 to 116.0, n=29
HEMRIS Inflammation	1.5 (1.0-5.0); 0.0 to 7.0, n=14	1.0 (0.5-4.0); 0.0 to 11.0, n=16	1.0 (1.0-5.0); 0.0 to 11.0, n=30
HEMRIS Structural	0.0 (0.0-0.0); 0.0 to 0.0, n=14	0.0 (0.0-0.0); 0.0 to 0.0, n=16	0.0 (0.0-0.0); 0.0 to 0.0, n=30
HIMRISS BML	0.0 (0.0-0.0); 0.0 to 0.0, n=14	0.0 (0.0-0.0); 0.0 to 0.0, n=17	0.0 (0.0-0.0); 0.0 to 0.0, n=31
HIMRISS Effusion	5.0 (2.0-7.0); 0.0 to 14.0, n=14	7.0 (4.0-11.0); 0.0 to 20.0, n=17	6.0 (3.0-10.0); 0.0 to 20.0, n=31
KIMRISS BML	3.0 (0.0-18.0); 0.0 to 32.0, n=13	7.0 (0.0-25.0); 0.0 to 66.0, n=17	5.5 (0.0-20.0); 0.0 to 66.0, n=30
Axial			
SPARCC Sacro-iliac	0.0 (0.0-2.0); 0.0 to 6.0, n=14	0.0 (0.0-1.5); 0.0 to 7.0, n=16	0.0 (0.0-2.0); 0.0 to 7.0, n=30
SPARCC Spine	0.0 (0.0-3.0); 0.0 to 6.0, n=14	0.0 (0.0-4.0); 0.0 to 21.0, n=16	0.0 (0.0-3.0); 0.0 to 21.0, n=30
CANDEN BMO	0.0 (0.0-2.0); 0.0 to 3.0, n=14	0.0 (0.0-3.0); 0.0 to 12.0, n=16	0.0 (0.0-2.0); 0.0 to 12.0, n=30
CANDEN Erosion	0.0 (0.0-0.0); 0.0 to 3.0, n=14	0.0 (0.0-0.0); 0.0 to 2.0, n=16	0.0 (0.0-0.0); 0.0 to 3.0, n=30
CANDEN Fat	0.0 (0.0-2.0); 0.0 to 8.0, n=14	0.0 (0.0-1.0); 0.0 to 4.0, n=16	0.0 (0.0-1.0); 0.0 to 8.0, n=30
CANDEN NBF	0.0 (0.0-0.0); 0.0 to 4.0, n=14	0.0 (0.0-0.0); 0.0 to 12.0, n=16	0.0 (0.0-0.0); 0.0 to 12.0, n=30

Variables presented as median (1st quartile to 3rd quartile), range, and number. MRI-WIPE = MRI Whole-Body Score for Inflammation in Peripheral Joints and Entheses in Inflammatory Arthritis; HEMRIS = Heel Enthesitis MRI Scoring; HIMRISS = Hip Inflammation MRI Scoring System; BML/BMO = Bone Marrow Lesion/Oedema; KIMRISS = Knee Inflammation MRI Scoring System; SPARCC = Spondyloarthritis Research Consortium of Canada; CANDEN = Canada-Denmark MRI Scoring System; NBF = New Bone Formation.

In particular, the median value of 37 of the MRI-WIPE score -among the 31 scans evaluated at baseline- points to overall low magnitude of inflammatory burden, as even the highest value recorded (scored value: 116) in GOLMePsA participants is far below the maximum score possible by MRI-WIPE (that is, a value of 738).

The variables that resulted in higher values scored (MRI-WIPE, HIMRISS, KIMRISS and HEMRIS inflammation) were influenced by the anatomical location of the disease activity they were designed to capture (that is, peripheral joints and peripheral entheses pathologies, against axial skeleton - Table 20). The reader is reminded that the eligibility criteria of the GOLMePsA trial (Appendix 2) emphasized the presence of active manifestations of PsA disease affecting the peripheral joints, not the axial skeleton. Therefore, the discrepancies in MRI scores may reflect a selection bias embedded in the trial design.

When the same variables were dichotomized (Table 21), the disproportion between axial and peripheral scores persisted, however, it became clear that the levels of inflammatory burden captured by MRI were more apparent when compared to clinical evaluation of axial PsA (for comparison see Table 9, where cases clinically categorized as axial were only 3.6% in total).

The dichotomized scores capturing the presence of inflammatory lesions in peripheral joints and enthesis also show that lesions, albeit usually low in intensity, were present virtually in all participants scanned.

The differences between the proportion of structural lesions (erosions, fatty lesions and new bone formation) detected by CANDEN (12.9%, 35.5% and 19.4%, respectively) and that of structural pathology detected by HEMRIS (absence of lesions) were substantial. However, the reader is reminded that scores such as HIMRISS, KIMRISS and MRI-WIPE do not capture structural lesions by design.

Table 21 Magnetic Resonance Imaging (Exploratory Outcomes), Dichotomized Scores at Baseline

Variable	Allocation		
	Arm 1 GOLMTX N=14	Arm 2 PBOMTX N=17	Total N=31
Peripheral			
MRI-WIPE			
Present	13 (92.9%)	16 (94.1%)	29 (93.5%)
Missing	1 (7.1%)	1 (5.9%)	2 (6.5%)
HEMRIS Inflammation			
Absent	2 (14.3%)	4 (23.5%)	6 (19.4%)
Present	12 (85.7%)	12 (70.6%)	24 (77.4%)
Missing	0 (0.0%)	1 (5.9%)	1 (3.2%)
HEMRIS Structural			
Absent	14 (100.0%)	16 (94.1%)	30 (96.8%)
Missing	0 (0.0%)	1 (5.9%)	1 (3.2%)
HIMRISS BML			
Absent	14 (100.0%)	17 (100.0%)	31 (100.0%)
HIMRISS Effusion			
Absent	3 (21.4%)	1 (5.9%)	4 (12.9%)
Present	11 (78.6%)	16 (94.1%)	27 (87.1%)
KIMRISS BML			
Absent	6 (42.9%)	6 (35.3%)	12 (38.7%)
Present	7 (50.0%)	11 (64.7%)	18 (58.1%)
Missing	1 (7.1%)	0 (0.0%)	1 (3.2%)
Axial			
SPARCC Sacro-iliac			
Absent	10 (71.4%)	11 (64.7%)	21 (67.7%)
Present	4 (28.6%)	5 (29.4%)	9 (29.0%)
Missing	0 (0.0%)	1 (5.9%)	1 (3.2%)
SPARCC Spine			
Absent	10 (71.4%)	9 (52.9%)	19 (61.3%)
Present	4 (28.6%)	7 (41.2%)	11 (35.5%)
Missing	0 (0.0%)	1 (5.9%)	1 (3.2%)
CANDEN BMO			
Absent	10 (71.4%)	9 (52.9%)	19 (61.3%)
Present	4 (28.6%)	7 (41.2%)	11 (35.5%)
Missing	0 (0.0%)	1 (5.9%)	1 (3.2%)
CANDEN Erosion			
Absent	12 (85.7%)	14 (82.4%)	26 (83.9%)
Present	2 (14.3%)	2 (11.8%)	4 (12.9%)
Missing	0 (0.0%)	1 (5.9%)	1 (3.2%)
CANDEN Fat			
Absent	8 (57.1%)	11 (64.7%)	19 (61.3%)
Present	6 (42.9%)	5 (29.4%)	11 (35.5%)
Missing	0 (0.0%)	1 (5.9%)	1 (3.2%)
CANDEN NBF			
Absent	11 (78.6%)	13 (76.5%)	24 (77.4%)
Present	3 (21.4%)	3 (17.6%)	6 (19.4%)
Missing	0 (0.0%)	1 (5.9%)	1 (3.2%)

Categorical variables presented as n (%). MRI-WIPE = MRI Whole-Body Score for Inflammation in Peripheral Joints and Entheses in Inflammatory Arthritis; HEMRIS = Heel Enthesitis MRI Scoring; HIMRISS = Hip Inflammation MRI Scoring System; BML/BMO = Bone Marrow Lesion/Oedema; KIMRISS = Knee Inflammation MRI Scoring System; SPARCC = Spondyloarthritis Research Consortium of Canada; CANDEN = Canada-Denmark MRI Scoring System; NBF = New Bone Formation.

The analysis of follow-up MRI data showed improvements in the MRI-WIPE score (Figure 30). Participants assigned to Arm 1 (GOLMTX) achieved median delta (the difference between time-points) of -10 at week 24 and -7 at week 36. Participants in Arm 2 (PBOMTX) achieved median delta of -6 and -9, respectively. There were no statistical differences between the two treatment arms, at any time-point. No participant achieved remission (that is, total score = 0) by criterion of MRI-WIPE.

Changes on MRI over time occurring to one emblematic GOLMePsA participant are presented in Figure 31.

The median HEMRIS inflammation score, however, improved only modestly (median delta -1) in participants allocated to Arm 1 and only at week 36. Again, there were no statistical differences between treatment groups. The same observations were recorded in regards with KIMRISS (BML). The HIMRISS effusion score worsened in participants allocated to Arm 1 at week 24, only to revert to baseline values at week 36 in the same group. Again, there were no statistical differences between treatment arms.

Data pertaining to the scores CANDEN and SPARCC MRI (both spine and sacroiliac joints) were sparse and required dichotomization to improvement achieved/not achieved. CANDEN BMO and SPARCC MRI spine scores improved in 7.1% of participants assigned to Arm 1 at both week 24 and week 36. No statistical difference was found between treatment groups. SPARCC MRI sacroiliac joints score improved in 7.1% (week 24) and 6.7% (week 36) of participants assigned to Arm 2. No statistical difference was found between treatment groups. CANDEN erosion score improved in 7.1% of participants assigned to Arm 1 and in 7.1% of participants assigned to Arm 2, at both week 24 and week 36. No statistical difference was found between treatment groups. Scores of CANDEN fatty lesions and new bone formation did not show improvements in either treatment group, at any time point.

Data pertaining to the scores HEMRIS structural and HIMRISS BML were also sparse and required dichotomization to improvement achieved/not achieved. Both did not show improvements in either treatment group, at any time point.

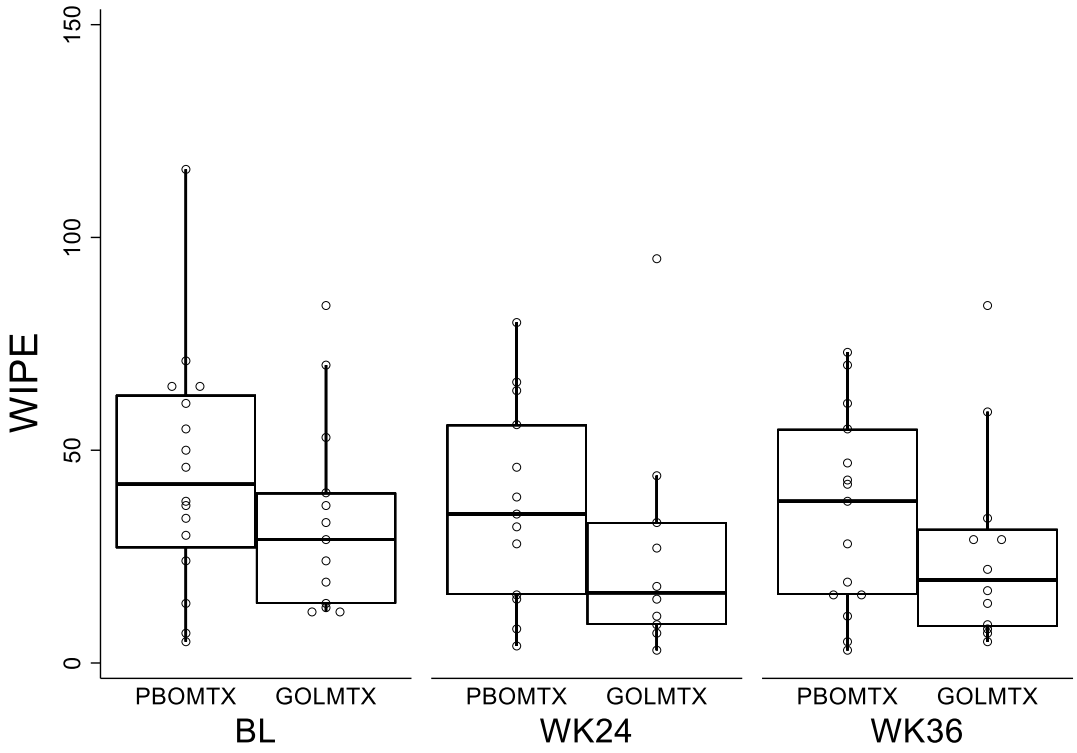

Figure 30 Plot of MRI-WIPE (Exploratory Outcomes), by Treatment Arm (Observed Data)

Population: Full analysis set (restricted to those with MRI data available)

Graphical summary of descriptive data for WIPE over time, by treatment arm. Observed data were plotted.

WIPE = MRI Whole-Body Score for Inflammation in Peripheral Joints and Entheses in Inflammatory Arthritis (MRI-WIPE); GOLMTX = combination of golimumab and methotrexate (Arm 1); PBOMTX = combination of placebo and methotrexate (Arm 2); BL = Baseline; WK12 = Week 12; WK24 = Week 24; WK36 = Week 36

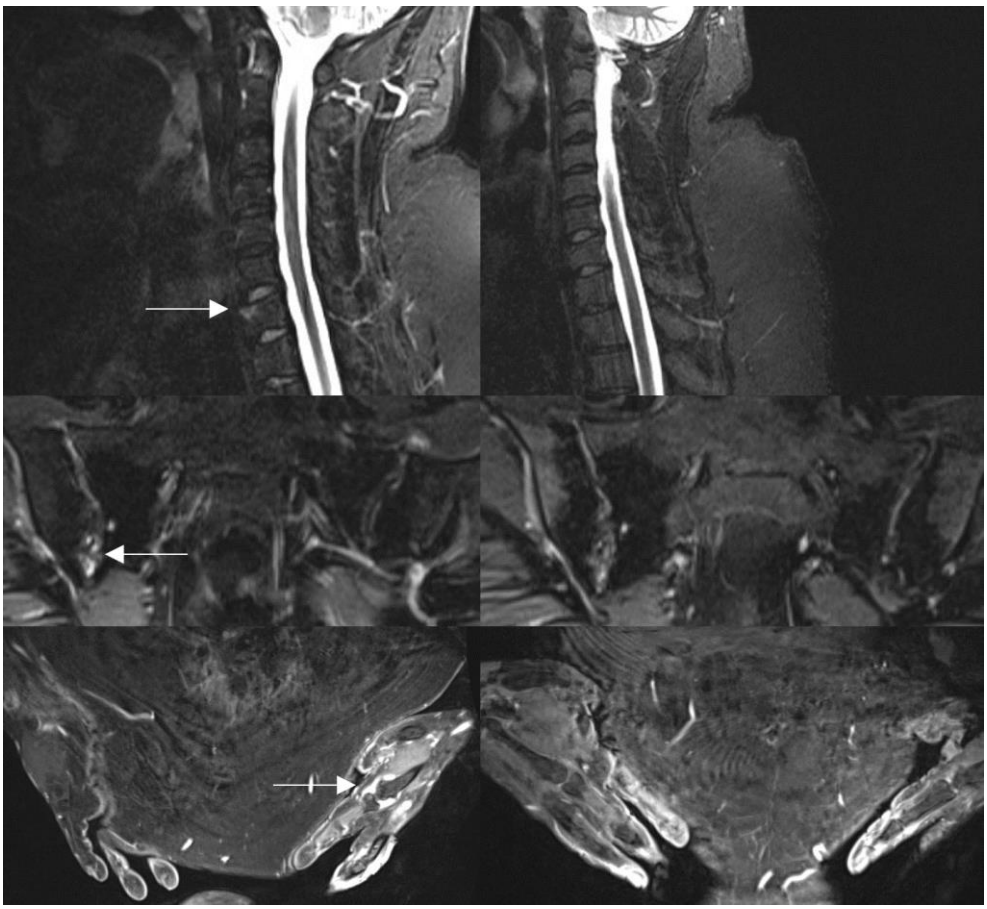

Figure 31 Effects of GOLMePsA Intervention on Magnetic Resonance Imaging Findings

Overweight man, 35-year-old at the time of GOLMePsA baseline (images on left side). Clinical polyarthritis associated with dactylitis. Cutaneous domains were involved, with extensive plaque psoriasis and psoriatic nail dystrophy.

HLA-B27 positive; anti-CCP (>300.0 U/mL) and RF (262 IU/mL) positive.

Baseline C-RP was 165 mg/L.

Participant allocated to Arm 1 (combination of golimumab and methotrexate).

The top panel shows presence of BMO in vertebra C6 (anterior-superior corner, arrow). The middle panel shows bilateral sacroiliac joints enthesitis and synovitis in the right sacroiliac joint (arrow). The lower panel shows gadolinium-enhanced synovitis in the metacarpal-phalangeal joint two of the left hand (arrow). The right-sided panels show the images of the same anatomical sites at week 24 (top to bottom). Improvement of all lesions described is apparent. CRP post-treatment was 10.8 mg/L.

Anti-CCP = Anti-Cyclic Citrullinated Peptides autoantibodies; RF = Rheumatoid Factor; C-RP = C-Reactive Protein; BMO = Bone Marrow Oedema

4.1.4 PASDAS Score Test-Retest Results

The PASDAS test-retest reliability was assessed in 37 consecutive participants. The average time between the two time-points used for this analysis (visit 1, screening; visit 2, baseline) was 1.9 weeks (range 0.4 to 4.0). Baseline characteristics of the test-retest subset compared to those of all GOLMePsA participants were similar (Table 22).

The ICC was 0.85 (95% CI 0.73-0.92). The observed ICC was identical to the value assumed in the sample size calculation for this analysis, yielding an acceptably narrow CI around the estimate. There was no substantial correlation between the means of the two measurements and the differences between them (Pearson's r=-0.26). The Bland-Altman limits of agreement were:

-0.11 ± 1.24 (-1.35 to 1.13).

There was no evidence of consistent bias and acceptably narrow 95% limits of agreement were recorded. There was no evidence that the extent of differences between repeated measurements was associated with their magnitude.

