SPondyloArthritis: inducing drug-free Remission by early TNF-Alpha bloCkade Under guidance of Single cell RNA sequencing and epigenetic profiling.

Short title	The SPARTACUS trial
Protocol version and date	v 5.1 – 04/06/2025
EU reference number	2023-510085-27-00
Local reference number	BC-6226
Sponsor	Ghent University Hospital Department of Rheumatology Corneel Heymanslaan 10, 9000 Ghent Belgium
Coordinating Investigators	Prof. Dr. Dirk Elewaut Prof. Dr. Filip Van den Bosch Prof. Dr. Philippe Carron

Protocol modification history

Version	Date	Description of modification
1.3	**2020-07-30**	**First approved version**
2.1	2021-02-09	- Rename Producer to Manufacturer in 6.2.2 - Update in section 6.2.5 - Addition of Site ZNA Jan Palfijn in 6.3.1 - Addition of exclusion criteria in 6.3.3 - Addition of location clarification and research samples in 'Procedures', Phase A (7.1.1) - Update footnote 'g' in flowchart Phase A - Update footnote 'e' in flowchart Phase B - Addition of a note to Addendum 7i at question 1, 2 and 3 - Addition of a note to Addendum 7j at question 1 and 2
2.2	2021-04-06	- Update in 'Prior and concomitant use of DMARDs, NSAIDs and glucocorticoids' Table 1, section 9 - Addition of comment to Addendum 6b
3.0	2022-10-06	- Addition of clarification to Section 3 that the SPARTACUS trial is part of a bigger SPARTACUS project of the VIB Grand Challenges Program - Clarification in Section 3 that the Uncertainty analysis will be performed by Maastricht University - Section 4.3: replace VIB Research unit with KU Leuven Research Unit - Correction of wording in Section 5: Trial replaced with project - Section 7: Update of Visit time window Phase A, Visit 1A and Visit 1B + clarification about TB, Hep B, Hep C, HIV and CLV IgG Screening + clarification of what test results are allowed from previous testing + clarification about research samples at Visit 5 and Visit 8 - Addition of Phase A – Unscheduled visit (Section 7.1.1, Flowchart Phase A) - Update footnote 'b,e,g a,d i' in Flowchart Phase A - Addition of 'Physician Global NRQ at Week 12 and update of footnote 'e' in Phase B Flowchart - Updated DSUR wording in Section 11

		- Addition of clarification about 'analysis of the samples' in Section 12.2 - Update in Section 12.3, Statistical analysis - Addendum 7k: update possible responses for Q13
3.1	2023-08-03	- Update of references to Global Safety Intake Form - Addition of Section 19 to include the addenda - Update of Addendum 10 and 11 (CIOMS form and Adverse Event Reporting Form)
3.2	2024-01-30	- Addition of Table of Content - Signature page: Name UZ Ghent investigators removed
3.3	2024-05-01	- AST test is no longer required
4.0	03/02/2025	- Use of new protocol template to ensure all needed sections are included. - make the document CTR compliant - Update contact information manufacturer blinded methotrexate - define MSD/Merck as distributor of Golimumab up until 30th of September 2024. - Update of Addendum 10 and 11 (CIOMS form and Adverse Event Reporting Form) - Removed stratification into groups of <3 months symptom duration and ≥3 month and <12 months symptom duration which has an impact on the sample size calculation. A sample size of at least 45 patients in each group is sufficient to obtain 80% power or more to detect a difference in proportions of 30% (20% versus 50%) at the alpha level of 5% using a Fisher's exact test.
5.0	03/04/2025	- Reference to the investigators brochure was removed. - Storage period biological samples is 10 years - Contraceptives must be used up until 6 months after last dose. - Donation of eggs (ova, oocytes) or sperm is not allowed during the study and for 6 months after the last dose of the study drug.
5.1	04/06/2025	- Administrative correction

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Inhoud

List of abbreviations

AE	=	Adverse Event
ASR	=	Annual Safety Report
CA	=	Competent Authority
CI	=	Co-ordinating Investigator
CT	=	Clinical Trial Unit
CTD	=	Clinical Trial Directive
CTIS	=	Clinical Trials Information System
CTR	=	Clinical Trial Regulation
DLP	=	Data Lock Point
DSMB	=	Data Safety Monitoring Board
DSUR	=	Development Safety Update Report
EC	=	Ethics Committee
eCRF	=	electronic Case Report Form
EDC	=	Electronic Data Capture
EMA	=	European Medicines Agency
EPD	=	Electronic Patient Dossier
EU	=	European Union
EV	=	Eudravigilance
FAMHP	=	Federal Agency for Medicines and Health Products
GCP	=	Good Clinical Practice
GDPR	=	General Data Protection Regulation
GMP	=	Good Manufacturing Practice
HIRUZ	=	Health, Innovation and Research Institute UZ Ghent
IB	=	Investigator’s Brochure
ICF	=	Informed Consent Form
IEC	=	Independent Ethics Committee
IMP	=	Investigational Medicinal Product
PI	=	Principal Investigator
RA	=	Regulatory Authority
RSI	=	Reference Safety Information
SAE	=	Serious Adverse Event
SmPC	=	Summary of Product Characteristics

SOP	=	Standard Operating Procedure
SUSAR	=	Suspected Unexpected Serious Adverse Reaction

Part I: Trial-related part of the protocol

1 Title of the trial

SPondyloArthritis: inducing drug-free Remission by early TNF-Alpha bloCkade Under guidance of Single cell RNA sequencing and epigenetic profiling. "The SPARTACUS trial"

2 Trial number

Protocol: BC-6226

EU Reference number: 2023-510085-27-00

3 General information

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3.3 Departments/laboratories involved in the study

Be-GIANT Consortium: Department of Rheumatology in different hospitals

VIB Inflammation Research Center Ghent – Single Cell Platform:
- Research Unit: Dirk Elewaut and Koen Venken
- Martin Guilliams

KU Leuven:
- Research Unit: Frederik de Smet and Rik Lories

Maastricht University Medical Center:
- Health Economics Research Unit: Annelies Boonen.