Table 22 PASDAS Tet-Retest Exercise - Demographic and clinical Characteristics of the GOLMePsA Participants at the Baseline Time-Point

Variable	All participants (n=84)	Test-retest subset (n=37)[A]
Age, in years (mean)	42.5 (SD 12.4)	39.9 (SD 12.7)
Sex – females/males (n)	38/46	18/19
Peripheral joints symptoms duration, in months (median)	10.5 (IQR 5.4-21.6)	10.5 (IQR 5.3-22.0)
PASDAS score (mean)[B]	5.7 (SD 1.2)	5.8 (SD 1.2)
Polyarticular phenotype (n)	61 (72.6%)	30 (81.1%)
Dactylitis present (n)	42 (50%)	22 (59.5%)
Leeds Enthesitis Index (median)	1.0 (IQR 0.0-2.0)	1.0 (IQR 0.0-2.0)
PASI score (median)	2.7 (IQR 0.6-6.0)	3.9 (IQR 0.6-6.7)

SD = Standard Deviation; IQR = inter-quartile ranges; PASDAS = Psoriatic Arthritis Disease Activity Score; PASI = Psoriasis Area and Severity Index

A) To estimate the $ICC_{(3,1)}$ between two repeated readings of the PASDAS with a Confidence Interval (CI) of width 0.2, it was calculated that at least 31 participants would be needed (assuming an ICC of 0.85, based on a published estimate of ICC=0.87 for participant's global assessment of disease activity Visual-Analogue Scale (VAS), which provides the greatest loading on the PASDAS score).

B) PASDAS mean scores reflected high disease activity levels.

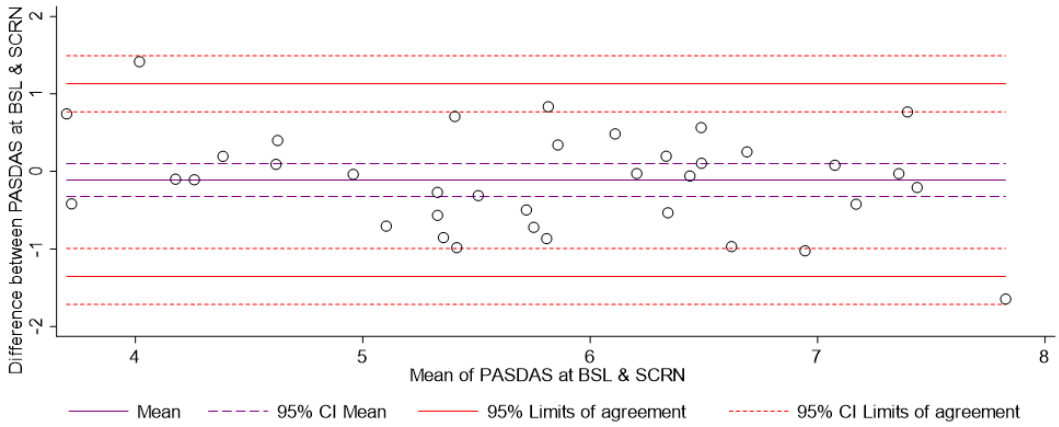

Figure 32 Bland-Altman Plot of PASDAS Test-Retest Exercise at Screening vs Baseline

Population: Full analysis set (observed data only).

In participants with PASDAS data available at both screening and baseline, the difference between the two measurements was plotted against the mean. In addition, the two-way mixed intraclass correlation coefficient (ICC) (absolute agreement definition; single measure) was calculated. This analysis was performed in the subgroup of GOLMePsA participants recruited since the collection of PASDAS components at screening was added in a specific amendment to protocol.

PASDAS = Psoriatic Arthritis Disease Activity Score; SCRN = Screening; BSL = Baseline

4.1.5 PsA Remission Results

The analysis of PsA remission data was out of the original scope of the GOLMePsA trial statistical analysis plan. No participant was in remission at the baseline (week 0) time-point, by any of the criteria or outcome measures evaluated in this post-hoc analysis. Results of the Fisher's exact test comparing binary remission outcomes between the treatment arms are presented in Table 23. No participant fulfilled the remission criteria of set C, at any time-point.

4.1.5.1.1 PASDAS Score Values in Participants Fulfilling Remission Criteria Set A

Overall, 7/84 participants (8.3%) fulfilled this set, in a total of fourteen instances across trial time-points. Four of these persons were allocated to Arm 1 (GOLMTX) and 3 were allocated to Arm 2 (PBOMTX). Four participants (4.8%) fulfilled remission criteria set A at week 24 (the primary endpoint of the trial).

Two participants met the set A remission criteria at week 12. both were in the treatment arm 2 (PBOMTX), their PASDAS scores were 0.78 and 1.25.

Four participants met the set A remission criteria at week 24. One was in the treatment arm 2 (PBOMTX; PASDAS score 1.48) and 3 were in the treatment arm 1 (GOLMTX); their PASDAS scores were: 0.43; 0.84; 0.87. The Mean PASDAS score of participants achieving remission criteria set A at week 24 was 0.905 (99% CI: -0.3587 to 2.1687), the SD was 0.4327, the median was 0.855.

Five participants met the remission set A criteria at week 36. One was in the treatment arm 2 (PBOMTX; PASDAS score 0.47) and 4 were in the treatment arm 1 (GOLMTX; PASDAS scores were: 0.89; 0.91; 1.31; 1.49). The Mean PASDAS score of participants achieving remission criteria set A at week 36 was 1.014 (99% CI: 0.1928 to 1.8352), the SD was 0.39885, the median was 0.91.

Three participants met the set A remission criteria at week 52. All these persons were allocated to treatment arm 1 (PASDAS scores were: 0.45; 0.75; 1.26 - mean 0.82; 99% CI: -1.53 to 3.17).

One participant (allocated to Arm 1, GOLMTX) achieved remission according to set A occasionally (that is, at one single time-point – namely week 36). Two participants (1 of these allocated to Arm 1, GOLMTX; the other allocated to Arm 2, PBOMTX) achieved remission (set A) on two separate occasions ("on-off" pattern, namely the first person at week 12 and at week 36; the other one at week 24 and at week 52). Three participants (2 allocated to Arm 1, GOLMTX; the other allocated to Arm 2, PBOMTX) achieved remission set A on two consecutive occasions ("transient" pattern). Interestingly, the participant allocated to Arm 2 who experienced remission set A transiently did so by the week 24 time-point; the other 2 persons achieved remission past week 24. Only 1 participant

(allocated to Arm 1, GOLMTX) achieved “sustained” remission set A (that is, remission fulfilled in three consecutive occasions).

Grouping all observed PASDAS values of participants who fulfilled remission criteria set A across trial time-points (14 observations), the mean was 0.9414 (99% CI: 0.6477 to 1.2352), the SD was 0.36486, the median was 0.88. These findings identified a novel subgrouping by PASDAS levels within -and probably distinct from- the so-called “near remission” [defined by PASDAS score ≤1.9 (Coates, L.C. and Helliwell, 2016a)].

No statistical differences in the rate of occurrence of remission set A -between treatment groups- was found at any time-point.

Notably, no participant who achieved remission according to criteria set A needed to start bDMARDs during the observational period (week 24 to week 52) of the GOLMePsA trial.

4.1.5.1.2 PASDAS Score Values in Participants Fulfilling Remission Criteria Set B

Overall, 4/84 participants (4.8%) fulfilled this set, in a total of seven instances across different time-points (baseline excluded). All persons classified in this subgroup also met remission criteria set A. Three of the participants who achieved remission criteria set B were allocated to Arm 1 (GOLMTX) and 1 was allocated to Arm 2 (PBOMTX). Only 1 participant (out of 84; 1.2%) fulfilled remission criteria set B at week 24 (the primary endpoint of the GOLMePsA trial).

One participant met the remission set B criteria at week 12. They were allocated to the treatment arm 2 (PBOMTX) and their PASDAS score was 0.78.

One participant met the remission set B criteria at week 24. They were randomized to treatment arm 1 (GOLMTX) and their PASDAS score was 0.87.

Three participants met the remission set B criteria at week 36. One was allocated to treatment arm 2 (PASDAS score: 0.47) and two were randomized to treatment arm 1 (PASDAS scores were: 0.89; 0.91).

Two participants met the remission set B criteria at week 52. both were allocated to treatment arm 1, their PASDAS scores were 0.45 and 0.75.

One participant (allocated to arm 1, GOLMTX) achieved remission according to set B occasionally (that is, at one single time-point – namely week 36). Two participants (1 allocated to Arm 1, GOLMTX; the other allocated to Arm 2, PBOMTX) achieved remission (set B) on two separate occasions (“on-off” pattern, namely the first at week 24 and at week 52; the other one at week 12 and at week 36). Another participant (allocated to Arm 1, GOLMTX) achieved remission set B on two consecutive occasions (“transient” pattern). Notably, the

patterns of remission set B matched almost perfectly the ones recorded for remission set A in all participants, with only one exception (namely, the participant who achieved sustained set A remission experienced transient set B remission).

Grouping all observed PASDAS values of participants who fulfilled remission criteria set B across trial time-points (7 observations), the corresponding mean was 0.7314 (99% CI: 0.4592 to 1.0037), the SD was 0.19429, the median was 0.78. Again, these findings identified a novel subgrouping by PASDAS levels within -and probably distinct from- the so-called “near remission” [defined by PASDAS score ≤1.9 (Coates, L.C. and Helliwell, 2016a)].

No statistical differences in the rate of occurrence of remission set B -between treatment groups- was found at any time-point.

No participant who achieved remission according to criteria set B needed to start bDMARDs during the observational period (week 24 to week 52) of the GOLMePsA trial.

4.1.5.1.3 PASDAS Score Values in Participants Fulfilling Remission Criteria Set C

As presented in Table 23, no participant achieved remission -according to set C- at any time-point during the GOLMePsA trial. Therefore, statistical comparison between treatment groups was not possible.

4.1.5.1.4 Remission and Very Low Disease Activity as Measured by Different Composite Outcome Measures

In general, GOLMePsA participants allocated to Arm 1 (GOLMTX) achieved rates of CPDAI remission or VLDA or PASDAS “near remission” in more than 30% of cases (Table 23), by the week 24 time-point. Following that, rates of VLDA and PASDAS “near remission” decreased, while rates of CPDAI remission remained stable – or even increased briefly (at week 36).

The figures recorded from GOLMePsA participants allocated to Arm 2 (PBOMTX) show that, by week 24, VLDA or PASDAS “near remission” or CPDAI remission were achieved by roughly 17%. Interestingly, the rates improved at week 36 (irrespective of the outcome measure considered). By week 52, only CPDAI remission rate and VLDA improved (compared to week 24) in participants allocated to treatment group 2.

Differences between treatment arms, irrespective of the time-points or the outcome measures considered, were not statistically significant in this post hoc analysis – with the exception of CPDAI remission at week 24 (modest difference in favour of Arm 1 – GOLMTX).

Table 23 GOLMePsA trial, Remission Outcomes

	Arm 1 GOLMTX n/N (%)	Arm 2 PBOMTX n/N (%)	p-value
Remission set A, week 12	0/43 (0.0)	2/40 (5.0)	0.229
Remission set A, week 24	3/43 (6.9)	1/39 (2.5)	0.617
Remission set A, week 36	4/43 (9.3)	1/40 (2.5)	0.361
Remission set A, week 52	3/41 (7.3)	0/36 (0.0)	0.243
Remission set B, week 12	0/43 (0.0)	1/40 (2.5)	0.482
Remission set B, week 24	1/43 (2.3)	0/39 (0.0)	1.0
Remission set B, week 36	2/42 (4.7)	1/40 (2.5)	1.0
Remission set B, week 52	2/39 (5.1)	0/33 (0.0)	0.453
Remission set C, week 12	0/39 (0.0)	0/37 (0.0)	Not computed
Remission set C, week 24	0/39 (0.0)	0/36 (0.0)	Not computed
Remission set C, week 36	0/36 (0.0)	0/37 (0.0)	Not computed
Remission set C, week 52	Not applicable	Not applicable	Not applicable
Very Low Disease Activity, week 12	9/43 (20.9)	7/41 (17.1)	0.783
Very Low Disease Activity, week 24	15/43 (34.9)	7/41 (17.1)	0.084
Very Low Disease Activity, week 36	12/43 (27.9)	13/40 (32.5)	0.811
Very Low Disease Activity, week 52	9/42 (21.4)	7/37 (18.9)	1.0
PASDAS near remission, week 12	9/43 (20.9)	6/40 (15.0)	0.059
PASDAS near remission, week 24	15/43 (34.9)	7/41 (17.1)	0.236
PASDAS near remission, week 36	12/43 (27.9)	8/40 (20.0)	0.841
PASDAS near remission, week 52	8/42 (19.0)	4/36 (11.1)	0.369
CPDAI remission, week 12	8/43 (18.6)	3/41 (7.3)	0.494
CPDAI remission, week 24	14/43 (32.6)	7/41 (17.1)	0.044
CPDAI remission, week 36	16/43 (37.2)	12/40 (30.0)	0.268
CPDAI remission, week 52	14/42 (33.3)	11/37 (29.7)	0.859

Note that very low disease activity data present higher denominators due to missing data.
GOLMTX = combination of golimumab and methotrexate; PBOMTX = combination of placebo and methotrexate; PASDAS = Psoriatic ArthritiS Disease Activity Score; CPDAI = Composite Psoriatic Disease Activity Index

Chapter 5

5.1 Discussion

This chapter offers the considerations of this candidate related to the data presented and analysed in this thesis.

5.1.1 Considerations related to the GOLMePsA Trial Design

There were several elements of originality in the design of this trial. The first was in its aim, as the study tried to address the PsA/PsD heterogeneity by a multiplicity of objectives.

Namely, one “aggressive” conventional synthetic DMARD (csDMARD) treatment element was chosen with the decision of planning the titration of the weekly dose of MTX up to 25 mg in all trial participants, regardless of which treatment arm they were randomized to. The timescale of MTX titration was also an element of originality, as well as another way to treat the condition aggressively, in that participants went from 0 to 25 mg weekly dose over the short period of 28 days since therapy inception. Aside from the specifics of any MTX treatment dose conventionally chosen in rheumatology, the csDMARD of choice for the GOLMePsA intervention arms was the one more likely to exert simultaneous beneficial effects on multiple PsD domains (joints, skin and possibly nails) (Coates, L.C. et al., 2022b). This, in the opinion of this candidate, is another relevant element of originality of the GOLMePsA trial.

On top of all the factors listed so far, all participants received at baseline one depot IM dose of methylprednisolone 120 mg [in theory equivalent to 4.7 mg/day of oral prednisolone; by three weeks’ time past each injection, levels would decrease gradually until they become undetectable (Choy et al., 1993)]. Again, the choice of a combination treatment with csDMARD and steroids is expected to exert beneficial effects on multiple PsD domains (joints, dactylitis, enthesitis, skin, possibly nails) in a simultaneous manner (Coates, L.C. et al., 2022b). On a slightly different consideration, it can be argued that GOLMePsA participants were “protected” from the feared -yet not so common (Long et al., 2022)- PsO rebound phenomenon following administration of steroids, by virtue of being treated simultaneously with MTX.

To mention one additional element of originality, 43 participants were randomly allocated to receive GOL in association with MTX and methylprednisolone. In theory, this would allow to cover all manifestations of the PsD clinical spectrum (Coates, L.C. et al., 2022b) in a simultaneous manner. Therefore, the treatment approach adopted in GOLMePsA was one targeting PsD comprehensively and it

could be seen as rather distinct from the approaches adopted in other trials (Mease et al., 2019b; van Mens et al., 2019). Specifically, the trial by Mease (SEAM-PSA) compared 1:1:1 MTX monotherapy (administered up to just 20 mg/week) against etanercept monotherapy and against combination of MTX (administered up to 20 mg/week) with etanercept. Moreover, no steroid bolus was given at baseline. The study by van Mens adopted a slower MTX up-titration regime (over 8 weeks, up to 25 mg/week), without baseline steroid bolus. It could be argued that, had they have chosen more aggressive MTX regimens and administered these in association with steroid boluses (across treatment arms), the primary outcome statistical analyses reported by Mease and by van Mens may have yielded non-significant results too. In the opinion of this candidate, it is also interesting to note that -in both these trials- recruited patients may not be exactly treatment-naïve (the specific proportions of csDMARD-naïve and steroids-naïve recruits -or previous use of these agents for indications different from PsA- are not presented clearly in the original reports).

One additional important consideration has to be offered here. Current recommendations for the management of PsA (Gossec et al., 2024) discourage the use of systemic glucocorticoids, except for instances where localized injections are expected to bring beneficial effects (the typical case being intra-articular injections of selected joints) or when a gap between the end of one therapeutic regimen and the start of a new one (for example, moving from csDMARD to bDMARDs) needs cover. The recommendations from Gossec and colleagues, however, while correctly inviting to caution with the use of steroids (due to lack of high-quality evidence), do not address the potential role of these agents as inducer -or booster- of therapeutic response. Some evidence -though from RA- suggests that steroids may mitigate the side effects of MTX in treatment-naïve (that is, to both steroids and MTX) RA patients (van der Leeuw et al., 2023). Importantly, these authors reported substantial efficacy on gastro-intestinal side effects like nausea and the anti-rheumatic therapy inception setting they described was very similar to that of GOLMePsA (in which ultimately the MTX retention over time was surprisingly good). It is hoped that the data from the GOLMePsA programme will contribute to the development of future evidence covering this specific subject.

Moving onto a different order of considerations, another element of originality within the GOLMePsA programme was the adoption of a highly regarded (Coates, L.C. et al., 2021) composite outcome measure -the PASDAS, one that assesses disease activity across multiple domains of PsA simultaneously- as primary endpoint. To the best of the candidate’s knowledge, only two other clinical trials in PsA -both still at the enrolment stage or unpublished by the time of writing

this thesis- adopted PASDAS as primary outcome (Coates, L., 2018; Mulder et al., 2020). The use of PASDAS as primary outcome measure, instead of the more popular -and designed for use in RA trials- ACR20 response criteria (Felson et al., 1995), presented the invaluable advantage of appreciating the effects of trial interventions on MSK extra-articular PsA domains, such as enthesitis and dactylitis. Other trials that shared with GOLMePsA substantial similarities in the design (Coates, L.C. et al., 2015; Mease et al., 2019b; van Mens et al., 2019) adopted instead the ACR20 response outcome measure or the Disease Activity Score [DAS (van der Heijde et al., 1990), another RA specific tool] outcome measure as primary endpoint.

The last element of originality was the design of the post-interventional part of the GOLMePsA trial (week 24 to week 52). Instead of starting participants originally assigned to arm 2 (PBOMTX) on the active comparator GOL -as commonly seen in clinical trials- the observational part of GOLMePsA aimed at treating participants by standard options available in the NHS. Such a design choice offered the opportunity to record data related to the tolerance of MTX (as well as other compounds with anti-rheumatic properties), to the persistence of the effects of the originally allocated intervention and to their ability to perform as maintenance regime for treating PsA.

Some limitations of the GOLMePsA research programme have to be presented. The design of the trial allowed to assess the heterogeneity of PsA and PsD in a more comprehensive way than studies conducted in the past, however, GOLMePsA was not intended to investigate the diversity of the PsD clinical spectrum, or its several treatment options, in full. In the opinion of this candidate, the major limitation in the trial design was the “limited” number of study arms planned, as only two interventions could be compared at one time. Consequently, no direct comparison was possible in a number of other areas, such as:

- Early vs late intervention in PsA.
- Intense (up to 25 mg/week) vs moderate (<25 mg/week) and more paced use of MTX.
- Multiple choices of csDMARD in early PsA (for example, MTX vs leflunomide or vs apremilast).
- Specific choices of bDMARD in early PsA (for example, TNFi vs IL-23-inhibitors[1]).