4 Introduction

4.1 Rationale + Background

Treatment of immune-mediated inflammatory diseases, such as SpA, with cytokine-directed bDMARDs, such as TNFi, has led to a revolution in the short and long-term control of symptoms, the improvement of quality of life and the prevention of irreversible structural damage. However, when started in the chronic phase of the disease (usually after failure of csDMARDs), these drugs need to be administered continuously, which in turn is associated with a major cost in healthcare expenditure (not only because of chronic treatment costs, but also as a consequence of the management of potential long-term side effects). The results of the proof-of-concept CRESPA trial suggest that by treating patients earlier, we can reach a state of sustained remission in which no long-term continuation of expensive drugs with potentially severe side effects is needed.
The SPARTACUS project aims to compare (cost-)effectiveness of inducing clinical remission in early forms of pSpA with a TNFi versus the current treatment paradigm with csDMARDs. Based on the preliminary CRESPA-trial-evidence, that intensive treatment in early phases of pSpA, is able to induce remission, we will also discontinue (biological) treatment in the second phase of this randomized, controlled clinical trial, once patients have achieved a status of sustained clinical remission; this will allow us to evaluate the possibility of drug-free remission. The time frame by which induction of drug-free remission is achievable is currently unclear. Therefore, we will analyse treatment responses in function of symptom duration (effect of symptom duration as a continuous variable, comparison between <3 months versus between 3 and 12 months). An additional unique feature of SPARTACUS project is the search of new biomarkers using state-of-the-art technologies both in synovial tissue and/or peripheral blood. Their ability to predict drug-free remission will be assessed in order to identify patients that may benefit from such an early induction therapy. The effect of improved patient selection and the potential better cost-effectiveness of intensive management of early pSpA will be estimated. Collectively, SPARTACUS should pave the path towards converting chronic lifelong therapy into a temporary intervention, which would result in a major societal impact on health and wealth.

References:

1. Rudwaleit M, et al. The Assessment of SpondyloArthritis international Society classification criteria for peripheral spondyloarthritis and for spondyloarthritis in general. Ann Rheum Dis 2011;70:25-31.
2. Mease P, et al. Randomized controlled trial of adalimumab in patients with nonpsoriatic peripheral spondyloarthritis. Arthritis Rheumatology 2015;67(4):914-23.
3. Van den Bosch F, et al. Long-term efficacy and predictors of remission following adalimumab treatment in peripheral spondyloarthritis: 3-year results from Ability-2. RMD Open 2018;4:e000566.
4. Carron P, et al. Anti-TNF-induced remission in very early peripheral spondyloarthritis: the CRESPA study. Ann Rheum Dis 2017;76:1389-95.
5. Carron P, et al. High rate of drug-free remission after induction therapy with golimumab in early peripheral spondyloarthritis. Arthritis Rheumatology 2018;70:1769-77.

4.2 Risk/Benefit assessment

Traditionally, management recommendations for rheumatic diseases (and reimbursement criteria in Belgium) follow a step-up strategy, starting with non-steroidal anti-inflammatory drugs (NSAIDs) and/or conventional synthetic disease modifying anti-rheumatic drugs (csDMARDs) as first line treatment options. Biologic DMARDs (bDMARDs), including TNFi, are recommended as second line treatment in patients with refractory disease. While treatment in these cases is still very effective, there is a significant percentage of patients that does not achieve a relevant improvement and in most cases prolonged (life-long) treatment will be necessary.

We hypothesized that by first line use of bDMARDs in an early disease stage, the clinical response would not only be better, but that early induction of remission could also permit the temporary use of a bDMARD (allowing the patient to reach a status of “drug-free remission”). We have tested this hypothesis in a proof of concept study, the CRESPA trial (Clinical Remission in very Early SPondyloArthritis), in which patients with peripheral SpA and less than 3 months of symptom duration, were randomized to TNF inhibition (TNFi) with golimumab versus placebo (Carron P, et al. Ann Rheum Dis. 2017; Carron P, et al. Arthritis Rheumatol. 2018). In this pilot trial we were able to demonstrate that 82% of all included patients achieved complete resolution of symptoms (arthritis, enthesitis, dactylitis), after which treatment with golimumab was discontinued. Intriguingly, over 50% of patients were staying in drug-free remission (with currently a follow-up of >2 years). Hence, the CRESPA trial pointed for the first time to the possibility of inducing drug-free remission in a significant proportion of patients suffering from a disease that had been previously considered to require lifelong medication.

There were some challenges and limitations with regard to the CRESPA trial:

- The main challenge was the fact that patients could not have signs or symptoms of arthritis/enthesitis/dactylitis for >3 months. This required an extensive referral network with fast-track consultations to check eligibility for trial inclusion. As a consequence, the CRESPA trial consisted of a very specific pSpA population with extremely short symptom duration. We do not know if the results (high rates of clinical remission with TNFi-treatment; significant percentage of patients in drug-

free remission after TNFi-withdrawal) can be extrapolated to a pSpA population with longer symptom duration.
- The main limitation of the CRESPA trial was the fact that the control group consisted of placebo. This was done in order to be able to estimate the rate of spontaneous clinical remission in this population (which was remarkably low), but one could argue that in daily practice such patients would have been treated with csDMARDs.

The current SPARTACUS trial will address both issues:
- Peripheral SpA patients with a symptom duration up to 1 year at screening will be eligible for inclusion. This will allow us to evaluate if there is a specific window of opportunity timeframe when the disease is more susceptible to effective treatment.
- In SPARTACUS, we will not compare the "TNFi-Induction" group with placebo, but with a more daily practice "csDMARD-Step-up" treatment strategy.

The obvious advantages for the patients participating in this trial will be the early access to bDMARD therapy (at a stage where Belgian reimbursement would not allow this effective therapy) and the fact that (compared to the CRESPA trial) there is no risk of placebo-treatment. While it could be considered that TNFi treatment can be associated with side effects, these drugs are currently indicated and reimbursed for multiple diseases in the SpA-concept, albeit in the more longstanding phases of the disease when there is already definitive structural damage.

4.3 Patient participation in trial design
Not applicable

5 Objective(s) of the study

5.1 Main objectives
The SPARTACUS study will explore the therapeutic efficacy of 2 different treatment strategies for patients suffering from peripheral Spondyloarthritis (pSpA), classified according to the "Assessment in SpondyloArthritis international Society" (ASAS) classification criteria (1) (see Addendum 1); it will be set up as a 48-week, prospective, randomized, active-comparator controlled, double-blind, double-dummy, clinical trial with a two-fold clinical objective:
- To compare a standard step-up approach using conventional synthetic Disease-Modifying Anti-Rheumatic Drugs (csDMARDs), such as methotrexate and/or sulphasalazine (the "csDMARD Step-Up"-strategy), with an early remission-induction treatment strategy that immediately introduces biological DMARDs (bDMARDs) as the first step in the treatment algorithm; in this group the Tumor Necrosis Factor inhibitor (TNFi) golimumab will be utilised (the "TNFi Induction"-strategy).

The double-blind phase of the study will compare the 2 treatment strategies with regard to the proportion of patients that achieve a status of (sustained) clinical remission.

In patients that reach sustained clinical remission, all study treatments (both in the “csDMARD Step-up”-group and the “TNFi Induction”-group) will be stopped, and long-term, clinical follow-up of these patients will allow to explore the possibility of “drug-free remission”; also with regard to this objective, the difference in symptom duration will be evaluated.

5.2 Secondary objectives

To try to define the window of opportunity within which temporary treatment with bDMARDs might be more effective, by analysing patients according to symptom duration, either as a continuous variable, or by comparing patients with shorter symptom duration (<3 months) versus those with more longstanding disease (between 3-12 months of symptom duration).

SPARTACUS trial is part of a bigger SPARTACUS project of the VIB Grand Challenges Program and will have several achievable goals:

1. To show superiority of early treatment of pSpA patients with bDMARDs as compared to standard of care.

In current practice, TNFi, the predominant bDMARDs in SpA, are only reimbursed in a restricted number of indications: they can be prescribed for axial spondyloarthritis (axSpA) and for the specific pSpA-entity, psoriatic arthritis (PsA); however, even in PsA, they are only reimbursed for longstanding, erosive disease, when patients have already failed (multiple) csDMARD(s). In patients with pSpA without psoriasis, rheumatologists can only prescribe csDMARDs, because TNFi are still off-label despite the overall good efficacy observed in several proof-of-concept studies, incl. one phase 3 trial (Ability-2) (2). For this subgroup of patients, the unmet need is therefore still unacceptably high. Moreover, the patients included in Ability-2 reflected the current step-up treatment paradigm: patients already had longstanding disease (symptom duration of approx. 7 years) and had used (and failed) conventional treatment options before trial entry (99% prior use of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), 69% prior csDMARD use). In this population, a statistically significant difference between adalimumab and placebo was observed, but clinical remission rates remained somehow disappointing with only 33% of patients reaching the predefined remission outcome after 3 years of continuous adalimumab use (3).

Until recently, no data were available regarding the treatment of early pSpA with bDMARDs. To address this knowledge gap, we designed a proof-of concept study to explore the therapeutic potential of TNFi in patients with pSpA with very short symptom duration, the CRESPA-trial (4). In this study, all patients had a symptom duration of less than 12 weeks: they were randomized to receive either immediate TNFi therapy (golimumab) or placebo. In summary, the results of this trial demonstrated that after 24 weeks of treatment, complete clinical remission could be achieved in 75% of golimumab-treated patients versus only 20% in patients treated with placebo (thus refuting the perception that a large majority of pSpA patients would go in spontaneous clinical remission). Due to the placebo-controlled design, the CRESPA trial did not provide any data on the percentage of patients that would have achieved clinical remission while on standard-of-care “csDMARD Step-up” treatment. The design of the SPARTACUS head-to-head trial will allow us to evaluate superiority of the new approach to current practice.