[1] Of note, the effective use of ustekinumab -the first bDMARD approved for PsA and not belonging to the TNFi class- was not reported until 2013/2014 (PSUMMIT trials). At that time, the GOLMePsA programme was already at advanced stage of set up.

Other issues not investigated by design choice were the role of different csDMARDs combinations (for example, MTX and sulphasalazine) as first line therapy in treatment naïve, early PsA or the potential for sequential therapy (either alternating different csDMARDs with bDMARDs or alternating bDMARDs with different mechanisms of action).

There is limited evidence, from one small trial of participants affected by established PsA (therefore, not specifically at early stage) that effectiveness of apremilast and methotrexate is not statistically different on signs and symptoms of the disease (Samanta et al., 2023). The same matter in early PsA remains not formally addressed.

Therefore, despite the considerations listed above, the GOLMePsA programme successfully added knowledge to the current body of evidence available in early, untreated PsA.

5.1.2 Considerations Related to the GOLMePsA Trial Clinical Results

As presented in paragraph 4.1.2, the retention of participants throughout the trial was very good and the rate of withdrawal within the interventional period of the study (that is, between week 0 and week 24) was 4/84 (4.8%) in total. These events of withdrawal did not lead to an instance of formal statistical underpower, nor the higher withdrawal rate occurred in Arm 1 (GOLMTX) was detrimental to the scientific integrity of the trial. The evaluation of the issue pertaining to incorrect stratification at baseline was analysed and, again, no significant statistical impact was uncovered.

The ethnicity representation of the participants enrolled in GOLMePsA was in line with current rheumatology experience in the wider Yorkshire region and the familial associations with PsO, IBDs or forms of SpA were prevalent as expected in PsA patients. It is important to note that the prevalence of weight excess (mean BMI 29.8; participants weighting ≥100 kg 15/84 – equalling 17.9% of total recruits) also reflected the reality among PsA cases as commonly appreciated by healthcare operators in standard clinical practice. Overall, PsA-related features were well represented, including the quite characteristically low severity pattern of PsO (BSA ≤3% in 63/84 participant – equalling 75% of total recruits; median PASI 2.7 at baseline). However, in the opinion of this candidate, one exception to the considerations presented above seemed to be the overrepresentation of baseline dactylitic digits in the GOLMePsA participants. It is not possible to rule out that this finding represented an unintended by-product of the classification criteria chosen for purposes of trial eligibility [CASPAR (Taylor et al., 2006)]. On the other hand, though, the presence of dactylitis is associated with more severe phenotypes of PsA disease (Brockbank et al., 2005; Dubash, S. et al., 2022),

including polyarthritis, and this candidate reported that PASDAS levels at trial baseline (average value of 5.7 in 84 recruits) indeed corresponded to high disease activity levels. Therefore, it is possible that the high prevalence of dactylitis in the GOLMePsA population simply reflected an association to the already acknowledged possibility of selection bias -by virtue of disease severity- stated in chapter 4 (paragraph 4.1.2.3).

As presented throughout the results sections (from 4.1.2.3 to 4.1.2.5.2), all clinical parameters of MSK disease activity improved upon treatment, though no statistically significant difference across allocation groups was captured. In general, levels of PsA disease activity -as measured by PASDAS- dropped from high level [at baseline, mean PASDAS was 5.91 in Arm 1 and 5.56 in Arm 2 – threshold of PASDAS high disease activity is 5.4 (Helliwell, P.S. et al., 2014)] to those corresponding to low disease activity or MDA (at week 24, mean PASDAS was 2.7 In Arm 1 and 3.09 in Arm 2 – threshold of PASDAS low disease activity is 3.2). Some MSK domains improved dramatically, as it was the case with dactylitis (Table 17).

It is important to draw the attention of the reader on the PASDAS score results at week 12, when a statistically significant difference between the two treatment arms was actually found. Though the trial design could not accommodate for such specific post-hoc analysis, it has to be stressed that -by the same time-point- participants could receive steroid injections (typically, methylprednisolone 120 mg IM) if they had no PsARC response achieved. It is therefore striking that the participants initially responding better were those allocated to Arm 1 (GOLMTX) and it is the opinion of this candidate that the supplementary beneficial effect exerted by steroid administration by week 12 (which was required more often in patients allocated to Arm 2) might have contributed to the improved outcomes of participants who were on PBO, in turn leading to nullification of a statistically significant result by week 24. Intriguingly, a combination of MTX and steroids treatment was not inferior -at achieving remission- to the bDMARD tocilizumab in one clinical trial in early RA (Ostergaard et al., 2023). This candidate is therefore tempted to argue that more important than the specific composition of the treatment strategy is the energetic treatment of PsA at the earliest stage possible.

From the perspective of the clinical results pertaining to the skin and nails domains, it is interesting to note that GOLMePsA participants did not achieve complete clearance (that is, for example, PASI score equal to zero) of nail/cutaneous manifestations of PsO in the majority of cases. At best, the proportion of 55.8% participants presenting absence of PsO lesions over their skin was achieved only at week 36 (notably, in those allocated to Arm 1). At first look, this would seem counterintuitive, as it could be argued that the exposure to

an intensive treatment regime -regardless of the specific group allocation- would be expected to exert considerable positive effects on skin and nail domains in patients never exposed to systemic drugs (or to DMARDs) prior to the study enrolment.

For comparison, the use of Risankizumab (one IL-23-inhibitor) solely for the treatment of PsO (Gordon et al., 2018) resulted in 74.8% of the patients exposed achieving PASI90 response (corresponding to almost clear skin). Recruits in the SEAM-PsA trial presented at baseline with substantial skin involvement as assessed by BSA (above 10% on average across treatment groups; 63-68% of participants had PsO lesions affecting ≥3% of BSA) and, by the time of primary endpoint (week 24 – like the GOLMePsA trial) the proportion of patients who achieved static Physician Global Assessment of PsO (sPGA) score of zero (clear) or one (almost clear) ranged between 59.3% and 87.5% - according to treatment allocation group.

Also, it would be reasonable to expect that positive effects on cutaneous domains would be maintained over time in people on sustained therapy. Though one of the design features of the GOLMePsA trial was not the comparison across bDMARDs with different action mechanisms (that is, there was no “Arm 3” where one IL-23-inhibitor or IL-17-inhibitor was administered), the low prevalence of total response of GOLMePsA participants in skin/nails domains merits two considerations. The first is that the findings reported in this thesis corroborate the common experience in rheumatology practice that PsA people tend to present with associated low severity cutaneous lesions [baseline data from the CORRONA registry (Mease et al., 2019a) show that PsA patients whom BSA <3% were roughly double than those affected by more severe skin disease]. It could be argued that this phenomenon points to the existence of a clinical phenotype of the PsD spectrum that subgroups distinctively from other forms of PsO and eventually results in PsA development. The second consideration is more speculative, though intriguing in the opinion of the candidate. That is, it is possible to postulate that the clinical response in MSK domains might be accentuated if patients exposed to therapy would simultaneously present full clearance of skin/nails lesions following treatment. Indeed, evidence supports the notion that the synchronous effective treatment of joints and skin improves the outcomes of PsA patients (Kavanaugh et al., 2019). It is a limit of the original analysis plan of the GOLMePsA trial that -among secondary analyses- none was performed looking into the association -or lack of it- of treatment effects onto MSK manifestations of PsA and changes in nail disease severity.

5.1.3 Considerations Related to the GOLMePsA Trial Imaging Results

GOLMePsA participants presented at baseline with levels of US GLOESS that were moderately elevated, across treatment groups. Changes in the same US score were modest in magnitude over time, regardless of treatment allocation. The distinction that would have captured the reader's attention is that, overall, the PD signal detected in the peripheral joints did show some improvement following exposure to treatment (though differences between treatment groups were not statistically significant). Conversely, the GS GLOESS scores remained substantially unchanged over time. One would be tempted to infer that this phenomenon may reflect at least a partial direct therapeutic action onto the deep inflammatory burden (the PD signal) occurring in PsA patients.

However, it would be expected that both GS scores (partly reflecting genuine synovial hypertrophy) and PD signal improved simultaneously upon treatment, as described in the ULTIMATE clinical trial (D'Agostino et al., 2022). Though challenging as a finding, this discrepancy recorded in the GOLMePsA data could be partially addressed by one consideration. That is, GS abnormalities are also commonly found (13% of cases) in healthy persons (Padovano et al., 2016) as well as in PsO patients without PsA (Naredo et al., 2011) - especially at the level of the feet joints. Although the data presented in this thesis did not offer a breakdown of US lesions by location, it is entirely plausible that the lack of decrement of GS lesions -as detectable by GLOESS- in GOLMePsA participants merely represented the persistence of thickened articular tissues of non-inflammatory origin.

This candidate is tempted to speculate that there could be an association between this observation (the discrepancy between GS and PD finding on GLOESS) and the prevalence of overweight persons in the GOLMePsA cohort (e. g.: weight ≥ 100kg was observed in 17.9% of participants). A slightly different explanation, again as speculated by this candidate, would be that people affected by long-established PsA [like the ULTIMATE trial recruits (D'Agostino et al., 2022)] presented thicker layers of synovial hypertrophy detectable on US while cases at early stage of PsA may not. Such difference -by mere virtue of disease duration- might exert a more relevant impact when recording treatment effects, as larger decreases of GS findings would be likelier to produce hefty changes in the GLOESS GS score.

It has to be noted, however, that the above considerations apply to the US scan findings of peripheral joints. The US assessment of entheses in GOLMePsA did not show substantial changes over time of the PD signal, regardless of treatment allocation. In this respect, the chosen clinical outcome measure of entheseal tenderness [the LEI (Healy and Helliwell, 2008)] covered merely six entheseal

anatomical sites (far outnumbered by the amount of entheses assessed by US – which were up to twelve), hindering the chances of assessing the extent of the discrepancy between clinical and imaging assessment of entheses. This appears to be a design flaw. The adoption of a different outcome measure for the assessment of clinical entheseal tenderness in the GOLMePsA trial would have broadened the range of anatomical sites appreciated at any time-point evaluation. Though no index has absolute prominence in the literature, a fair choice would be the enthesitis index developed and validated by the SPARCC (Maksymowych et al., 2009) – a measure that assesses sixteen entheses. It has to be highlighted, however, that the anatomical sites evaluated by the SPARCC enthesitis index and those evaluated by the LEI do not overlap entirely, making LEI irreplaceable for the original purposes of the GOLMePsA trial (as described in paragraph 3.2.1, LEI is an integral part of the calculation formula of PASDAS – the primary outcome measure of the trial). Though this issue may be felt as a missed opportunity, ultimately the researchers involved in setting up the GOLMePsA trial -conscious of the sheer amount of data points collected from each participant- took a “trade-off” decision and privileged the feasibility of the total data collection over an even more extended clinical entheseal evaluation.

Moving the reader’s attention onto the matter of MRI data, the most interesting consideration about MRI findings from the GOLMePsA cohort stems from the discrepancy between clinical data and imaging at baseline. Namely, the prevalence of PsA cases classified as axial by the clinical assessors at week 0 (3.6%) pales in comparison with the prevalence of MRI-detected inflammatory lesions (29%) scored by SPARCC MRI sacroiliac joints method.

Though consensus on one specific definition of axial PsA is lacking, one recent review on this subject suggested that its prevalence ranges between 12.5% and 78%, largely dependent on the methodology used for definition of axial PsA across different studies (Michelena et al., 2020). The authors of this review reported that the heterogeneity in methodology varied from clinical-based assessment to detection of axial skeleton pathology by imaging (itself reliant on different techniques such as CR or CT or MRI).

It needs to be highlighted that the clinical assessors who performed the baseline evaluations of the GOLMePsA participants could only rely on their clinical judgement. Among data collected, the CR of pelvis and lumbar spine were not part of the scheduled procedures of the trial. HLA-B27 status ascertainment by conventional laboratory test was also not a scheduled trial procedure. On top of this, clinical assessors were kept blinded to the MRI data until the time of statistical analysis of the data. As a result, it was not possible to apply systematically the AxSpA classification criteria (Rudwaleit et al., 2009) commonly

used in clinical trials and standard rheumatology practice. The inability to access some relevant imaging data prevented the clinical assessors from having the information needed to establish the presence of axial SpA with confidence, leading in part to the underrepresentation of participants classified as axial PsA.

To complicate matters a bit further, it is postulated that axial SpA may not be the only condition that characterizes the axial skeleton involvement in patients affected by PsA (McGonagle, D. et al., 2023). According to McGonagle, the heterogeneity of lesions comprised in this PsA subset is considerable and may overlap with the condition known as diffuse idiopathic skeletal hyperostosis. Although data pertaining to this feature were not collected in the GOLMePsA programme (no CR of pelvis or spine were performed as scheduled trial procedures), no participant presented with -or developed while on follow-up- clinical manifestations suggestive of ankylosis in the spine.

On a slightly different order of considerations, the axial SpA classification system created by Rudwaleit and coauthors allows for patients who are affected by peripheral arthritis, dactylitis and PsO to fulfil the classification criteria. As a result, the subset of GOLMePsA participants whom MRI scans uncovered inflammatory lesions in the sacroiliac joints formally fulfil both CASPAR criteria (Taylor et al., 2006) and Rudwaleit's criteria. Though such classification overlap could not be formally resolved by virtue of additional investigations (there is not diagnostic test available for axial SpA or for PsA), it is the opinion of this candidate -who met and followed-up personally all GOLMePsA participants- that this matter does not constitute a research protocol violation and it did not undermine the scientific integrity of the programme. To the contrary, this classification overlap is well in keeping with the concept of the SpA spectrum and the PsD heterogeneous manifestations earlier described in this thesis (Chapter 1 and Figure 1).

The changes in MRI-related scores that occurred over time demand a bit of the reader's attention, as at a first look one would argue that the data from GOLMePsA pointed to discrepancies by lesion topography. Namely, the data from MRI-WIPE highlighted a trend to improvement -yet still within the same spectrum of magnitude- following treatment. This happened despite of treatment allocation and no statistically significant difference between treatment groups was found. This trend to improvement of lesions in peripheral joints and peripheral entheses was apparently not mirrored by the findings from axial-centred scores such as SPARCC MRI or CANDEN.

However, it is worth mentioning that participants randomized to Arm 1 (GOLMTX) tended to show improvements in CANDEN and SPARCC MRI more frequently than patients assigned to Arm 2. This phenomenon is in keeping with the expected effects of TNFi agents on axial SpA (Danve and Deodhar, 2022). This

candidate invites the readership to caution when considering these results, however, as the differences were not statistically significant and the MRI scoring data pertaining to axial disease were substantially affected by sparsity. In the opinion of this candidate, the trial intervention exerted effects that reflected on both MRI manifestations located in peripheral joints, peripheral entheses and in the axial skeleton of GOLMePsA participants.

Overall, during follow-up the use of imaging techniques did not uncover unexpected levels of inflammatory burden in the participants to the trial. The changes in imaging scores -either US or MRI ones- over follow-up were consistent with a decrease in inflammatory activity, likely due to the trial interventions and regardless of the treatment group of allocation.

In parallel, the clinical measures of outcome improved on follow-up, again irrespective of treatment allocation. Notably, the average levels of PASDAS achieved at week 24 corresponded to the ones that fit in the category of MDA (Coates, L.C. and Helliwell, 2016a).

The residual inflammatory lesions found on imaging of GOLMePsA participants after treatment were, in the opinion of this candidate, in keeping with a state of MDA. As such, no disproportionate inflammatory burden was uncovered by US or MRI in these patients.

5.1.4 Considerations related to the PASDAS Test-Retest Exercise

One of the advantages of utilising the GOLMePsA programme as a platform for this thesis was the opportunity to formally expand on the validation of the PASDAS score (Tillett et al., 2021a), focusing solely on a group of early-stage and treatment-naïve PsA patients. The design of the GOLMePsA trial, with a screening period of up to four weeks preceding the exposure to any intervention -as well as the eligibility criteria of treatment-naïve participants (Appendix 2)- allowed for supplemental data collection aimed at looking into the test-retest reliability of the PASDAS outcome measure in people affected by PsA at early stage.

A nice number of recruits (37 persons – 44% of those who fulfilled the trial eligibility criteria) had data available for the purposes of the test-retest exercise, substantially more than the amount needed (31 individuals) to satisfy the sample size estimate (see section 3.4).

There was a high ICC (0.85) between repeated measurements of PASDAS, with no evidence of consistent bias and acceptably narrow 95% limits of agreement. In this test-retest exercise, the candidate found no evidence that the extent of the differences between repeated measurements of PASDAS -performed over a

short period of time (the mean interval was inferior to two weeks), as well as in absence of perturbations related to treatment changes- were by any means associated with their magnitude. These results confirmed the excellent test-retest reliability of PASDAS in early, untreated PsA, supporting its use as an outcome measure in interventional studies in newly diagnosed PsA disease of short-duration.

5.1.5 Considerations related to Remission in Early Psoriatic Arthritis

In the GOLMePsA trial, the notable proportion of 34.9% (15/43) of participants randomized to Arm 1 (GOLMTX) achieved VLDA (Coates, L.C. and Helliwell, 2016a) or PASDAS “near remission” [that is, PASDAS value ≤1.9 threshold (Coates, L.C. and Helliwell, 2016a)] at week 24 (primary endpoint). Although at the same time-point the proportion of participants achieving VLDA or PASDAS ≤1.9 (in both cases 7/41 or 17.1%) in Arm 2 (PBOMTX) was inferior to the other treatment group, such difference was not statistically significant. It is important to highlight here that the GOLMePsA trial was not designed to assess the occurrence of VLDA or of PASDAS “near remission” at week 24 as primary endpoint. Therefore, different sample size and power calculations would be needed to investigate these outcomes and the results presented in this thesis are purely exploratory.

Taking a more stringent approach with the outlined definition of remission in PsA offered by other authors (Mease and Coates, 2018), the remission set A proposed in this thesis assesses through all the main PsA domains (MSK) and was intended as a more comprehensive tool as compared to VLDA or PASDAS “near remission” or CPDAI remission (Mumtaz et al., 2011; Coates, L.C. and Helliwell, 2016a). It is notable that 7/84 (8.3%) GOLMePsA participants met the proposed set A of remission criteria at any time-point, however, out of the 4 participants who fulfilled remission set A at week 24, 3 were randomized to Arm 1 (GOLMTX). Only 1/84 participant (1.2%) fulfilled the remission criteria set B (the set that assesses skin/nail domains alongside MSK ones and is more adherent to the concept of remission proposed by Mease et al.) at week 24 - they were randomized to Arm 1. Interestingly, though, 3/84 (3.6%) GOLMePsA participants fulfilled the requirements of remission set B at a later time-point (week 36). Overall, the numbers were too low to allow even basic statistics, however, it is possible to speculate that the combination of TNFi, MTX 25 mg/week and steroids may have better potential in inducing remission in early PsA – whatever the definition adopted.

It is interesting to appreciate that -in the GOLMePsA trial- the total of participants who achieved VLDA or PASDAS ≤1.9 at week 24 was 22/84 (26.2%). These

results are strikingly similar to the proportion of remission instances (26%) reported in one Irish study of early -likely treatment-naïve (that is, not exposed to csDMARDs or bDMARDs prior to inclusion)- PsA (Kane et al., 2003), where one MSK-focused definition (inclusive of dactylitis and enthesitis) was adopted. In Kane's study, recruited patients who presented with polyarthritis were 59.7% (slightly lower prevalence when compared to GOLMePsA participants).

One would expect that the use of less stringent criteria of remission would be met by larger proportions of patients, however, 17.8% in remission was the result reported in a study on early -likely treatment-naïve (that is, not exposed to csDMARDs or bDMARDs prior to inclusion)- PsA (Theander et al., 2014) where the definition adopted encompassed just four items (absence of tender and swollen joints alongside low ESR and low CRP). In this Swedish study, recruited patients who presented polyarthritis were 39.6% (lower prevalence when compared to GOLMePsA participants). Considered together, these observations suggest that MDA, VLDA and "near-remission" are achievable goals for the treatment of people at early stage of PsA – possibly regardless of the use of bDMARDs.

It is not surprising, instead, to appreciate that the stringent definition of remission adopted in this thesis yielded low numbers of patients fulfilling this candidate's proposed remission criteria sets (A, B and C). Irrespective of the low numbers, however, the analyses performed in this project characterized a subgroup of patients who ultimately experienced lower levels of disease activity following treatment. The distinction held even when PASDAS values were applied to this remission subsets (namely, PASDAS score in recruits fulfilling remission set A was not superior to 1.2, with a median of 0.88). Due to the paucity of data, it was not possible to investigate further the PASDAS score overlap between remission set A and remission set B. The lack of substantial numbers in the occurrence of remission set B is felt by this candidate as a sorely missed opportunity, in consideration that some evidence (Helliwell, P.S. et al., 2022) points to the presence of nail dystrophy (prior to treatment exposure) as a factor associated with higher chances of achieving MDA and PASDAS low disease activity (threshold score 3.2). This candidate deliberately chose not to explore the CPDAI score overlap with remission sets A and B, as that outcome measure underwent a less structured process of development and -ultimately- was not specifically recommended by GRAPPA for use in clinical trials of PsA (Tillett et al., 2021a).

There are several limitations to the work presented in this thesis. First, the remission criteria proposed by the candidate are not validated in a different external dataset of early PsA patients – either from clinical trials or standard rheumatology care. Though the single items that make up remission criteria sets

A, B and C were selected in accordance to suggestions available from the literature (Orbai et al., 2017; Mease and Coates, 2018), no formal construct validity exercise was possible at this stage, thereby representing more of an expert opinion rather than data-driven process. The reader will surely notice that none of the remission criteria sets proposed by this candidate encompass items assessing QoL or physical function. Some authors deem such evaluations pertinent to outcomes of PsD, not to the contingent assessment of disease activity (Schoels, M.M. et al., 2016), however, the relevance of QoL and physical function in any set of remission criteria should be evaluated through a formal construct validity exercise.

Secondly, no appreciation of the criteria set C was possible, as no GOLMePsA patient fulfilled the most stringent of the three remission sets proposed in this thesis. It is entirely possible to speculate that the imaging thresholds adopted for the definition of absence of inflammation (GS <2 and absence of PD signal on US; absence of inflammatory lesions on MRI) were excessively restrictive – as abnormalities on imaging might not reflect genuine inflammation in all instances (Padovano et al., 2016).

Thirdly, the long-term significance of the newly proposed remission criteria could not be investigated in the GOLMePsA dataset due to lack of long term (that is, superior to 52 weeks) follow-up – both by clinical and imaging (including CR) means. Therefore, the potential for anatomical damage ablation and disability prevention when stringent remission criteria be met was not assessed in the line of work presented in this thesis.

Finally, the remission criteria sets proposed in this manuscript address only items that belong to the inner core of PsA domains endorsed by OMERACT [updated version (Orbai et al., 2017)], with the exception of structural damage (a feature detectable by imaging techniques, namely US and MRI in the GOLMePsA trial). The remission criteria sets A, B and C did not assess other “outer” elements of the wider PsD spectrum, such as IBD and IED. In addition to this, no GOLMePsA trial participant reported episodes of IED by week 52. Only 1 participant was confirmed as affected by IBD (namely, Crohn’s Disease) before being exposed to the intervention (they were allocated to PBO and did not report exacerbations of their IBD until the end of trial).

Chapter 6

6.1 Future Directions and Conclusions

6.1.1 Future Directions

The GOLMePsA trial programme was completed -that is, clinical and imaging data acquisition activities, data cleaning and statistical analysis- in 2023. The study provided valuable, extended data to assess the use of intensive treatment strategies -and to measure the related effects across the clinical manifestations of the PsD spectrum- in PsA patients who are simultaneously at the early stages of the disease course and treatment-naïve.

However, many research questions did arise from analysing the data presented so far and this allowed the identification of unmet needs that may influence the research agenda on PsD.

6.1.1.1 Definition of Remission in Early Psoriatic Arthritis and Established Psoriatic Arthritis

Data from this thesis show that the application of more stringent criteria to defining remission identified a subgroup of patients who present PASDAS levels that are lower than the threshold identified for “near-remission” (≤1.9). One obvious area of focus for future research, therefore, would be the formal construct validity exercise of the remission criteria proposed by this candidate (namely, sets A, B and C). Though the choice of items making up the proposed remission criteria followed the principles of representation across the PsD spectrum (clinical, PROMs, laboratory and imaging), it would be appropriate to gather the opinion of experts in the field to expand the potential components of new remission criteria. For example, a formal Delphi exercise within the context of GRAPPA network would be the ideal setting to bring together stakeholders (healthcare professionals and people affected by PsD) to discuss proposals. This exercise could be followed by one construct validity programme intended at testing the potential remission items components onto an adequately large dataset of patients – similar to the one that led to the development of PASDAS. Once the newly developed remission criteria were defined, formal test-retest reliability and responsiveness evaluation should be conducted, again in adequate samples of PsD patients, in the context of both early and established PsA and PsD. External validation of the new remission criteria, again in early and established and diverse cohorts of patients affected by PsD, as well as the estimation of feasibility, would complete the process and ready the newly developed criteria for wider adoption (in clinical trials and possibly in standard

practice). In the opinion of this candidate, the proposed remission sets B and C have the best potential for future adoption.

Further work is needed to explore the implications of achieving -and maintaining- disease remission. Exploring the consequences of remission-induction at early stage of PsA -instead of later in the disease course- could provide useful data about the impact of disease ablation on anatomical damage progression in the longer term. The set up of longitudinal, observational series assessing the prevalence of remission following treatment could inform strategies aimed at disability prevention and offer opportunities for studies focused on the economic impact of treatment pathways. In this respect, the possibility of incorporating items assessing QoL or physical functioning in future remission criteria would be very interesting.

Another opportunity for future research would be the setup of longitudinal studies aimed at assessing the role of imaging modalities that integrate the new definitions of remission proposed in this thesis. Worth of attention is the consideration of their potential use as predictors of sustained remission status - in the medium and longer term. Such programme could be associated with the investigation and development of biomarkers of remission, as well as with the assessment of treatment strategies aimed at the induction of drug-free remission state.

6.1.1.2 Exploring the Transition from Psoriasis to Early Psoriatic Arthritis

Further research is needed to investigate the phase of transition that precedes the clinical onset of PsA. Most cases present with a history of years-long, sub-optimally treated PsO and non-specific arthralgia (Eder et al., 2017).

This area of investigation is attracting considerable attention and international organizations involved in rheumatology -EULAR, for example- are promoting projects to explore the transition from PsO to full PsA development (De Marco, G. et al., 2023; Zabotti et al., 2023).

Key to understanding transition to PsA will be the creation of novel prospective cohorts recruiting people affected by PsO and at risk of developing PsA. The expected long-term observations will support the investigation of the role of imaging and novel potential biomarkers for disease prediction and severity stratification.

Ultimately, setting up –and running- such projects will offer the opportunity to consider interventions with drugs aimed at preventing altogether the development of PsA. If realized, this line of research would have potential for entirely shifting the current attitudes toward the treatment of PsD. The new concept of

‘intercepting PsA’ (McGonagle, D.G. et al., 2022) before its clinical development would take the place of the principle of pursuing a ‘therapeutic window of opportunity’ that is described (Snoeck Henkemans et al., 2024) in current rheumatology practice.

6.1.2 Conclusions

A few final considerations can be offered, listed by the order presented in paragraph 2.2.2 (thesis’ objectives).

Participants in the GOLMePsA randomized clinical trial -the data collection platform used by the candidate to produce this thesis- were exposed to two intensive treatment regimens for PsA. They achieved brilliant PASDAS responses, in that levels of this outcome measure dropped from 5.91 (high disease activity, at baseline) to 2.7 (low disease activity, at week 24 – primary endpoint time) in participants allocated to Arm 1 (combination of GOL, MTX and steroids). PASDAS levels in participants assigned to Arm 2 dropped from 5.56 (at baseline – high disease activity) to 3.09 (at week 24 – low disease activity). As a consequence, considerable proportions of participants (34.9% in Arm 1 and 17.1% in Arm 2) achieved very low disease activity status by week 24. Although in this regard no statistical difference across treatment groups was appreciated, it was notable to observe that participants allocated to Arm 1 presented with a faster PASDAS response profile (3.01 versus 3.7 recorded in Arm 2 at week 12; p-value 0.007). PASDAS score differences across treatment groups disappeared at the predefined primary endpoint time (week 24), however, more participants allocated to Arm 2 received additional steroids (48.8% versus 20.9% recorded in Arm 1; p-value 0.009). This observation may point to a steroid-sparing effect linked to the treatment assigned to Arm 1.

The response to trial interventions was recorded across the clinical spectrum of PsD (trial exploratory outcomes), the subset of GOLMePsA participants presenting with more severe PsO at baseline responding better (achievement of PASI75 response) if randomized to Arm 1.

The use of advanced imaging in the GOLMePsA cohort showed moderate levels of inflammation-related lesions at baseline, with low levels of structural lesions. The response to trial interventions recorded by US and MRI reflected clinical MDA levels of disease.

The appraisal of the literature that provided the background of this thesis allowed the identification of knowledge gaps pertaining to the validation and construct validity of outcome measures used in clinical trials of PsA. The test-retest exercise reported here formally confirmed the high ICC between repeated measurements of PASDAS and further advanced its validation in early PsA.

Achieving remission in treatment naïve, early PsA uncommonly (8.3%) followed the intense treatment strategies adopted in the GOLMePsA trial. The proposed sets of remission presented in this thesis followed the principles suggested by experts and explored disease activity across the PsA clinical spectrum as well as across the PsD clinical spectrum. However, their construct validity requires more formal testing. Regardless of these limitations, the analysis performed in this thesis identified novel subgroupings by PASDAS levels associated with remission (namely, the threshold of ≤1.2). Sustained levels of remission over time were even less common in the GOLMePsA cohort, though notably patients who achieved remission did not need to start bDMARDs during follow-up.

The significance of the residual inflammatory burden detectable on imaging in persons who achieved remission is uncertain, though the potential for complete ablation of the deepest features of PsA and PsD (on US and MRI) using intensive treatment strategies is considerable.

More research is needed for determining which treatment regimens -by means of agents of choice, intensity and safety- would be more likely to induce remission in early PsA.

List of References - Bibliography

- Alharbi, S., Ye, J.Y., Lee, K.A., Chandran, V., Cook, R.J. and Gladman, D.D. 2020. Remission in psoriatic arthritis: Definition and predictors. *Semin Arthritis Rheum.* **50**(6), pp.1494-1499.
- Antoni, C., Krueger, G.G., de Vlam, K., Birbara, C., Beutler, A., Guzzo, C., Zhou, B., Dooley, L.T., Kavanaugh, A. and Investigators, I.T. 2005. Infliximab improves signs and symptoms of psoriatic arthritis: results of the IMPACT 2 trial. *Ann Rheum Dis.* **64**(8), pp.1150-1157.
- Araujo, E.G., Englbrecht, M., Hoepken, S., Finzel, S., Kampylafka, E., Kleyer, A., Bayat, S., Schoenau, V., Hueber, A., Rech, J. and Schett, G. 2019. Effects of ustekinumab versus tumor necrosis factor inhibition on enthesitis: Results from the enthesial clearance in psoriatic arthritis (ECLIPSA) study. *Semin Arthritis Rheum.* **48**(4), pp.632-637.
- Aydin, S.Z., Bas, E., Basci, O., Filippucci, E., Wakefield, R.J., Celikel, C., Karahan, M., Atagunduz, P., Benjamin, M., Direskeneli, H. and McGonagle, D. 2010. Validation of ultrasound imaging for Achilles entheseal fibrocartilage in bovines and description of changes in humans with spondyloarthritis. *Ann Rheum Dis.* **69**(12), pp.2165-2168.
- Basra, M.K., Fenech, R., Gatt, R.M., Salek, M.S. and Finlay, A.Y. 2008. The Dermatology Life Quality Index 1994-2007: a comprehensive review of validation data and clinical results. *Br J Dermatol.* **159**(5), pp.997-1035.
- Begg, C., Cho, M., Eastwood, S., Horton, R., Moher, D., Olkin, I., Pitkin, R., Rennie, D., Schulz, K.F., Simel, D. and Stroup, D.F. 1996. Improving the quality of reporting of randomized controlled trials. The CONSORT statement. *JAMA.* **276**(8), pp.637-639.
- Behrens, F., Meier, L., Prinz, J.C., Jobst, J., Lippe, R., Loschmann, P.A. and Lorenz, H.M. 2018. Simultaneous Response in Several Domains in Patients with Psoriatic Disease Treated with Etanercept as Monotherapy or in Combination with Conventional Synthetic Disease-modifying Antirheumatic Drugs. *J Rheumatol.* **45**(6), pp.802-810.
- Benjamin, M. and McGonagle, D. 2001. The anatomical basis for disease localisation in seronegative spondyloarthropathy at entheses and related sites. *J Anat.* **199**(Pt 5), pp.503-526.
- Benjamin, M. and McGonagle, D. 2007. Histopathologic changes at "synovio-entheseal complexes" suggesting a novel mechanism for synovitis in osteoarthritis and spondylarthritis. *Arthritis Rheum.* **56**(11), pp.3601-3609.
- Boehncke, W.H., Boehncke, S., Tobin, A.M. and Kirby, B. 2011. The 'psoriatic march': a concept of how severe psoriasis may drive cardiovascular comorbidity. *Exp Dermatol.* **20**(4), pp.303-307.
- Bond, S.J., Farewell, V.T., Schentag, C.T. and Gladman, D.D. 2007. Predictors for radiological damage in psoriatic arthritis: results from a single centre. *Ann Rheum Dis.* **66**(3), pp.370-376.
- Boyd, T.A., Huynh, D.H., Temple, J. and Kavanaugh, A. 2022. Anti-citrullinated protein antibodies in patients with psoriatic arthritis. *Rheumatology.* **61**(1), pp.462-464.
- Brockbank, J.E., Stein, M., Schentag, C.T. and Gladman, D.D. 2005. Dactylitis in psoriatic arthritis: a marker for disease severity? *Ann Rheum Dis.* **64**(2), pp.188-190.

- Cantini, F., Niccoli, L., Cassara, E., Kaloudi, O. and Nannini, C. 2012. Sustained maintenance of clinical remission after adalimumab dose reduction in patients with early psoriatic arthritis: a long-term follow-up study. *Biologics.* **6**, pp.201-206.
- Cantini, F., Niccoli, L., Nannini, C., Cassara, E., Pasquetti, P., Olivieri, I. and Salvarani, C. 2008. Frequency and duration of clinical remission in patients with peripheral psoriatic arthritis requiring second-line drugs. *Rheumatology (Oxford).* **47**(6), pp.872-876.
- Caron, B., Jouzeau, J.Y., Miossec, P., Petitpain, N., Gillet, P., Netter, P. and Peyrin-Biroulet, L. 2022. Gastroenterological safety of IL-17 inhibitors: a systematic literature review. *Expert Opin Drug Saf.* **21**(2), pp.223-239.
- Cassell, S.E., Bieber, J.D., Rich, P., Tutuncu, Z.N., Lee, S.J., Kalunian, K.C., Wu, C.W. and Kavanaugh, A. 2007. The modified Nail Psoriasis Severity Index: validation of an instrument to assess psoriatic nail involvement in patients with psoriatic arthritis. *J Rheumatol.* **34**(1), pp.123-129.
- Cauli, A., Gladman, D.D., Mathieu, A., Olivieri, I., Porru, G., Tak, P.P., Sardu, C., Ujfalussy, I., Scarpa, R., Marchesoni, A., Taylor, W.J., Spadaro, A., Fernandez-Sueiro, J.L., Salvarani, C., Kalden, J.R., Lubrano, E., Carneiro, S., Desiati, F., Flynn, J.A., D'Angelo, S., Vacca, A., AW, V.A.N.K., Catanoso, M.G., Gruenke, M., Peluso, R., Parsons, W.J., Ferrara, N., Contu, P., Helliwell, P.S., Mease, P.J. and Group, G.P.S. 2011. Patient global assessment in psoriatic arthritis: a multicenter GRAPPA and OMERACT study. *J Rheumatol.* **38**(5), pp.898-903.
- Chimenti, M.S., Caso, F., Alivernini, S., De Martino, E., Costa, L., Tolusso, B., Triggianese, P., Conigliaro, P., Gremese, E., Scarpa, R. and Perricone, R. 2019. Amplifying the concept of psoriatic arthritis: The role of autoimmunity in systemic psoriatic disease. *Autoimmun Rev.* **18**(6), pp.565-575.
- Choy, E.H., Kingsley, G.H., Corkill, M.M. and Panayi, G.S. 1993. Intramuscular methylprednisolone is superior to pulse oral methylprednisolone during the induction phase of chrysotherapy. *Br J Rheumatol.* **32**(8), pp.734-739.
- Ciocon, D.H. and Kimball, A.B. 2007. Psoriasis and psoriatic arthritis: separate or one and the same? *Br J Dermatol.* **157**(5), pp.850-860.
- Clegg, D.O., Reda, D.J., Mejias, E., Cannon, G.W., Weisman, M.H., Taylor, T., Budiman-Mak, E., Blackburn, W.D., Vasey, F.B., Mahowald, M.L., Cush, J.J., Schumacher, H.R., Jr., Silverman, S.L., Alepa, F.P., Luggen, M.E., Cohen, M.R., Makkena, R., Haakenson, C.M., Ward, R.H., Manaster, B.J., Anderson, R.J., Ward, J.R. and Henderson, W.G. 1996a. Comparison of sulfasalazine and placebo in the treatment of psoriatic arthritis. A Department of Veterans Affairs Cooperative Study. *Arthritis Rheum.* **39**(12), pp.2013-2020.
- Clegg, D.O., Reda, D.J., Weisman, M.H., Blackburn, W.D., Cush, J.J., Cannon, G.W., Mahowald, M.L., Schumacher, H.R., Jr., Taylor, T., Budiman-Mak, E., Cohen, M.R., Vasey, F.B., Luggen, M.E., Mejias, E., Silverman, S.L., Makkena, R., Alepa, F.P., Buxbaum, J., Haakenson, C.M., Ward, R.H., Manaster, B.J., Anderson, R.J., Ward, J.R. and Henderson, W.G. 1996b. Comparison of sulfasalazine and placebo in the treatment of ankylosing spondylitis. A Department of Veterans Affairs Cooperative Study. *Arthritis Rheum.* **39**(12), pp.2004-2012.
- Coates, L. 2015. Outcome Measures in Psoriatic Arthritis. *Rheum Dis Clin North Am.* **41**(4), pp.699-710.
- Coates, L. 2018. *Severe Psoriatic arthritis – Early intervEntion to control Disease: the SPEED trial.* [Online]. [Accessed 2023]. Available from: https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01909380/full