2. To delineate the window of opportunity for intensive treatment of pSpA: a transient time frame in which a disease is more susceptible to treatment.
In the proof-of-concept CRESPA trial, all included patients had a symptom duration of less than 12 weeks. In these patients very high clinical remission rates were observed when patients were immediately treated with a TNFi. Interestingly, when the bDMARD treatment was interrupted after reaching sustained remission, 53% of patients remained in drug-free remission at long-term follow-up (5), providing preliminary evidence for the "window of opportunity" hypothesis: by effectively tackling pSpA (with bDMARDs) in a very early phase of the disease, drug-free remission might be an achievable goal in a significant number of patients. However, the CRESPA-trial does not allow to generalize the findings to pSpA patients with longer symptom duration. Moreover, the above-mentioned extension of the Ability-2 study would suggest that patients with a symptom duration of multiple years would have lower remission rates and would need chronic, life-long bDMARD treatment. The SPARTACUS trial will still focus on early treatment of pSpA (symptom duration <12 months), and will analyse the effect of symptom duration on reaching the different outcomes. The goal is to demonstrate that drug-free remission is a feasible outcome when an early intensive treatment strategy is adopted and to delineate the window of opportunity (in terms of symptom duration) in which such a remission-induction strategy is successful, leading to significant health economic benefits (goals 4 and 5).

3. To unravel new biomarkers of therapy response using cutting-edge single cell technology.
In the CRESPA trial, we observed that despite the fact that 53% of patients were able to achieve drug-free remission, a significant proportion nevertheless relapsed. In this small proof-of-concept study, we were not able to detect significant predictors or remission or relapse. Also, 18% of patients did not achieve sustained clinical remission, but nevertheless experienced a significant improvement of signs and symptoms; in these patients long-term treatment was necessary. These results indicate that clinical response to TNFi is heterogeneous and underscores the need for biomarkers that can identify at baseline different pathogenic subsets that are associated with the (lack of) response to a TNFi. The recent introduction of new procedures such as ultrasound-guided synovial biopsy sampling in our early arthritis clinic has permitted to access synovial samples of virtually all peripheral joints (incl. wrists and small finger joints). By using innovative and unbiased tools recently developed in the area of single-cell analyses (RNA-sequencing and epigenetic profiling) by VIB and KU Leuven, we will obtain profound insights into the cellular heterogeneity of these unique patient samples.

4. To determine health-economic and societal impact of early, intensive bDMARD treatment of patients with recent-onset pSpA (compared to the currently reimbursed csDMARD Step-up strategy).
A unique feature of SPARTACUS is that clinical trial and biomarker discovery will be coupled to calculation of the health-economic benefits of such an approach. We aim to determine from a healthcare and a societal perspective, the 2 years´ cost-utility, as well as a model-based lifelong incremental cost-utility of the innovative strategy compared to usual care. Uncertainty analyses will be performed and budget impact for the Belgian healthcare and social security (work disability) system will be calculated by Maastricht University. Consistent with the increased call for transparency in health economic modelling, we aim to make our model available as a semi-open source model.

5. To increase awareness among referring physicians (general practitioners, other specialties that may evaluate patients with early SpA) and patient-advocacy groups about the value of early recognition and treatment in rheumatology.
It is still a great challenge to diagnose patients in an early stage of their disease. The delay between symptoms and diagnosis in SpA is still several years. As discussed above, it has been shown that in later stages of the disease, the treatment effect (even with bDMARDs) may be less impressive and chronic therapy is needed without possibility of drug withdrawal (leading to a high socioeconomic burden). The broad set-up of SPARTACUS across health institutes in Flanders will greatly facilitate the awareness and direct implementation of early arthritis strategies among physicians. Finally, results from SPARTACUS will provide evidence that will facilitate discussions with patients about treatment choices and ensure realistic treatment expectations and optimal health behaviour in patients with early pSpA.

6 End points

6.1 Primary end points

The primary endpoint of the study will be the comparison between the 2 treatment strategies at week 24 with regard to achievement of clinical remission (defined as complete absence of arthritis, dactylitis or enthesitis on clinical examination). At the week 24 timepoint, there are 3 possible scenario's (figure 3):

1. In patients that do not reach a state of clinical remission at week 24, blinded study medication will be interrupted and all patients will start open-label SC golimumab for an additional 36 weeks (up to max. week 60).
2. In patients that achieve sustained clinical remission at week 24, defined as absence of clinical arthritis, enthesitis and dactylitis at both week 12 and week 24, all study medication will be discontinued and prospective follow-up will be planned in SPARTACUS Phase B.
3. In patients that reach a state of clinical remission at week 24, but that did not yet reach this status at week 12, blinded study medication will be continued without any change in the treatment schedule for another 12 weeks.

6.2 Secondary end points

In addition to this, several secondary endpoints will be evaluated:

- Comparison between the "TNFi induction" group and the "csDMARD Step-up" group regarding:
    - Achievement of "sustained clinical remission" at week 24 (and week 36 for the patients remaining on blinded study medication).
    - Improvement from baseline to week 12 and 24 in individual clinical assessments (78-Tender Joint Count, 76-Swollen Joint Count, Dactylitis Count, SPARCC Enthesitis Score) and composite scores (ASDAS: Axial Spondyloarthritis Disease Activity Score).

    - Improvement from baseline to week 12 and 24 in patient-reported outcomes (Patient global assessment of disease activity and pain, BASDAI, BASFI, ASAS Health Index.
    - Improvement from baseline to week 12 and 24 in inflammatory parameters (ESR, CRP).
    - Changes in concomitant NSAID intake (NSAID-index) and “escape” intra-articular glucocorticoid injections between baseline and week 24
- Difference in occurrence of (serious) adverse events (AEs) and AEs of specific interest between the 2 treatment strategies from baseline to week 24 (and week 36 for patients remaining on blinded study medication). Descriptive analysis of the number and type of adverse events between both strategies
- Percentage of patients achieving (sustained) clinical remission with open-label golimumab treatment after failure of the initial randomized, blinded treatment strategy.
- Exploration of difference in percentage of patients that reach (sustained) clinical remission according to symptom duration (<3 months versus ≥3 month and <12 months). The interaction between treatment group and symptom duration as a continuous predictor will also be analyzed to investigate the effect of symptom duration with regard to reaching the specified primary and secondary outcomes.
- For patients in SPARTACUS Phase B (drug-free remission period):
    - Exploration of the duration of drug-free remission.
    - Time to (documented) pSpA disease flare.
    - Time to restart of “standard-of-care” pSpA treatment.
    - Exploration of clinical parameters that could be predictive for reaching (sustained) clinical remission and/or flare.
- Correlation between the “Patient Acceptable Signs & Symptoms Improvement” (“PASSI”) and different clinical assessments, laboratory values and patient-reported outcomes (or combinations thereof).

7 Trial Design - The present study

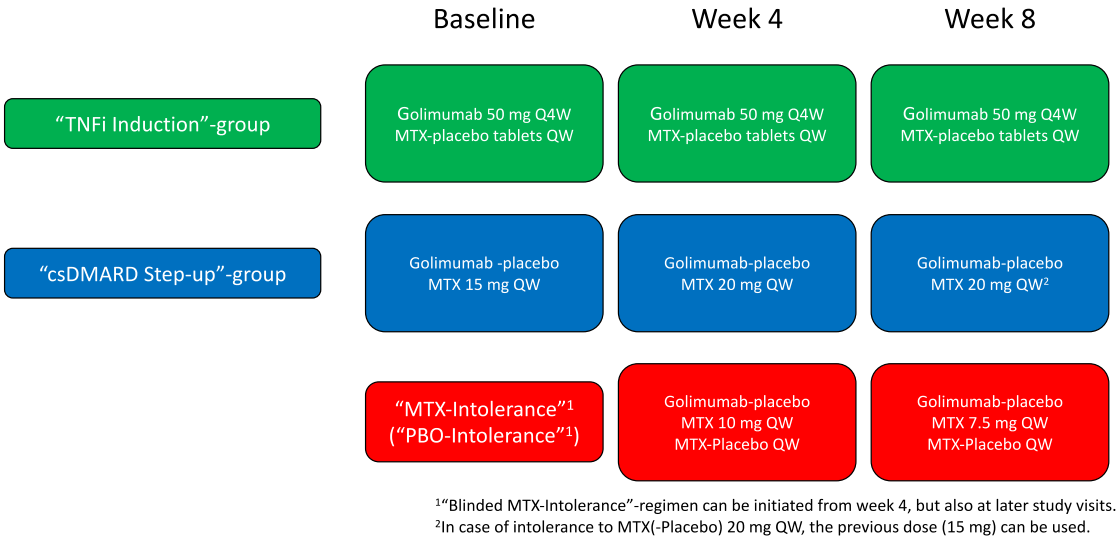
7.1 Study design description

The SPARTACUS clinical trial is a prospective, randomized, active-comparator controlled, double-blind, double-dummy, phase III, national multicentric clinical trial which consists of 2 phases (duration phase A is up to 60 weeks, phase B up to 3 years):

SPARTACUS Phase A: "Remission-Induction Phase":
(Baseline to (maximum) week 60: for a global overview see Addendum 2)
All patients (n=90) will be randomized (1:1) to either immediately receiving TNFi (golimumab) monotherapy ("TNFi Induction"-group) (n=45), or to the step-up regimen with csDMARDs ("csDMARD Step-up"-group) (n=45) (figure 1).
Synovial biopsies will be harvested during the screening period by ultrasound (US) guided biopsy for small joints (Metacarpophalangeal- (MCP) and proximal interphalangeal- joints (PIP) of the hands, metatarsophalangeal joints (MTP) of the feet) or certain large joints (elbow, wrist, knee, ankle). In case of multiple small joint involvement, a joint with a score of 2 or more on Grey Scale/Power Doppler US assessment will be chosen to sample.

The patients in the TNFi-induction group will receive golimumab at a standard dose of 50 mg subcutaneously (SC) every 4 weeks (with matching methotrexate (MTX)-placebo) (figure 1). In case of potential intolerance or toxicity to MTX-placebo (see paragraph 9.5.8 for known side effects of MTX) , the dose will be gradually tapered to a minimum of 7.5 mg per week. When there are no tolerability/toxicity issues, the weekly dose of MTX-placebo will be increased to 20 mg at week 4.