- Coates, L.C., Fransen, J. and Helliwell, P.S. 2010. Defining minimal disease activity in psoriatic arthritis: a proposed objective target for treatment. *Ann Rheum Dis.* **69**(1), pp.48-53.
- Coates, L.C. and Helliwell, P.S. 2016a. Defining Low Disease Activity States in Psoriatic Arthritis using Novel Composite Disease Instruments. *J Rheumatol.* **43**(2), pp.371-375.
- Coates, L.C. and Helliwell, P.S. 2016b. Methotrexate Efficacy in the Tight Control in Psoriatic Arthritis Study. *J Rheumatol.* **43**(2), pp.356-361.
- Coates, L.C., Hodgson, R., Conaghan, P.G. and Freeston, J.E. 2012. MRI and ultrasonography for diagnosis and monitoring of psoriatic arthritis. *Best Pract Res Clin Rheumatol.* **26**(6), pp.805-822.
- Coates, L.C., Lubrano, E., Perrotta, F.M., Emery, P., Conaghan, P.G. and Helliwell, P.S. 2019. What Should Be the Primary Target of "Treat to Target" in Psoriatic Arthritis? *J Rheumatol.* **46**(1), pp.38-42.
- Coates, L.C., Merola, J.F., Mease, P.J., Ogdie, A., Gladman, D.D., Strand, V., van Mens, L.J.J., Liu, L., Yen, P.K., Collier, D.H., Kricorian, G., Chung, J.B. and Helliwell, P.S. 2021. Performance of composite measures used in a trial of etanercept and methotrexate as monotherapy or in combination in psoriatic arthritis. *Rheumatology (Oxford).* **60**(3), pp.1137-1147.
- Coates, L.C., Moverley, A.R., McParland, L., Brown, S., Navarro-Coy, N., O'Dwyer, J.L., Meads, D.M., Emery, P., Conaghan, P.G. and Helliwell, P.S. 2015. Effect of tight control of inflammation in early psoriatic arthritis (TICOPA): a UK multicentre, open-label, randomised controlled trial. *Lancet.* **386**(10012), pp.2489-2498.
- Coates, L.C., Smolen, J.S., Mease, P.J., Husni, M.E., Merola, J.F., Lespessailles, E., Kishimoto, M., Macpherson, L., Bradley, A.J., Bolce, R. and Helliwell, P.S. 2022a. Comparative performance of composite measures from two phase III clinical trials of ixekizumab in psoriatic arthritis. *RMD Open.* **8**(2).
- Coates, L.C., Soriano, E.R., Corp, N., Bertheussen, H., Callis Duffin, K., Campanholo, C.B., Chau, J., Eder, L., Fernandez-Avila, D.G., FitzGerald, O., Garg, A., Gladman, D.D., Goel, N., Helliwell, P.S., Husni, M.E., Jadon, D.R., Katz, A., Laheru, D., Latella, J., Leung, Y.Y., Lindsay, C., Lubrano, E., Mazzuoccolo, L.D., Mease, P.J., O'Sullivan, D., Ogdie, A., Olsder, W., Palominos, P.E., Schick, L., Steinkoenig, I., de Wit, M., van der Windt, D.A., Kavanaugh, A. and subcommittees, G.T.R.d. 2022b. Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA): updated treatment recommendations for psoriatic arthritis 2021. *Nat Rev Rheumatol.* **18**(8), pp.465-479.
- D'Agostino, M.A., Haavardsholm, E.A. and van der Laken, C.J. 2016. Diagnosis and management of rheumatoid arthritis; What is the current role of established and new imaging techniques in clinical practice? *Best Pract Res Clin Rheumatol.* **30**(4), pp.586-607.
- D'Agostino, M.A. and Olivieri, I. 2006. Enthesitis. *Best Pract Res Clin Rheumatol.* **20**(3), pp.473-486.
- D'Agostino, M.A., Schett, G., Lopez-Rdz, A., Senolt, L., Fazekas, K., Burgos-Vargas, R., Maldonado-Cocco, J., Naredo, E., Carron, P., Duggan, A.M., Goyanka, P., Boers, M. and Gaillez, C. 2022. Response to secukinumab on synovitis using Power Doppler ultrasound in psoriatic arthritis: 12-week results from a phase III study, ULTIMATE. *Rheumatology (Oxford).* **61**(5), pp.1867-1876.
- D'Agostino, M.A., Terslev, L., Aegerter, P., Backhaus, M., Balint, P., Bruyn, G.A., Filippucci, E., Grassi, W., Iagnocco, A., Jousse-Joulin, S., Kane, D., Naredo, E., Schmidt, W., Szkudlarek, M., Conaghan, P.G. and Wakefield, R.J. 2017. Scoring ultrasound synovitis in rheumatoid arthritis: a EULAR-OMERACT

ultrasound taskforce-Part 1: definition and development of a standardised, consensus-based scoring system. *RMD Open.* **3**(1), pe000428.

- Danve, A. and Deodhar, A. 2022. Treatment of axial spondyloarthritis: an update. *Nat Rev Rheumatol.* **18**(4), pp.205-216.
- De Marco, G., Berekmeri, A., Coates, L.C., Dubash, S., Emmel, J., Gladman, D.D., Lubrano, E., McGonagle, D.G., Mahmood, F., Marchesoni, A., Mason, L., Ogdie, A., Wittmann, M., Helliwell, P.S. and Marzo-Ortega, H. 2020. Systematic literature review of non-topical treatments for early, untreated (systemic therapy naive) psoriatic disease: a GRAPPA initiative. *Rheumatol Adv Pract.* **4**(2), prkaa032.
- *Systematic review of non-topical treatments for early, untreated (systemic therapy naïve) psoriatic disease: a GRAPPA initiative.* 2018. [Online database].
- De Marco, G., Helliwell, P., McGonagle, D., Emery, P., Coates, L.C., Hensor, E.M.A. and Marzo-Ortega, H. 2017. The GOLMePsA study protocol: an investigator-initiated, double-blind, parallel-group, randomised, controlled trial of GOLimumab and methotrexate versus methotrexate in early diagnosed psoriatic arthritis using clinical and whole body MRI outcomes. *BMC Musculoskelet Disord.* **18**(1), p303.
- De Marco, G., Zabotti, A., Baraliakos, X., Iagnocco, A., Aletaha, D., Gisondi, P., Emmel, J., Smolen, J.S., McGonagle, D.G. and Gossec, L. 2023. Characterisation of prodromal and very early psoriatic arthritis: a systematic literature review informing a EULAR taskforce. *RMD Open.* **9**(2).
- Deodhar, A., Helliwell, P.S., Boehncke, W.H., Kollmeier, A.P., Hsia, E.C., Subramanian, R.A., Xu, X.L., Sheng, S., Agarwal, P., Zhou, B., Zhuang, Y., Ritchlin, C.T. and Group, D.-S. 2020. Guselkumab in patients with active psoriatic arthritis who were biologic-naive or had previously received TNFalpha inhibitor treatment (DISCOVER-1): a double-blind, randomised, placebo-controlled phase 3 trial. *Lancet.* **395**(10230), pp.1115-1125.
- Doward, L.C., Spoorenberg, A., Cook, S.A., Whalley, D., Helliwell, P.S., Kay, L.J., McKenna, S.P., Tennant, A., van der Heijde, D. and Chamberlain, M.A. 2003. Development of the ASQoL: a quality of life instrument specific to ankylosing spondylitis. *Ann Rheum Dis.* **62**(1), pp.20-26.
- Dubash, S., Alabas, O.A., Michelena, X., Garcia-Montoya, L., Wakefield, R.J., Helliwell, P.S., Emery, P., McGonagle, D.G., Tan, A.L. and Marzo-Ortega, H. 2022. Dactylitis is an indicator of a more severe phenotype independently associated with greater SJC, CRP, ultrasound synovitis and erosive damage in DMARD-naive early psoriatic arthritis. *Ann Rheum Dis.* **81**(4), pp.490-495.
- Dubash, S.R., Alabas, O.A., Michelena, X., Garcia-Montoya, L., De Marco, G., Merashli, M., Wakefield, R.J., Emery, P., McGonagle, D., Tan, A.L. and Marzo-Ortega, H. 2021. Ultrasound shows swollen joints are the better proxy for synovitis than tender joints in DMARD-naive early psoriatic arthritis. *Rheumatol Adv Pract.* **5**(3), prkab086.
- Dubash, S.R., De Marco, G., Wakefield, R.J., Tan, A.L., McGonagle, D. and Marzo-Ortega, H. 2020. Ultrasound Imaging in Psoriatic Arthritis: What Have We Learnt in the Last Five Years? *Front Med (Lausanne).* **7**, p487.
- Eder, L., Polachek, A., Rosen, C.F., Chandran, V., Cook, R. and Gladman, D.D. 2017. The Development of Psoriatic Arthritis in Patients With Psoriasis Is Preceded by a Period of Nonspecific Musculoskeletal Symptoms: A Prospective Cohort Study. *Arthritis Rheumatol.* **69**(3), pp.622-629.
- Espinoza, L.R. 2018. The History of Psoriatic Arthritis (PsA): From Moll and Wright to Pathway-Specific Therapy. *Curr Rheumatol Rep.* **20**(10), p58.

- Felbo, S.K., Wiell, C., Ostergaard, M., Poggenborg, R.P., Boyesen, P., Hammer, H.B., Boonen, A., Pedersen, S.J., Sorensen, I.J., Madsen, O.R., Slot, O., Moller, J.M., Szkudlarek, M. and Terslev, L. 2022. Do tender joints in active psoriatic arthritis reflect inflammation assessed by ultrasound and magnetic resonance imaging? *Rheumatology (Oxford).* **61**(2), pp.723-733.
- Felson, D.T., Anderson, J.J., Boers, M., Bombardier, C., Furst, D., Goldsmith, C., Katz, L.M., Lightfoot, R., Jr., Paulus, H., Strand, V. and et al. 1995. American College of Rheumatology. Preliminary definition of improvement in rheumatoid arthritis. *Arthritis Rheum.* **38**(6), pp.727-735.
- FitzGerald, O., Haroon, M., Giles, J.T. and Winchester, R. 2015. Concepts of pathogenesis in psoriatic arthritis: genotype determines clinical phenotype. *Arthritis Res Ther.* **17**(1), p115.
- Fredriksson, T. and Pettersson, U. 1978. Severe psoriasis--oral therapy with a new retinoid. *Dermatologica.* **157**(4), pp.238-244.
- Freeston, J.E., Coates, L.C., Nam, J.L., Moverley, A.R., Hensor, E.M., Wakefield, R.J., Emery, P., Helliwell, P.S. and Conaghan, P.G. 2014. Is there subclinical synovitis in early psoriatic arthritis? A clinical comparison with grey-scale and power Doppler ultrasound. *Arthritis Care Res (Hoboken).* **66**(3), pp.432-439.
- Fries, J.F., Spitz, P., Kraines, R.G. and Holman, H.R. 1980. Measurement of patient outcome in arthritis. *Arthritis Rheum.* **23**(2), pp.137-145.
- Furer, V., Polachek, A., Levartovsky, D., Wollman, J., Zureik, M., Paran, D., Sarbagil-Maman, H., Lev-Ran, S.B., Berman, M., Kaufman, I., Broide, A., Aloush, V., Goldstein, Y.L., Nevo, S., Eshed, I. and Elkayam, O. 2020. Subclinical Joint Inflammation of Hands by Magnetic Resonance Imaging in Patients with Psoriatic Arthritis in Clinical Remission Compared to Active Disease. *Arthritis & Rheumatology.* **72**.
- Garrett, S., Jenkinson, T., Kennedy, L.G., Whitelock, H., Gaisford, P. and Calin, A. 1994. A new approach to defining disease status in ankylosing spondylitis: the Bath Ankylosing Spondylitis Disease Activity Index. *J Rheumatol.* **21**(12), pp.2286-2291.
- Gessl, I., Hana, C.A., Deimel, T., Durechova, M., Hucke, M., Konzett, V., Popescu, M., Studenic, P., Supp, G., Zauner, M., Smolen, J.S., Aletaha, D. and Mandl, P. 2023. Tenderness and radiographic progression in rheumatoid arthritis and psoriatic arthritis. *Ann Rheum Dis.* **82**(3), pp.344-350.
- Gialouri, C.G., Pappa, M., Evangelatos, G., Nikiphorou, E. and Fragoulis, G.E. 2023. Effect of body mass index on treatment response of biologic/targeted-synthetic DMARDs in patients with rheumatoid arthritis, psoriatic arthritis or axial spondyloarthritis. A systematic review. *Autoimmun Rev.* **22**(7), p103357.
- Girolimetto, N., Giovannini, I., Crepaldi, G., De Marco, G., Tinazzi, I., Possemato, N., Macchioni, P., McConnell, R., McGonagle, D., Iagnocco, A. and Zabotti, A. 2021. Psoriatic Dactylitis: Current Perspectives and New Insights in Ultrasonography and Magnetic Resonance Imaging. *J Clin Med.* **10**(12).
- Gladman, D., Rigby, W., Azevedo, V.F., Behrens, F., Blanco, R., Kaszuba, A., Kudlacz, E., Wang, C., Menon, S., Hendrikx, T. and Kanik, K.S. 2017. Tofacitinib for Psoriatic Arthritis in Patients with an Inadequate Response to TNF Inhibitors. *N Engl J Med.* **377**(16), pp.1525-1536.
- Gladman, D.D. 2009. Psoriatic arthritis. *Dermatol Ther.* **22**(1), pp.40-55.
- Gladman, D.D. 2012. Early psoriatic arthritis. *Rheum Dis Clin North Am.* **38**(2), pp.373-386.

- Gladman, D.D., Mease, P.J., Strand, V., Healy, P., Helliwell, P.S., Fitzgerald, O., Gottlieb, A.B., Krueger, G.G., Nash, P., Ritchlin, C.T., Taylor, W., Adebajo, A., Braun, J., Cauli, A., Carneiro, S., Choy, E., Dijkmans, B., Espinoza, L., van der Heijde, D., Husni, E., Lubrano, E., McGonagle, D., Qureshi, A., Soriano, E.R. and Zochling, J. 2007. Consensus on a core set of domains for psoriatic arthritis. *J Rheumatol.* **34**(5), pp.1167-1170.
- Gladman, D.D., Shuckett, R., Russell, M.L., Thorne, J.C. and Schachter, R.K. 1987. Psoriatic arthritis (PSA)--an analysis of 220 patients. *Q J Med.* **62**(238), pp.127-141.
- Gordon, K.B., Strober, B., Lebwohl, M., Augustin, M., Blauvelt, A., Poulin, Y., Papp, K.A., Sofen, H., Puig, L., Foley, P., Ohtsuki, M., Flack, M., Geng, Z., Gu, Y., Valdes, J.M., Thompson, E.H.Z. and Bachelez, H. 2018. Efficacy and safety of risankizumab in moderate-to-severe plaque psoriasis (UltIMMa-1 and UltIMMa-2): results from two double-blind, randomised, placebo-controlled and ustekinumab-controlled phase 3 trials. *Lancet.* **392**(10148), pp.650-661.
- Gossec, L., Baraliakos, X., Kerschbaumer, A., de Wit, M., McInnes, I., Dougados, M., Primdahl, J., McGonagle, D.G., Aletaha, D., Balanescu, A., Balint, P.V., Bertheussen, H., Boehncke, W.H., Burmester, G.R., Canete, J.D., Damjanov, N.S., Kragstrup, T.W., Kvien, T.K., Landewe, R.B.M., Lories, R.J.U., Marzo-Ortega, H., Poddubnyy, D., Rodrigues Manica, S.A., Schett, G., Veale, D.J., Van den Bosch, F.E., van der Heijde, D. and Smolen, J.S. 2020. EULAR recommendations for the management of psoriatic arthritis with pharmacological therapies: 2019 update. *Ann Rheum Dis.* **79**(6), pp.700-712.
- Gossec, L., Kerschbaumer, A., Ferreira, R.J.O., Aletaha, D., Baraliakos, X., Bertheussen, H., Boehncke, W.H., Esbensen, B.A., McInnes, I.B., McGonagle, D., Winthrop, K.L., Balanescu, A., Balint, P.V., Burmester, G.R., Canete, J.D., Claudepierre, P., Eder, L., Hetland, M.L., Iagnocco, A., Kristensen, L.E., Lories, R., Queiro, R., Mauro, D., Marzo-Ortega, H., Mease, P.J., Nash, P., Wagenaar, W., Savage, L., Schett, G., Shoop-Worrall, S.J.W., Tanaka, Y., Van den Bosch, F.E., van der Helm-van Mil, A., Zabotti, A., van der Heijde, D. and Smolen, J.S. 2024. EULAR recommendations for the management of psoriatic arthritis with pharmacological therapies: 2023 update. *Ann Rheum Dis.*
- Greb, J.E., Goldminz, A.M., Elder, J.T., Lebwohl, M.G., Gladman, D.D., Wu, J.J., Mehta, N.N., Finlay, A.Y. and Gottlieb, A.B. 2016. Psoriasis. *Nat Rev Dis Primers.* **2**, p16082.
- Guldberg-Moller, J., Mogensen, M., Ellegaard, K., Zavareh, A., Wakefield, R.J., Tan, A.L., Boesen, M., Dehmeshki, J., Kubassova, O., Dreyer, L., Henriksen, M. and Kristensen, L.E. 2022. Multimodal imaging of the distal interphalangeal-joint synovio-entheseal complex in psoriatic arthritis (MIDAS): a cross-sectional study on the diagnostic accuracy of different imaging modalities comparing psoriatic arthritis to psoriasis and osteoarthritis. *RMD Open.* **8**(1).
- Haroon, M., Gallagher, P. and FitzGerald, O. 2015. Diagnostic delay of more than 6 months contributes to poor radiographic and functional outcome in psoriatic arthritis. *Ann Rheum Dis.* **74**(6), pp.1045-1050.
- Hays, R.D., Sherbourne, C.D. and Mazel, R.M. 1993. The RAND 36-Item Health Survey 1.0. *Health Econ.* **2**(3), pp.217-227.
- Healy, P.J. and Helliwell, P.S. 2007. Measuring dactylitis in clinical trials: which is the best instrument to use? *J Rheumatol.* **34**(6), pp.1302-1306.
- Healy, P.J. and Helliwell, P.S. 2008. Measuring clinical enthesitis in psoriatic arthritis: assessment of existing measures and development of an instrument specific to psoriatic arthritis. *Arthritis Rheum.* **59**(5), pp.686-691.