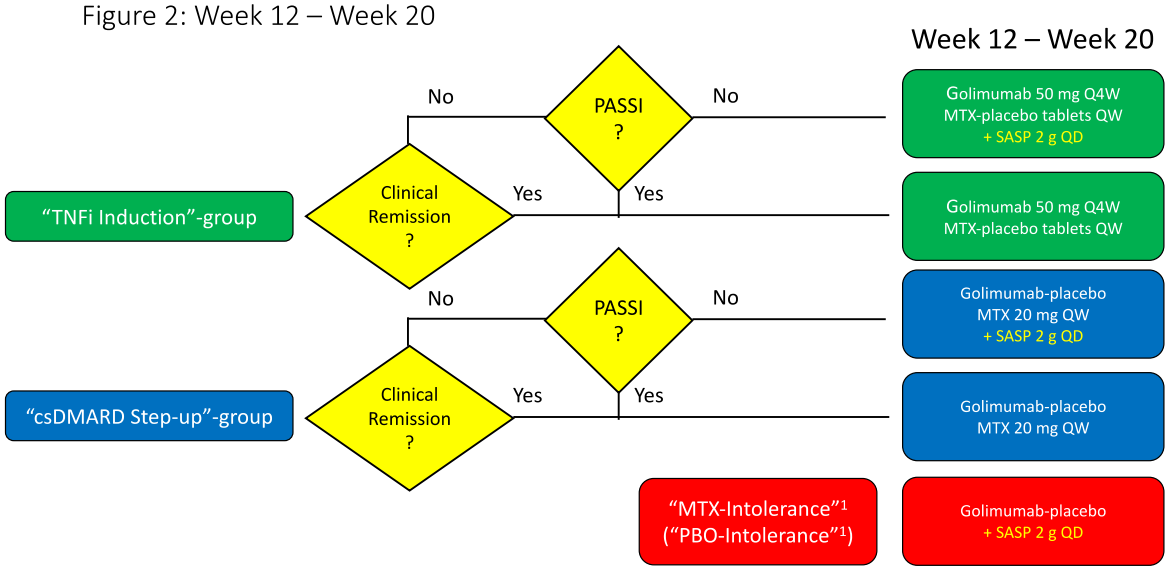
Figure 1: Baseline – Week 8



¹"Blinded MTX-Intolerance"-regimen can be initiated from week 4, but also at later study visits.
²In case of intolerance to MTX(-Placebo) 20 mg QW, the previous dose (15 mg) can be used.

The patients in the csDMARD-Step-up group (figure 1) will start with oral methotrexate (MTX) at a weekly dose of 15 mg for 4 weeks (with matching TNFi-placebo injections). In case of potential intolerance or toxicity to MTX (see paragraph 9.5.8 for known side effects of MTX), the dose will be gradually tapered to a minimum of 7.5 mg per week. When there are no tolerability/toxicity issues, the weekly dose of MTX will be increased to 20 mg at week 4. At week 12, a "Patient Acceptable Signs & Symptoms Improvement" ('PASSI') will be assessed by asking the question "*Taking into account both efficacy and side effects, did you experience over the past 12 weeks enough improvement in signs and symptoms of your' arthritis-enthesitis-dactylitis to consider continuation of the same treatment schedule for the next 12 weeks?*" (see Addendum 3). If yes, all study medication will be kept stable until week 24; if no, oral sulphasalazine at a dose of 2 g per day will be started (escape medication) (figure 2).

Figure 2: Week 12 – Week 20



[1]Continued "MTX-Intolerance" after tapering to 7.5 mg QW results in MTX-discontinuation
'PASSI': Patient Acceptable Signs & Symptoms Improvement

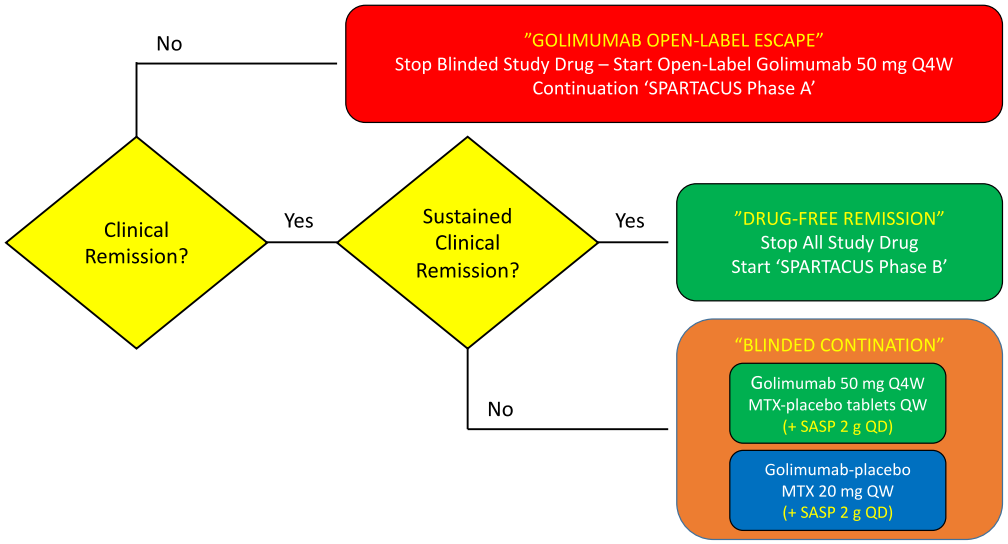
The need for concomitant intake of NSAIDs will be recorded (by calculating the NSAID-index); in case of persistent severe arthritis, a maximum of 2 intra-articular corticosteroid injections will be allowed (starting at week 12 after the clinical evaluations, but before the week 20 assessment). Both NSAID-index and number of corticosteroid injections will be considered as surrogate (in)efficacy markers. From week 20, all concomitant medication (see section 9) should be kept stable until the assessment of the primary endpoint at week 24.

The primary endpoint of the study will be the comparison between the 2 treatment strategies at week 24 with regard to achievement of clinical remission (defined as complete absence of arthritis, dactylitis or enthesitis on clinical examination). At the week 24 timepoint, there are 3 possible scenario's (figure 3):

1. In patients that do not reach a state of clinical remission at week 24, blinded study medication will be interrupted and all patients will start open-label SC golimumab for an additional 36 weeks (up to max. week 60).

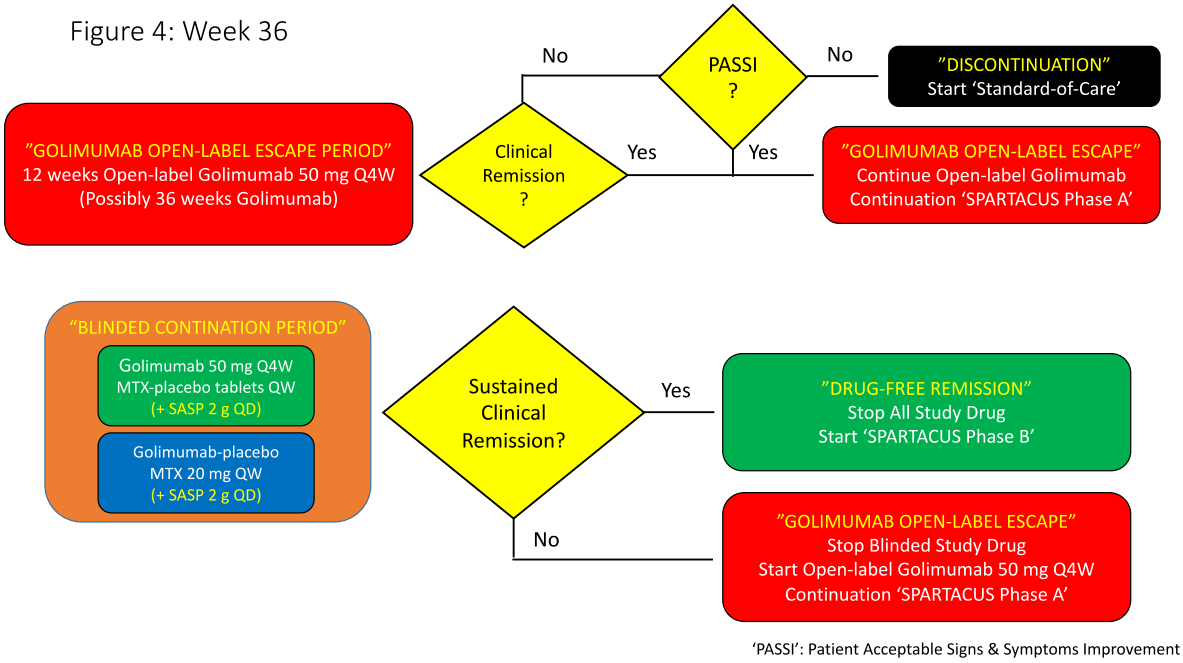
2. In patients that achieve sustained clinical remission at week 24, defined as absence of clinical arthritis, enthesitis and dactylitis at both week 12 and week 24, all study medication will be discontinued and prospective follow-up will be planned in SPARTACUS Phase B.
3. In patients that reach a state of clinical remission at week 24, but that did not yet reach this status at week 12, blinded study medication will be continued without any change in the treatment schedule for another 12 weeks.

Figure 3: Week 24 (Primary Endpoint)



At week 36 (figure 4), patients that have continued the blinded study medication, will be re-assessed regarding sustained clinical remission (at week 24 and 36): if yes, all study medication will again be discontinued and prospective follow-up will be planned in SPARTACUS Phase B. If no, these patients will start open-label SC golimumab for an additional 24 weeks (up to max. week 60).
If patients were in the "open-label golimumab treatment arm", effectiveness of the treatment will be assessed by using the "PASSI"-question. Inadequate responders will be discontinued from the study and will be treated with standard-of-care medication at the discretion of their treating rheumatologist, whereas patients with an acceptable improvement in signs and symptoms will continue with the same (open-label) medication schedule.