- Helliwell, P., Marchesoni, A., Peters, M., Barker, M. and Wright, V. 1991. A re-evaluation of the osteoarticular manifestations of psoriasis. *Br J Rheumatol.* **30**(5), pp.339-345.
- Helliwell, P.S., Firth, J., Ibrahim, G.H., Melsom, R.D., Shah, I. and Turner, D.E. 2005. Development of an assessment tool for dactylitis in patients with psoriatic arthritis. *J Rheumatol.* **32**(9), pp.1745-1750.
- Helliwell, P.S., FitzGerald, O. and Fransen, J. 2014. Composite disease activity and responder indices for psoriatic arthritis: a report from the GRAPPA 2013 meeting on development of cutoffs for both disease activity states and response. *J Rheumatol.* **41**(6), pp.1212-1217.
- Helliwell, P.S., FitzGerald, O., Fransen, J., Gladman, D.D., Kreuger, G.G., Callis-Duffin, K., McHugh, N., Mease, P.J., Strand, V., Waxman, R., Azevedo, V.F., Beltran Ostos, A., Carneiro, S., Cauli, A., Espinoza, L.R., Flynn, J.A., Hassan, N., Healy, P., Kerzberg, E.M., Lee, Y.J., Lubrano, E., Marchesoni, A., Marzo-Ortega, H., Porru, G., Moreta, E.G., Nash, P., Raffayova, H., Ranza, R., Raychaudhuri, S.P., Roussou, E., Scarpa, R., Song, Y.W., Soriano, E.R., Tak, P.P., Ujfalussy, I., de Vlam, K. and Walsh, J.A. 2013. The development of candidate composite disease activity and responder indices for psoriatic arthritis (GRACE project). *Ann Rheum Dis.* **72**(6), pp.986-991.
- Helliwell, P.S. and Kavanaugh, A. 2014. Comparison of composite measures of disease activity in psoriatic arthritis using data from an interventional study with golimumab. *Arthritis Care Res (Hoboken).* **66**(5), pp.749-756.
- Helliwell, P.S., Mease, P.J., Kavanaugh, A., Coates, L.C., Ogdie, A., Deodhar, A., Strand, V., Kricorian, G., Liu, L.X.H., Collier, D. and Gladman, D.D. 2022. Impact of clinical domains other than arthritis on composite outcomes in psoriatic arthritis: comparison of treatment effects in the SEAM-PsA trial. *RMD Open.* **8**(2).
- Helliwell, P.S. and Ruderman, E.M. 2015. Natural History, Prognosis, and Socioeconomic Aspects of Psoriatic Arthritis. *Rheum Dis Clin North Am.* **41**(4), pp.581-591.
- Hen, O., Di Matteo, A., Dubash, S.R., De Marco, G., Tan, A.L., Emery, P., Wakefield, R.J., McGonagle, D.G., Helliwell, P. and Marzo-Ortega, H. 2024a. High prevalence of radiographic erosions in early, untreated PsA: results from the SpARRO cohort. *RMD Open.* **10**(2).
- Hen, O., Harrison, S.R., De Marco, G. and Marzo-Ortega, H. 2024b. Early psoriatic arthritis: when is the right time to start advanced therapy? *Ther Adv Musculoskelet Dis.* **16**, p1759720X241266727.
- Higgins, J.P.T. and Cochrane Collaboration. 2020. *Cochrane handbook for systematic reviews of interventions.* Second edition. ed. Hoboken, NJ: Wiley-Blackwell.
- Husic, R., Gretler, J., Felber, A., Graninger, W.B., Duftner, C., Hermann, J. and Dejaco, C. 2014. Disparity between ultrasound and clinical findings in psoriatic arthritis. *Ann Rheum Dis.* **73**(8), pp.1529-1536.
- Jaremko, J.L., Jeffery, D., Buller, M., Wichuk, S., McDougall, D., Lambert, R.G. and Maksymowych, W.P. 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. *RMD Open.* **3**(1), pe000355.
- Kaltwasser, J.P., Nash, P., Gladman, D., Rosen, C.F., Behrens, F., Jones, P., Wollenhaupt, J., Falk, F.G., Mease, P. and Treatment of Psoriatic Arthritis Study, G. 2004. Efficacy and safety of leflunomide in the treatment of psoriatic

arthritis and psoriasis: a multinational, double-blind, randomized, placebo-controlled clinical trial. *Arthritis Rheum.* **50**(6), pp.1939-1950.

- Kane, D., Stafford, L., Bresnihan, B. and FitzGerald, O. 2003. A prospective, clinical and radiological study of early psoriatic arthritis: an early synovitis clinic experience. *Rheumatology (Oxford).* **42**(12), pp.1460-1468.
- Karmacharya, P., Chakradhar, R. and Ogdie, A. 2021. The epidemiology of psoriatic arthritis: A literature review. *Best Pract Res Clin Rheumatol.* **35**(2), p101692.
- Kavanaugh, A., Gottlieb, A., Morita, A., Merola, J.F., Lin, C.Y., Birt, J., Shuler, C.L., Hufford, M.M. and Thaci, D. 2019. The contribution of joint and skin improvements to the health-related quality of life of patients with psoriatic arthritis: a post hoc analysis of two randomised controlled studies. *Ann Rheum Dis.* **78**(9), pp.1215-1219.
- Kavanaugh, A., McInnes, I., Mease, P., Krueger, G.G., Gladman, D., Gomez-Reino, J., Papp, K., Zrubek, J., Mudivarthy, S., Mack, M., Visvanathan, S. and Beutler, A. 2009. Golimumab, a new human tumor necrosis factor alpha antibody, administered every four weeks as a subcutaneous injection in psoriatic arthritis: Twenty-four-week efficacy and safety results of a randomized, placebo-controlled study. *Arthritis Rheum.* **60**(4), pp.976-986.
- Kavanaugh, A., Mease, P.J., Gomez-Reino, J.J., Adebajo, A.O., Wollenhaupt, J., Gladman, D.D., Lespessailles, E., Hall, S., Hochfeld, M., Hu, C., Hough, D., Stevens, R.M. and Schett, G. 2014. Treatment of psoriatic arthritis in a phase 3 randomised, placebo-controlled trial with apremilast, an oral phosphodiesterase 4 inhibitor. *Ann Rheum Dis.* **73**(6), pp.1020-1026.
- Kerschbaumer, A., Baker, D., Smolen, J.S. and Aletaha, D. 2017. The effects of structural damage on functional disability in psoriatic arthritis. *Ann Rheum Dis.* **76**(12), pp.2038-2045.
- Kilic, G., Kilic, E., Tekeoglu, I., Sargin, B., Cengiz, G., Balta, N.C., Alkan, H., Kasman, S.A., Sahin, N., Orhan, K., Gezer, I.A., Keskin, D., Mulkoglu, C., Resorlu, H., Ataman, S., Bal, A., Duruoz, M.T., Kucukakkas, O., Sen, N., Toprak, M., Yurdakul, O.V., Melikoglu, M.A., Ayhan, F.F., Baykul, M., Bodur, H., Calis, M., Capkin, E., Devrimsel, G., Hizmetli, S., Kamanli, A., Keskin, Y., Ecesoy, H., Kutluk, O., Sendur, O.F., Tolu, S., Tuncer, T. and Nas, K. 2023. Diagnostic delay in psoriatic arthritis: insights from a nationwide multicenter study. *Rheumatol Int.*
- Krabbe, S., Eshed, I., Gandjbakhch, F., Pedersen, S.J., Bird, P., Mathew, A.J., Lambert, R.G., Maksymowych, W.P., Glinatsi, D., Stoenoiu, M.S., Poggenborg, R., Jans, L., Jaremko, J.L., Herregods, N., Foltz, V., Conaghan, P.G., Althoff, C.E., Paschke, J., Peterfy, C., Hermann, K.A., Ostergaard, M. and Group, O.M.i.A.W. 2019a. Development and Validation of an OMERACT MRI Whole-Body Score for Inflammation in Peripheral Joints and Entheses in Inflammatory Arthritis (MRI-WIPE). *J Rheumatol.* **46**(9), pp.1215-1221.
- Krabbe, S., Ostergaard, M., Pedersen, S.J., Weber, U., Krober, G., Makysmowych, W. and Lambert, R.G.W. 2019b. 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. *RMD Open.* **5**(2), pe001057.
- Kristensen, L.E., Keiserman, M., Papp, K., McCasland, L., White, D., Lu, W., Wang, Z., Soliman, A.M., Eldred, A., Barcomb, L. and Behrens, F. 2022. Efficacy and safety of risankizumab for active psoriatic arthritis: 24-week results from the randomised, double-blind, phase 3 KEEPsAKE 1 trial. *Ann Rheum Dis.* **81**(2), pp.225-231.

- Landewe, R., Ritchlin, C.T., Aletaha, D., Zhang, Y., Ganz, F., Hojnik, M. and Coates, L.C. 2019. Inhibition of radiographic progression in psoriatic arthritis by adalimumab independent of the control of clinical disease activity. *Rheumatology (Oxford).* **58**(6), pp.1025-1033.
- Lie, E., van der Heijde, D., Uhlig, T., Heiberg, M.S., Koldingsnes, W., Rodevand, E., Kaufmann, C., Mikkelsen, K. and Kvien, T.K. 2010. Effectiveness and retention rates of methotrexate in psoriatic arthritis in comparison with methotrexate-treated patients with rheumatoid arthritis. *Ann Rheum Dis.* **69**(4), pp.671-676.
- Lindstrom, U., di Giuseppe, D., Exarchou, S., Alenius, G.M., Olofsson, T., Klingberg, E., Jacobsson, L., Askling, J. and Wallman, J.K. 2023. Methotrexate treatment in early psoriatic arthritis in comparison to rheumatoid arthritis: an observational nationwide study. *RMD Open.* **9**(2).
- Loginova, E., T, K., E, G., S, G.-H. and E, N. 2018. Attainment of remission and minimal disease activity after starting methotrexate subcutaneous therapy.
- Long, V., Yew, Y.W., Chandran, N.S. and Choi, E.C. 2022. Psoriasis flares and rebound phenomenon following exposure and withdrawal of systemic steroids: A systematic review and meta-analysis. *J Am Acad Dermatol.* **87**(3), pp.660-661.
- Lories, R.J., Matthys, P., de Vlam, K., Derese, I. and Luyten, F.P. 2004. Ankylosing enthesitis, dactylitis, and onychoperiostitis in male DBA/1 mice: a model of psoriatic arthritis. *Ann Rheum Dis.* **63**(5), pp.595-598.
- Maharaj, A.B. and Adebajo, A. 2021. Psoriatic arthritis in Africa. *Clin Rheumatol.* **40**(9), pp.3411-3418.
- Maksymowych, W.P., Cibere, J., Loeuille, D., Weber, U., Zubler, V., Roemer, F.W., Jaremko, J.L., Sayre, E.C. and Lambert, R.G. 2014. Preliminary validation of 2 magnetic resonance image scoring systems for osteoarthritis of the hip according to the OMERACT filter. *J Rheumatol.* **41**(2), pp.370-378.
- Maksymowych, W.P., Inman, R.D., Salonen, D., Dhillon, S.S., Krishnananthan, R., Stone, M., Conner-Spady, B., Palsat, J. and Lambert, R.G. 2005a. Spondyloarthritis Research Consortium of Canada magnetic resonance imaging index for assessment of spinal inflammation in ankylosing spondylitis. *Arthritis Rheum.* **53**(4), pp.502-509.
- Maksymowych, W.P., Inman, R.D., Salonen, D., Dhillon, S.S., Williams, M., Stone, M., Conner-Spady, B., Palsat, J. and Lambert, R.G. 2005b. Spondyloarthritis research Consortium of Canada magnetic resonance imaging index for assessment of sacroiliac joint inflammation in ankylosing spondylitis. *Arthritis Rheum.* **53**(5), pp.703-709.
- Maksymowych, W.P., Mallon, C., Morrow, S., Shojania, K., Olszynski, W.P., Wong, R.L., Sampalis, J. and Conner-Spady, B. 2009. Development and validation of the Spondyloarthritis Research Consortium of Canada (SPARCC) Enthesitis Index. *Ann Rheum Dis.* **68**(6), pp.948-953.
- Mander, M., Simpson, J.M., McLellan, A., Walker, D., Goodacre, J.A. and Dick, W.C. 1987. Studies with an enthesis index as a method of clinical assessment in ankylosing spondylitis. *Ann Rheum Dis.* **46**(3), pp.197-202.
- Marchesoni, A., De Marco, G., Merashli, M., McKenna, F., Tinazzi, I., Marzo-Ortega, H. and McGonagle, D.G. 2018. The problem in differentiation between psoriatic-related polyenthesitis and fibromyalgia. *Rheumatology (Oxford).* **57**(1), pp.32-40.
- Mathew, A.J., Krabbe, S., Eshed, I., Gandjbakhch, F., Bird, P., Pedersen, S.J., Stoenoiu, M.S., Foltz, V., Glinatsi, D., Lambert, R.G., Hermann, K.G.A.,

Maksymowych, W.P., Haugen, I.K., Jaremko, J.L., Poggenborg, R.P., Paschke, J., Laredo, J.D., Carron, P., Conaghan, P.G. and Ostergaard, M. 2019. The OMERACT MRI in Enthesitis Initiative: Definitions of Key Pathologies, Suggested MRI Sequences, and a Novel Heel Enthesitis Scoring System. *J Rheumatol.* **46**(9), pp.1232-1238.

- Mathew, A.J., Ostergaard, M. and Eder, L. 2021. Imaging in psoriatic arthritis: Status and recent advances. *Best Pract Res Clin Rheumatol.* **35**(2), p101690.
- McGonagle, D., Aydin, S.Z., Gul, A., Mahr, A. and Direskeneli, H. 2015. 'MHC-I-opathy'-unified concept for spondyloarthritis and Behcet disease. *Nat Rev Rheumatol.* **11**(12), pp.731-740.
- McGonagle, D., David, P., Macleod, T. and Watad, A. 2023. Predominant ligament-centric soft-tissue involvement differentiates axial psoriatic arthritis from ankylosing spondylitis. *Nat Rev Rheumatol.* **19**(12), pp.818-827.
- McGonagle, D. and Emery, P. 1999. Classification of inflammatory arthritis. *Lancet.* **353**(9153), p671.
- McGonagle, D., Khan, M.A., Marzo-Ortega, H., O'Connor, P., Gibbon, W. and Emery, P. 1999. Enthesitis in spondyloarthropathy. *Curr Opin Rheumatol.* **11**(4), pp.244-250.
- McGonagle, D., Lories, R.J., Tan, A.L. and Benjamin, M. 2007. The concept of a "synovio-entheseal complex" and its implications for understanding joint inflammation and damage in psoriatic arthritis and beyond. *Arthritis Rheum.* **56**(8), pp.2482-2491.
- McGonagle, D., Tan, A.L., Moller Dohn, U., Ostergaard, M. and Benjamin, M. 2009. Microanatomic studies to define predictive factors for the topography of periarticular erosion formation in inflammatory arthritis. *Arthritis Rheum.* **60**(4), pp.1042-1051.
- McGonagle, D.G., Zabotti, A., Watad, A., Bridgewood, C., De Marco, G., Kerschbaumer, A. and Aletaha, D. 2022. Intercepting psoriatic arthritis in patients with psoriasis: buy one get one free? *Ann Rheum Dis.* **81**(1), pp.7-10.
- McInnes, I.B., Kavanaugh, A., Gottlieb, A.B., Puig, L., Rahman, P., Ritchlin, C., Brodmerkel, C., Li, S., Wang, Y., Mendelsohn, A.M., Doyle, M.K. and Group, P.S. 2013. Efficacy and safety of ustekinumab in patients with active psoriatic arthritis: 1 year results of the phase 3, multicentre, double-blind, placebo-controlled PSUMMIT 1 trial. *Lancet.* **382**(9894), pp.780-789.
- McInnes, I.B., Mease, P.J., Kirkham, B., Kavanaugh, A., Ritchlin, C.T., Rahman, P., van der Heijde, D., Landewe, R., Conaghan, P.G., Gottlieb, A.B., Richards, H., Pricop, L., Ligozio, G., Patekar, M., Mpofu, S. and Group, F.S. 2015. Secukinumab, a human anti-interleukin-17A monoclonal antibody, in patients with psoriatic arthritis (FUTURE 2): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet.* **386**(9999), pp.1137-1146.
- Mease, P.J. and Coates, L.C. 2018. Considerations for the definition of remission criteria in psoriatic arthritis. *Semin Arthritis Rheum.* **47**(6), pp.786-796.
- Mease, P.J., Etzel, C.J., Huster, W.J., Muram, T.M., Armstrong, A.W., Lisse, J.R., Rebello, S., Dodge, R., Murage, M.J., Greenberg, J.D. and Malatestinic, W.N. 2019a. Understanding the association between skin involvement and joint activity in patients with psoriatic arthritis: experience from the Corrona Registry. *RMD Open.* **5**(1), pe000867.
- Mease, P.J., Fleischmann, R., Deodhar, A.A., Wollenhaupt, J., Khraishi, M., Kielar, D., Woltering, F., Stach, C., Hoepken, B., Arledge, T. and van der Heijde, D. 2014. Effect of certolizumab pegol on signs and symptoms in patients

with psoriatic arthritis: 24-week results of a Phase 3 double-blind randomised placebo-controlled study (RAPID-PsA). *Ann Rheum Dis.* **73**(1), pp.48-55.

- Mease, P.J., Gladman, D.D., Collier, D.H., Ritchlin, C.T., Helliwell, P.S., Liu, L., Kricorian, G. and Chung, J.B. 2019b. Etanercept and Methotrexate as Monotherapy or in Combination for Psoriatic Arthritis: Primary Results From a Randomized, Controlled Phase III Trial. *Arthritis Rheumatol.* **71**(7), pp.1112-1124.
- Mease, P.J., Gladman, D.D., Ritchlin, C.T., Ruderman, E.M., Steinfeld, S.D., Choy, E.H., Sharp, J.T., Ory, P.A., Perdok, R.J., Weinberg, M.A. and Adalimumab Effectiveness in Psoriatic Arthritis Trial Study, G. 2005. Adalimumab for the treatment of patients with moderately to severely active psoriatic arthritis: results of a double-blind, randomized, placebo-controlled trial. *Arthritis Rheum.* **52**(10), pp.3279-3289.
- Mease, P.J., Goffe, B.S., Metz, J., VanderStoep, A., Finck, B. and Burge, D.J. 2000. Etanercept in the treatment of psoriatic arthritis and psoriasis: a randomised trial. *Lancet.* **356**(9227), pp.385-390.
- Mease, P.J., Gottlieb, A.B., van der Heijde, D., FitzGerald, O., Johnsen, A., Nys, M., Banerjee, S. and Gladman, D.D. 2017a. Efficacy and safety of abatacept, a T-cell modulator, in a randomised, double-blind, placebo-controlled, phase III study in psoriatic arthritis. *Ann Rheum Dis.* **76**(9), pp.1550-1558.
- Mease, P.J., Lertratanakul, A., Anderson, J.K., Papp, K., Van den Bosch, F., Tsuji, S., Dokoupilova, E., Keiserman, M., Wang, X., Zhong, S., McCaskill, R.M., Zueger, P., Pangan, A.L. and Tillett, W. 2021. Upadacitinib for psoriatic arthritis refractory to biologics: SELECT-PsA 2. *Ann Rheum Dis.* **80**(3), pp.312-320.
- Mease, P.J., van der Heijde, D., Ritchlin, C.T., Okada, M., Cuchacovich, R.S., Shuler, C.L., Lin, C.Y., Braun, D.K., Lee, C.H., Gladman, D.D. and Group, S.-P.S. 2017b. Ixekizumab, an interleukin-17A specific monoclonal antibody, for the treatment of biologic-naive patients with active psoriatic arthritis: results from the 24-week randomised, double-blind, placebo-controlled and active (adalimumab)-controlled period of the phase III trial SPIRIT-P1. *Ann Rheum Dis.* **76**(1), pp.79-87.
- Melis, L. and Elewaut, D. 2009. Progress in spondylarthritis. Immunopathogenesis of spondyloarthritis: which cells drive disease? *Arthritis Res Ther.* **11**(3), p233.
- Merola, J.F., Landewe, R., McInnes, I.B., Mease, P.J., Ritchlin, C.T., Tanaka, Y., Asahina, A., Behrens, F., Gladman, D.D., Gossec, L., Gottlieb, A.B., Thaci, D., Warren, R.B., Ink, B., Assudani, D., Bajracharya, R., Shende, V., Coarse, J. and Coates, L.C. 2023. Bimekizumab in patients with active psoriatic arthritis and previous inadequate response or intolerance to tumour necrosis factor-alpha inhibitors: a randomised, double-blind, placebo-controlled, phase 3 trial (BE COMPLETE). *Lancet.* **401**(10370), pp.38-48.
- Michalek, I.M., Loring, B., John, S.M. and World Health, O. 2016. *Global report on psoriasis.* Geneva: World Health Organization.
- Michelena, X., Poddubnyy, D. and Marzo-Ortega, H. 2020. Axial Psoriatic Arthritis: A Distinct Clinical Entity in Search of a Definition. *Rheum Dis Clin North Am.* **46**(2), pp.327-341.
- Michelsen, B., Fiane, R., Diamantopoulos, A.P., Soldal, D.M., Hansen, I.J., Sokka, T., Kavanaugh, A. and Haugeberg, G. 2015. A comparison of disease burden in rheumatoid arthritis, psoriatic arthritis and axial spondyloarthritis. *PLoS One.* **10**(4), pe0123582.

- Moher, D., Liberati, A., Tetzlaff, J., Altman, D.G. and Group, P. 2009. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *J Clin Epidemiol.* **62**(10), pp.1006-1012.
- Moll, J.M., Haslock, I., Macrae, I.F. and Wright, V. 1974. Associations between ankylosing spondylitis, psoriatic arthritis, Reiter's disease, the intestinal arthropathies, and Behcet's syndrome. *Medicine (Baltimore).* **53**(5), pp.343-364.
- Moll, J.M. and Wright, V. 1973a. Familial occurrence of psoriatic arthritis. *Ann Rheum Dis.* **32**(3), pp.181-201.
- Moll, J.M. and Wright, V. 1973b. Psoriatic arthritis. *Semin Arthritis Rheum.* **3**(1), pp.55-78.
- Moly, M., Lukas, C., Morel, J., Combe, B. and Mouterde, G. 2020. In Psoriatic Arthritis Patients Considered in Remission by Their Rheumatologist, Can Discordance in Disease Activity Assessment between Patient and Rheumatologist Be Explained by Residual Inflammation as Measured by Ultrasonographic Examination? *Annals of the Rheumatic Diseases.* **79**, pp.504-504.
- Mulder, M.L.M., Bertram, A.M., Wenink, M.H. and Vriezekolk, J.E. 2022. Defining the minimal important change (MIC) and meaningful change value (MCV) for the Psoriatic Arthritis Disease Activity Score (PASDAS) in a routine practice cohort of patients with psoriatic arthritis. *Rheumatology (Oxford).* **61**(10), pp.4119-4123.
- Mulder, M.L.M., Vriezekolk, J.E., den Broeder, N., Mahler, E.A.M., Helliwell, P.S., van den Hoogen, F.H.J., den Broeder, A.A. and Wenink, M.H. 2020. Comparing methotrexate monotherapy with methotrexate plus leflunomide combination therapy in psoriatic arthritis: protocol of a randomized, placebo-controlled, double-blind clinical trial (COMPLETE-PsA). *Trials.* **21**(1), p155.
- Mumtaz, A., Gallagher, P., Kirby, B., Waxman, R., Coates, L.C., Veale, J.D., Helliwell, P. and FitzGerald, O. 2011. Development of a preliminary composite disease activity index in psoriatic arthritis. *Ann Rheum Dis.* **70**(2), pp.272-277.
- Naredo, E., Moller, I., de Miguel, E., Batlle-Gualda, E., Acebes, C., Brito, E., Mayordomo, L., Moragues, C., Uson, J., de Agustin, J.J., Martinez, A., Rejon, E., Rodriguez, A., Dauden, E., Ultrasound School of the Spanish Society of, R. and Spanish, E.C.O.A.G. 2011. High prevalence of ultrasonographic synovitis and enthesopathy in patients with psoriasis without psoriatic arthritis: a prospective case-control study. *Rheumatology (Oxford).* **50**(10), pp.1838-1848.
- Orbai, A.M., de Wit, M., Mease, P.J., Callis Duffin, K., Elmamoun, M., Tillett, W., Campbell, W., FitzGerald, O., Gladman, D.D., Goel, N., Gossec, L., Hoejgaard, P., Leung, Y.Y., Lindsay, C., Strand, V., van der Heijde, D.M., Shea, B., Christensen, R., Coates, L., Eder, L., McHugh, N., Kalyoncu, U., Steinkoenig, I. and Ogdie, A. 2017. Updating the Psoriatic Arthritis (PsA) Core Domain Set: A Report from the PsA Workshop at OMERACT 2016. *J Rheumatol.* **44**(10), pp.1522-1528.
- Ostergaard, M., van Vollenhoven, R.F., Rudin, A., Hetland, M.L., Heiberg, M.S., Nordstrom, D.C., Nurmohamed, M.T., Gudbjornsson, B., Ornbjerg, L.M., Boyesen, P., Lend, K., Horslev-Petersen, K., Uhlig, T., Sokka, T., Grondal, G., Krabbe, S., Lindqvist, J., Gjertsson, I., Glinatsi, D., Kapetanovic, M.C., Aga, A.B., Faustini, F., Parmanne, P., Lorenzen, T., Giovanni, C., Back, J., Hendricks, O., Vedder, D., Rannio, T., Grenholm, E., Ljosa, M.K., Brodin, E., Lindegaard, H., Soderbergh, A., Rizk, M., Kastbom, A., Larsson, P., Uhrenholt, L., Just, S.A., Stevens, D.J., Bay Laurbjerg, T., Bakland, G., Olsen, I.C., Haavardsholm, E.A., Lampa, J. and group, N.-S.s. 2023. Certolizumab pegol, abatacept, tocilizumab

or active conventional treatment in early rheumatoid arthritis: 48-week clinical and radiographic results of the investigator-initiated randomised controlled NORD-STAR trial. *Ann Rheum Dis.* **82**(10), pp.1286-1295.

- Padovano, I., Costantino, F., Breban, M. and D'Agostino, M.A. 2016. Prevalence of ultrasound synovial inflammatory findings in healthy subjects. *Ann Rheum Dis.* **75**(10), pp.1819-1823.
- Palominos, P.E., Fernandez-Avila, D.G., Coates, L.C., Adebajo, A., Toukap, A.N., Abogamal, A., Polachek, A., van Kuijk, A.W.R., Caso, F., de Marco, G., Kaeley, G.S., Steinkoenig, I., Chau, J., Feletar, M., Vis, M., Elkayam, O., Sewerin, P., d'Angelo, S., Aydin, S.Z., AlShehhi, W. and Helliwell, P.S. 2023. Management of Dactylitis in Patients With Psoriatic Arthritis: An Updated Literature Review Informing the 2021 GRAPPA Treatment Recommendations. *J Rheumatol.* **50**(2), pp.265-278.
- Park, E.H. and Fritz, J. 2023. The role of imaging in osteoarthritis. *Best Pract Res Clin Rheumatol.* **37**(2), p101866.
- Perruccio, A.V., Got, M., Li, S., Ye, Y., Gladman, D.D. and Chandran, V. 2020. Treating Psoriatic Arthritis to Target: Defining the Psoriatic Arthritis Disease Activity Score That Reflects a State of Minimal Disease Activity. *J Rheumatol.* **47**(3), pp.362-368.
- Petitpain, N., D'Amico, F., Yelehe-Okouma, M., Jouzeau, J.Y., Netter, P., Peyrin-Biroulet, L. and Gillet, P. 2021. IL-17 Inhibitors and Inflammatory Bowel Diseases: A Postmarketing Study in Vigibase. *Clin Pharmacol Ther.* **110**(1), pp.159-168.
- Pezzolo, E. and Naldi, L. 2019. The relationship between smoking, psoriasis and psoriatic arthritis. *Expert Rev Clin Immunol.* **15**(1), pp.41-48.
- Pinals, R.S., Masi, A.T. and Larsen, R.A. 1981. Preliminary criteria for clinical remission in rheumatoid arthritis. *Arthritis Rheum.* **24**(10), pp.1308-1315.
- Poddubnyy, D., Jadon, D.R., Van den Bosch, F., Mease, P.J. and Gladman, D.D. 2021. Axial involvement in psoriatic arthritis: An update for rheumatologists. *Semin Arthritis Rheum.* **51**(4), pp.880-887.
- Poggenborg, R.P., Wiell, C., Boyesen, P., Boonen, A., Bird, P., Pedersen, S.J., Sorensen, I.J., Madsen, O.R., Slot, O., Moller, J.M., Hasselquist, M., Kubassova, O. and Ostergaard, M. 2014. No overall damage progression despite persistent inflammation in adalimumab-treated psoriatic arthritis patients: results from an investigator-initiated 48-week comparative magnetic resonance imaging, computed tomography and radiography trial. *Rheumatology (Oxford).* **53**(4), pp.746-756.
- Polachek, W.S., Baker, H.P., Dahm, J.S., Strelzow, J.A. and Hynes, K.K. 2022. Diabetic Kidney Disease Is Associated With Increased Complications Following Operative Management of Ankle Fractures. *Foot Ankle Orthop.* **7**(3), p24730114221112106.
- Prevoo, M.L., van Gestel, A.M., van, T.H.M.A., van Rijswijk, M.H., van de Putte, L.B. and van Riel, P.L. 1996. Remission in a prospective study of patients with rheumatoid arthritis. American Rheumatism Association preliminary remission criteria in relation to the disease activity score. *Br J Rheumatol.* **35**(11), pp.1101-1105.
- Richard, M.A., Paul, C., Nijsten, T., Gisondi, P., Salavastru, C., Taieb, C., Trakatelli, M., Puig, L., Stratigos, A. and team, E.b.o.s.d.p. 2022. Prevalence of most common skin diseases in Europe: a population-based study. *J Eur Acad Dermatol Venereol.* **36**(7), pp.1088-1096.
- Rida, M.A. and Chandran, V. 2020. Challenges in the clinical diagnosis of psoriatic arthritis. *Clin Immunol.* **214**, p108390.

- Ritchlin, C. 2007. Psoriatic disease--from skin to bone. *Nat Clin Pract Rheumatol.* **3**(12), pp.698-706.
- Ritchlin, C., Rahman, P., Kavanaugh, A., McInnes, I.B., Puig, L., Li, S., Wang, Y., Shen, Y.K., Doyle, M.K., Mendelsohn, A.M., Gottlieb, A.B. and Group, P.S. 2014. Efficacy and safety of the anti-IL-12/23 p40 monoclonal antibody, ustekinumab, in patients with active psoriatic arthritis despite conventional non-biological and biological anti-tumour necrosis factor therapy: 6-month and 1-year results of the phase 3, multicentre, double-blind, placebo-controlled, randomised PSUMMIT 2 trial. *Ann Rheum Dis.* **73**(6), pp.990-999.
- Ritchlin, C.T., Colbert, R.A. and Gladman, D.D. 2017. Psoriatic Arthritis. *N Engl J Med.* **376**(10), pp.957-970.
- Rudwaleit, M., van der Heijde, D., Landewe, R., Listing, J., Akkoc, N., Brandt, J., Braun, J., Chou, C.T., Collantes-Estevez, E., Dougados, M., Huang, F., Gu, J., Khan, M.A., Kirazli, Y., Maksymowych, W.P., Mielants, H., Sorensen, I.J., Ozgocmen, S., Roussou, E., Valle-Onate, R., Weber, U., Wei, J. and Sieper, J. 2009. The development of Assessment of SpondyloArthritis international Society classification criteria for axial spondyloarthritis (part II): validation and final selection. *Ann Rheum Dis.* **68**(6), pp.777-783.
- Ruta, S., Marin, J., Acosta Felquer, M.L., Ferreyra-Garrot, L., Rosa, J., Garcia-Monaco, R. and Soriano, E.R. 2017. Utility of Power Doppler Ultrasound-detected Synovitis for the Prediction of Short-term Flare in Psoriatic Patients with Arthritis in Clinical Remission. *J Rheumatol.* **44**(7), pp.1018-1023.
- Samanta, J., Naidu, G.S.R.S.N.K., Chattopadhyay, A., Basnet, A., Narang, T., Dhir, V., Dogra, S., Jain, S. and Sharma, A. 2023. Comparison between methotrexate and apremilast in Psoriatic Arthritis-a single blind randomized controlled trial (APREMEPsA study). *Rheumatology International.*
- Scarpa, R., Altomare, G., Marchesoni, A., Balato, N., Matucci Cerinic, M., Lotti, T., Olivieri, I., Vena, G.A., Salvarani, C., Valesini, G. and Giannetti, A. 2010. Psoriatic disease: concepts and implications. *J Eur Acad Dermatol Venereol.* **24**(6), pp.627-630.
- Scarpa, R., Ayala, F., Caporaso, N. and Olivieri, I. 2006. Psoriasis, psoriatic arthritis, or psoriatic disease? *J Rheumatol.* **33**(2), pp.210-212.
- Scarpa, R., Caso, F., Costa, L., Peluso, R., Del Puente, A. and Olivieri, I. 2017. Psoriatic Disease 10 Years Later. *J Rheumatol.* **44**(9), pp.1298-1301.
- Scarpa, R., Cosentini, E., Manguso, F., Oriente, A., Peluso, R., Atteno, M., Ayala, F., D'Arienzo, A. and Oriente, P. 2003. Clinical and genetic aspects of psoriatic arthritis "sine psoriasis". *J Rheumatol.* **30**(12), pp.2638-2640.
- Scarpa, R., Peluso, R., Atteno, M., Manguso, F., Spano, A., Iervolino, S., Di Minno, M.N.D., Costa, L. and Del Puente, A. 2008. The effectiveness of a traditional therapeutical approach in early psoriatic arthritis: results of a pilot randomised 6-month trial with methotrexate. *Clinical Rheumatology.* **27**(7), pp.823-826.
- Scher, J.U., Ogdie, A., Merola, J.F. and Ritchlin, C. 2019. Preventing psoriatic arthritis: focusing on patients with psoriasis at increased risk of transition. *Nat Rev Rheumatol.* **15**(3), pp.153-166.
- Schlosstein, L., Terasaki, P.I., Bluestone, R. and Pearson, C.M. 1973. High association of an HL-A antigen, W27, with ankylosing spondylitis. *N Engl J Med.* **288**(14), pp.704-706.
- Schoels, M., Aletaha, D., Funovits, J., Kavanaugh, A., Baker, D. and Smolen, J.S. 2010. Application of the DAREA/DAPSA score for assessment of disease activity in psoriatic arthritis. *Ann Rheum Dis.* **69**(8), pp.1441-1447.

- Schoels, M.M., Aletaha, D., Alasti, F. and Smolen, J.S. 2016. Disease activity in psoriatic arthritis (PsA): defining remission and treatment success using the DAPSA score. *Ann Rheum Dis.* **75**(5), pp.811-818.
- Sieper, J., Rudwaleit, M., Baraliakos, X., Brandt, J., Braun, J., Burgos-Vargas, R., Dougados, M., Hermann, K.G., Landewe, R., Maksymowych, W. and van der Heijde, D. 2009a. The Assessment of SpondyloArthritis international Society (ASAS) handbook: a guide to assess spondyloarthritis. *Ann Rheum Dis.* **68 Suppl 2**, pp.ii1-44.
- Sieper, J., van der Heijde, D., Landewe, R., Brandt, J., Burgos-Vagas, R., Collantes-Estevez, E., Dijkmans, B., Dougados, M., Khan, M.A., Leirisalo-Repo, M., van der Linden, S., Maksymowych, W.P., Mielants, H., Olivieri, I. and Rudwaleit, M. 2009b. New criteria for inflammatory back pain in patients with chronic back pain: a real patient exercise by experts from the Assessment of SpondyloArthritis international Society (ASAS). *Ann Rheum Dis.* **68**(6), pp.784-788.
- Snoeck Henkemans, S.V.J., de Jong, P.H.P., Luime, J.J., Kok, M.R., Tchetverikov, I., Korswagen, L.A., van der Kooij, S.M., van Oosterhout, M., Baudoin, P., Bijsterbosch, J., van der Kaap, J.H., van der Helm-van Mil, A.H.M. and Vis, M. 2024. Window of opportunity in psoriatic arthritis: the earlier the better? *RMD Open.* **10**(1).
- Taylor, W., Gladman, D., Helliwell, P., Marchesoni, A., Mease, P., Mielants, H. and Group, C.S. 2006. Classification criteria for psoriatic arthritis: development of new criteria from a large international study. *Arthritis Rheum.* **54**(8), pp.2665-2673.
- Terslev, L., Naredo, E., Aegerter, P., Wakefield, R.J., Backhaus, M., Balint, P., Bruyn, G.A.W., Iagnocco, A., Jousse-Joulin, S., Schmidt, W.A., Szkudlarek, M., Conaghan, P.G., Filippucci, E. and D'Agostino, M.A. 2017. Scoring ultrasound synovitis in rheumatoid arthritis: a EULAR-OMERACT ultrasound taskforce-Part 2: reliability and application to multiple joints of a standardised consensus-based scoring system. *RMD Open.* **3**(1), pe000427.
- Terslev, L., Naredo, E., Iagnocco, A., Balint, P.V., Wakefield, R.J., Aegerter, P., Aydin, S.Z., Bachta, A., Hammer, H.B., Bruyn, G.A., Filippucci, E., Gandjbakhch, F., Mandl, P., Pineda, C., Schmidt, W.A., D'Agostino, M.A. and Outcome Measures in Rheumatology Ultrasound Task, F. 2014. Defining enthesitis in spondyloarthritis by ultrasound: results of a Delphi process and of a reliability reading exercise. *Arthritis Care Res (Hoboken).* **66**(5), pp.741-748.
- Theander, E., Husmark, T., Alenius, G.M., Larsson, P.T., Teleman, A., Geijer, M. and Lindqvist, U.R. 2014. Early psoriatic arthritis: short symptom duration, male gender and preserved physical functioning at presentation predict favourable outcome at 5-year follow-up. Results from the Swedish Early Psoriatic Arthritis Register (SwePsA). *Ann Rheum Dis.* **73**(2), pp.407-413.
- Tillett, W., FitzGerald, O., Coates, L.C., Packham, J., Jadon, D.R., Massarotti, M., Brook, M., Lane, S., Creamer, P., Antony, A., Korendowych, E., Rambojun, A., McHugh, N.J., Helliwell, P.S. and Group, P.S. 2021a. Composite Measures for Clinical Trials in Psoriatic Arthritis: Testing Pain and Fatigue Modifications in a UK Multicenter Study. *J Rheumatol Suppl.* **97**, pp.39-44.
- Tillett, W., FitzGerald, O., Coates, L.C., Packham, J., Jadon, D.R., Massarotti, M., Brook, M., Lane, S., Creamer, P., Antony, A., Korendowych, E., Rambojun, A., McHugh, N.J., Helliwell, P.S. and Group, P.S. 2021b. Composite Measures for Routine Clinical Practice in Psoriatic Arthritis: Testing of Shortened Versions in a UK Multicenter Study. *J Rheumatol Suppl.* **97**, pp.45-49.

- Tillett, W., Jadon, D., Shaddick, G., Cavill, C., Korendowych, E., de Vries, C.S. and McHugh, N. 2013. Smoking and delay to diagnosis are associated with poorer functional outcome in psoriatic arthritis. *Ann Rheum Dis.* **72**(8), pp.1358-1361.
- Unknown. 2017. *comparison between methotrexate versus methotrexate plus leflunomide treatment in arthritis associated with psoriasis.* [Online]. Available from: https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01885872/full
- van de Kerkhof, P.C., Reich, K., Kavanaugh, A., Bachelez, H., Barker, J., Girolomoni, G., Langley, R.G., Paul, C.F., Puig, L. and Lebwohl, M.G. 2015. Physician perspectives in the management of psoriasis and psoriatic arthritis: results from the population-based Multinational Assessment of Psoriasis and Psoriatic Arthritis survey. *J Eur Acad Dermatol Venereol.* **29**(10), pp.2002-2010.
- van der Heijde, D.M., van 't Hof, M.A., van Riel, P.L., Theunisse, L.A., Lubberts, E.W., van Leeuwen, M.A., van Rijswijk, M.H. and van de Putte, L.B. 1990. Judging disease activity in clinical practice in rheumatoid arthritis: first step in the development of a disease activity score. *Ann Rheum Dis.* **49**(11), pp.916-920.
- van der Leeuw, M.S., Tekstra, J., van Laar, J.M. and Welsing, P.M.J. 2023. Concomitant prednisone may alleviate methotrexate side-effects in rheumatoid arthritis patients. *BMC Rheumatol.* **7**(1), p8.
- van Mens, L.J.J., de Jong, H.M., Fluri, I., Nurmohamed, M.T., van de Sande, M.G.H., Kok, M., van Kuijk, A.W.R. and Baeten, D. 2019. Achieving remission in psoriatic arthritis by early initiation of TNF inhibition: a double-blind, randomised, placebo-controlled trial of golimumab plus methotrexate versus placebo plus methotrexate. *Ann Rheum Dis.* **78**(5), pp.610-616.
- van Schie, K.A., Ooijevaar-de Heer, P., Dijk, L., Kruithof, S., Wolbink, G. and Rispens, T. 2016. Therapeutic TNF Inhibitors can Differentially Stabilize Trimeric TNF by Inhibiting Monomer Exchange. *Sci Rep.* **6**, p32747.
- Wakefield, R.J., Balint, P.V., Szkudlarek, M., Filippucci, E., Backhaus, M., D'Agostino, M.A., Sanchez, E.N., Iagnocco, A., Schmidt, W.A., Bruyn, G.A., Kane, D., O'Connor, P.J., Manger, B., Joshua, F., Koski, J., Grassi, W., Lassere, M.N., Swen, N., Kainberger, F., Klauser, A., Ostergaard, M., Brown, A.K., Machold, K.P., Conaghan, P.G. and Group, O.S.I. 2005. Musculoskeletal ultrasound including definitions for ultrasonographic pathology. *J Rheumatol.* **32**(12), pp.2485-2487.
- Wervers, K., Luime, J.J., Tchetverikov, I., Gerards, A.H., Kok, M.R., Appels, C.W.Y., van der Graaff, W.L., van Groenendael, J., Korswagen, L.A., Veris-van Dieren, J.J., Hazes, J.M.W., Vis, M. and for, C. 2019. Comparison of disease activity measures in early psoriatic arthritis in usual care. *Rheumatology (Oxford).* **58**(12), pp.2251-2259.
- Whitehead, A.L., Julious, S.A., Cooper, C.L. and Campbell, M.J. 2016. Estimating the sample size for a pilot randomised trial to minimise the overall trial sample size for the external pilot and main trial for a continuous outcome variable. *Stat Methods Med Res.* **25**(3), pp.1057-1073.
- Wirth, T., Balandraud, N., Boyer, L., Lafforgue, P. and Pham, T. 2022. Biomarkers in psoriatic arthritis: A meta-analysis and systematic review. *Front Immunol.* **13**, p1054539.
- Wright, V. 1959. Rheumatism and psoriasis: a re-evaluation. *Am J Med.* **27**, pp.454-462.
- Zabotti, A., De Marco, G., Gossec, L., Baraliakos, X., Aletaha, D., Iagnocco, A., Gisondi, P., Balint, P.V., Bertheussen, H., Boehncke, W.H.,

Damjanov, N.S., de Wit, M., Errichetti, E., Marzo-Ortega, H., Protopopov, M., Puig, L., Queiro, R., Ruscitti, P., Savage, L., Schett, G., Siebert, S., Stamm, T.A., Studenic, P., Tinazzi, I., Van den Bosch, F.E., van der Helm-van Mil, A., Watad, A., Smolen, J.S. and McGonagle, D.G. 2023. EULAR points to consider for the definition of clinical and imaging features suspicious for progression from psoriasis to psoriatic arthritis. *Ann Rheum Dis.* **82**(9), pp.1162-1170.

- Ziade, N., Bou Absi, M. and Baraliakos, X. 2022. Peripheral spondyloarthritis and psoriatic arthritis sine psoriase: are we dealing with semantics or clinically meaningful differences? *RMD Open.* **8**(2).

Appendices

Appendix 1 – PICO Questions Underpinning a Systematic Review on Treatments for Early Psoriatic Arthritis

This Appendix lists the PICO questions formulated as the basis of the systematic review of the medical literature described in paragraph 1.5.

In order to define a search strategy that would address the heterogeneous features of PsA as well as those of PsD as thoroughly as possible, several, diverse research questions were produced. After a round of teleconference meetings, there was agreement on the wording of the following seven research questions:

1. Among patients with early, untreated (DMARD-naïve, systemic therapy-näive) psoriatic disease[1], is pharmacological therapy (systemic or intra-articular) more effective than placebo (or any pharmacological therapy comparator) in obtaining control[2] of overall disease activity [as defined by Arithmetic Mean of the Desirability Function (AMDF-GRACE), CPDAI, MDA]?
2. Among patients with early, untreated (DMARD-naïve, systemic therapy-näive) psoriatic disease, is pharmacological therapy (systemic or intra-articular) more effective than placebo (or any pharmacological therapy comparator) in improving peripheral arthritis [as defined by joint counts, American College of Rheumatology (ACR) response criteria 20/50/70, AMDF-GRACE, CPDAI, Disease Activity Index for Psoriatic Arthritis (DAREA/DAPSA), Disease Activity Score (DAS/DAS28), PASDAS, PsARC]?
3. Among patients with early, untreated (DMARD-naïve, systemic therapy-näive) psoriatic disease, is pharmacological therapy (systemic or intra-digital) more effective than placebo (or any pharmacological therapy

---

[1] The reader will notice that the wording chosen to address the P (Patients) component of the PICO questions structure was "*untreated (DMARD-naïve, systemic therapy-näive) psoriatic disease*", without directly mentioning PsA. This would allow for building search terms that would cover as much domains as possible across the PsD spectrum (that "includes" PsA). It was chosen to apply this principle across all the seven PICO questions that made up the systematic review. However, question 2 (the one addressing manifestations of peripheral arthritis) was addressed building into the search terms specific features targeting PsA in regards with the P (Patients) component.

[2] In the rounds of discussion, the wording "*obtaining control*" was chosen as a proxy of remission. This decision was taken due to the background lack of established definition of remission -both for PsA and for PsD- in the medical literature.

comparator) in improving dactylitis [as defined by Antoni's dactylitic digits rating, Clegg's tender dactylitic digits rating, LDI, Salvarani's tender dactylitic digits count]?

4. Among patients with early, untreated (DMARD-naïve, systemic therapy-näive) psoriatic disease, is pharmacological therapy more effective than placebo (or any pharmacological therapy comparator) in improving psoriatic spondylitis/axial involvement (as defined by Assessment of SpondyloArthritis international Society (ASAS20/50/70, ASAS5/6), Ankylosing Spondylitis Disease Activity Score (ASDAS), BASDAI, BASDAI50, Bath Ankylosing Spondylitis Functional Index (BASFI), VAS spinal/axial pain]?
5. Among patients with early, untreated (DMARD-naïve, systemic therapy-näive) psoriatic disease, is pharmacological therapy (systemic or via peri-entheseal injection) more effective than placebo (or any pharmacological therapy comparator) in improving entheseal involvement [as defined by Braun's mayor index, Gladman's index, LEI, Maastricht Ankylosing Spondylitis Enthesitis Score (MASES), Mander Enthesitis Index (MEI), Spondyloarthritis Research Consortium of Canada Enthesitis Index (SPARCC-EI)]?
6. Among patients with early, untreated (DMARD-naïve, systemic therapy-näive) psoriatic disease, is systemic pharmacological therapy more effective than placebo (or any pharmacological therapy comparator) in improving skin involvement [as defined by BSA, physician's global assessment (physician's GA) of the skin, PASI]?
7. Among patients with early, untreated (DMARD-naïve, systemic therapy-näive) psoriatic disease, is systemic pharmacological therapy more effective than placebo (or any pharmacological therapy comparator) in improving nail involvement (as defined by NAPSI, modified NAPSI)?

Appendix 2 – GOLMePsA Trial Eligibility Criteria

This appendix lists the eligibility criteria as mandated by the GOLMePsA trial protocol.

Inclusion criteria

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

Criteria	Definition
INCL1.	Male and female patients aged ≥18 years at the time of signing the Informed Consent Form.
INCL2.	Patients with a diagnosis of psoriatic arthritis as per the Classification for Psoriatic Arthritis (CASPAR) criteria (Taylor et al., 2006) confirmed up to 24 months prior to screening.
INCL3.	Patients 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.
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 patients of childbearing potential must test negative for pregnancy. Female persons must agree to not donate eggs (ova, oocytes) during the study and for 6 months after last dose of study agent. Male persons 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 Tuberculosis (TB) criteria:
INCL6.1.	Have no history of latent or active TB prior to screening. An exception is made for patients 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 anti-tuberculous 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.
INCL 6.5.	In the event of 2 indeterminate QuantiFERON-TB Gold in-tube tests results, the patients 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.	Haemoglobin (Hb) ≥8.5 g/dL or ≥5.3 mmol/L
INCL6.7.2.	White blood cell (WBC) count ≥3.5x10^3 cells/µL
INCL6.7.3.	Neutrophils ≥1.5 x10^3 cells/µL

INCL6.7.4.	Platelets ≥100x10^3 cells/µL
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
* 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.	

Exclusion criteria

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

Criteria	**Definition**
EXCL 1.	Previous treatment with any conventional or biological DMARDs, where “treatment” is defined as a therapeutic dosage according to each product’s Summary of Product Characteristics (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.

EXCL3.	Patients with significant concurrent medical diseases including uncompensated congestive heart failure, myocardial infarction within 52 weeks from screening, unstable angina pectoris, uncontrolled hypertension (blood pressure >160/95 mmHg), 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 intravenous 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 Non-Alcoholic SteatoHepatitis (NASH) at the time of screening or abnormal blood tests as shown by: • ASpartase aminoTransferase (AST)/ALanine aminoTransferase (ALT) > 3x Upper Limit of Normality (ULN), OR • Bilirubin >51µmol/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, leukopenia, neutropenia 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.	Patients must undergo screening for hepatitis B and C virus (HBV, HCV). 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),
	• Patients who test positive for surface antigen (HBsAg+) are not eligible for this study, regardless of the results of other hepatitis B tests.
	• Patients 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 patients 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 patient is not eligible for this study.
	  • If the HBV DNA test is negative, the patient is eligible for this study.
	  • In the event the DNA test cannot be performed, the patient 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 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 [e.g.: a therapeutic infectious agent such as Bacillus Calmette-Guérin (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 Investigational Medicinal Product (IMP) active substance, or any of the excipients detailed in the SmPC.
* 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 3 GOLMePsA Trial - List of Screening Procedures

This appendix lists the procedures performed at the time of screening period (that is, visit 1 and up to four weeks afterwards) in order to obtain participants' consent and assess eligibility to trial participation.

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 electronic Case Report Form (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 electrocardiogram.
- Articular examination (76 swollen and 78 tender joint counts and grading).
- Laboratory tests:
    - Haematology, blood chemistry.
    - CRP and ESR.
    - Immunology tests (ANA, anti-double-stranded-deoxyribonucleic-acid-antibodies, anti-CCP, RF - (unless already performed within 20 days prior to screening visit).

  - Infectious hepatitis screen (Hepatitis B virus surface antigen, anti-Hepatitis B virus core antibody, anti-Hepatitis C virus antibody).
  - QuantiFERON test for tuberculosis testing.
  - Human immunodeficiency virus testing.
  - Urinary tests:
    - Pregnancy test in female patients with child-bearing potential (see Appendix 2).
    - 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 patients 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 for the duration of the study, in order to reduce assessment bias.

Appendix 4 – Magnetic Resonance Imaging Scoring Methods

SPARCC – SPINAL INFLAMMATION

Description:

Scoring method of MRI lesions | The scoring method (www.altarheum.com/research.html) for active inflammatory lesions in the spine relies on the use of a T2-weighted sequence that incorporated suppression of normal marrow fat signal. Scorers can choose the STIR sequence, which offers greater reliability when using large fields of view compared with T2 spin echo with spectral pre-saturation. Signal from marrow fat frequently obscures signal emanating from BMO 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 disco-vertebral unit is used: the region between two virtual lines through the middle of each vertebra, that includes the intervertebral disc and the adjacent vertebral endplates. Each vertebral endplate is scored independently for BMO. T1 spin echo images can be included for anatomic reference only and are not scored. For each lesion, a total of three consecutive sagittal slices are assessed. This allows assessment of the extent of the lesion in the coronal and the sagittal planes. Discal lesions are 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 constitutes the reference for designation of normal signal.

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

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

SPARCC – SACRO-ILIAC JOINTS INFLAMMATION

Description:

Scoring of MRI lesions | The scoring method for active inflammatory lesions in the sacroiliac joint relies 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 BMO associated with inflammation. Consequently, the use of fat suppression improves sensitivity for detection of abnormal water content. Scorers can also choose the STIR sequence.

Scoring of the sacroiliac joints is confined to those coronal slices depicting the synovial portion of the joint. In a preliminary overview of sacroiliac joint magnetic resonance images from patients with ankylosing spondylitis, the synovial portion was consistently evident in 6 consecutive coronal slices. Of the twelve acquisitions from posterior to anterior, this was typically slices 4 to 9. Therefore, six consecutive coronal slices, from posterior to anterior, are scored. T1-weighted spin echo images can be included for anatomic reference only and are not scored. All lesions within the iliac bone and within the sacrum up to the sacral foramina are scored. Increased signal within the sacroiliac joint space or in the ligamentous portion of the joint is not scored.

Definition of abnormal lesion on STIR sequence | Sacral inter-foraminal bone marrow signal forms the reference for assignment of normal signal in the joint.

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

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

HIMRISS

Description:

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-weighted 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 five slices that are anterior and five that are posterior to these central slices. The image where the femoral head is largest defines the most central slice of the five 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 two 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 five central slices being divided into three sectors (superolateral, superomedial, and medial), and five anterior and five 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

Description:

The KIMRISS web interface is accessible for free to registered users, at www.carearthritis.com. This website 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 (five immediately subarticular and five deeper). Using 3 mm MRI slice thickness, pilot work established that knees are covered by twenty-nine slices containing the tibia (ten medial, ten lateral, and nine 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, twenty-nine 3-mm slices provide full coverage of the femur (ten slices for each condyle and nine central slices for the trochlea). Each slice contains thirteen 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). There are eight segments per slice (four immediately subarticular and four 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. 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 touchscreen 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

Description and 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

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.

T1w = T1-weighted; post-GD = post-gadolinium injection; T2wFS = T2-weighted fat saturated

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, eighty-three peripheral joints and thirty-three 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.		