Figure 4: Week 36

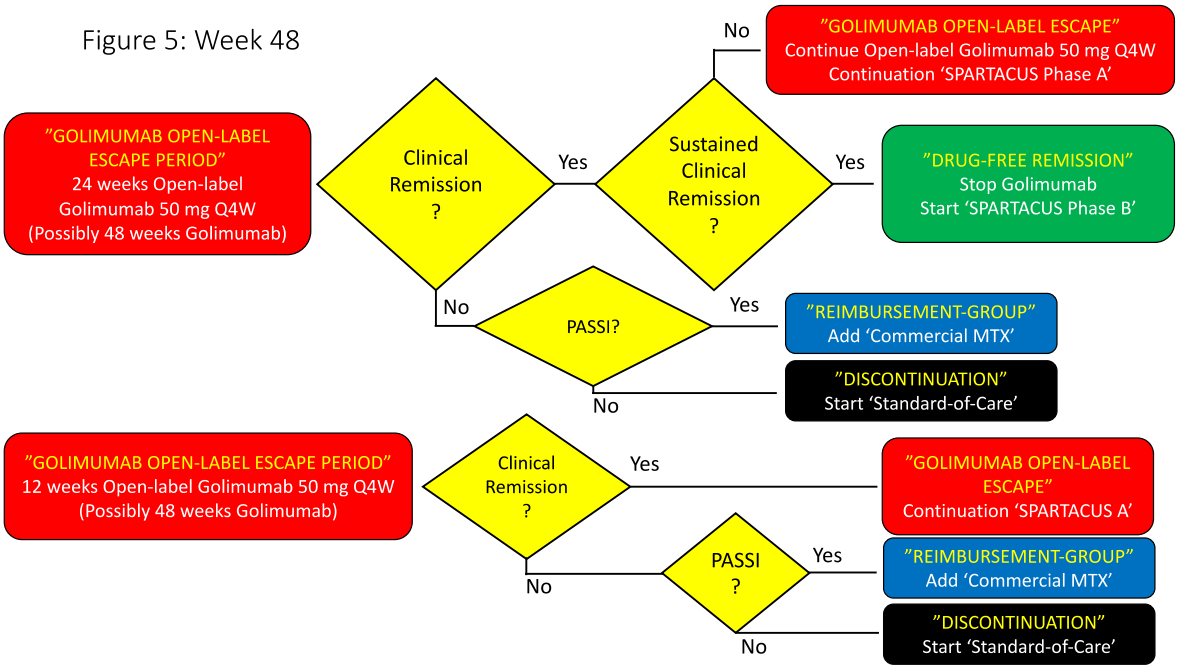


'PASSI': Patient Acceptable Signs & Symptoms Improvement

At week 48 (figure 5), all patients still remaining in SPARTACUS Phase A will have been treated with open-label golimumab (for a minimum of 12 weeks, but potentially up to 48 weeks). In patients reaching at this timepoint sustained clinical remission (at week 36 and 48), golimumab will be discontinued and prospective follow-up will be planned in SPARTACUS Phase B. For the other patients there are 3 possible scenarios:

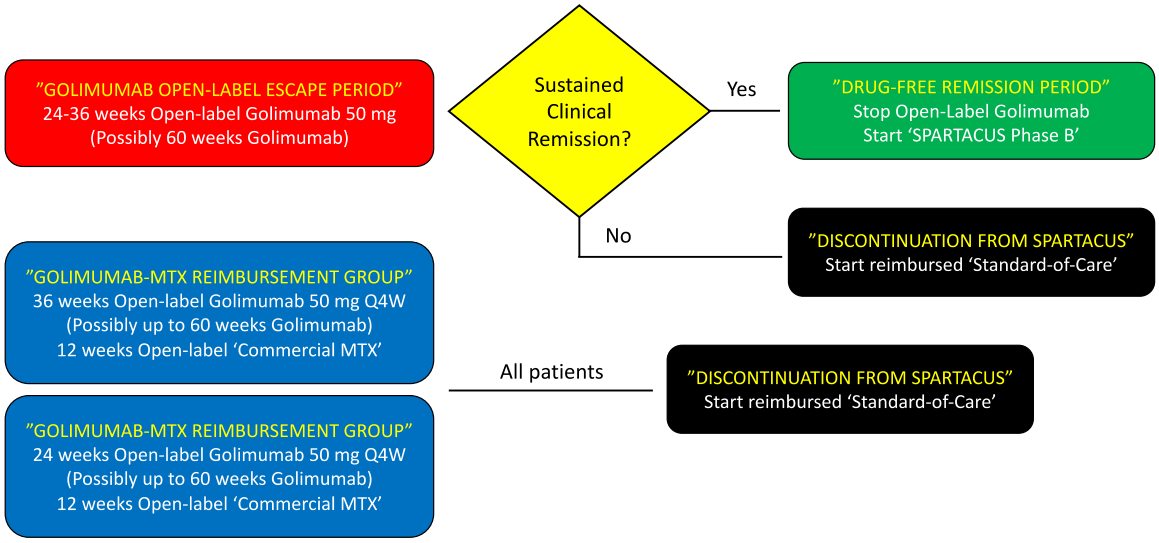
1. Patients reaching clinical remission for the first time at week 48 will continue without any change in the treatment schedule for another 12 weeks.
2. Patients with an inadequate response (based on the "PASSI"-question), will be discontinued from the study and will be treated with standard-of-care medication at the discretion of their treating rheumatologist.
3. Patient with an acceptable improvement (but no clinical remission) will continue open-label golimumab treatment for an additional 12 weeks, but in these patients open-label methotrexate will be associated (unless contra-indicated) to fulfil Belgian reimbursement criteria for TNFi.

Figure 5: Week 48



At week 60 (final study visit of SPARTACUS Phase A) (figure 6), patients reaching sustained clinical remission (at week 48 and 60), will roll-over into SPARTACUS Phase B. All other patients will be discontinued and will be treated with standard-of-care medication (including TNFi, if in accordance with Belgian reimbursement criteria).

Figure 6: Week 60



SPARTACUS Phase B: "Drug-Free Remission Phase": cessation of therapy and exploration of drug-free remission in patients that achieve sustained clinical remission while on therapy in phase A:

(Duration: max. 3 years)

After reaching 'sustained clinical remission', as defined above, all medication will be discontinued (possible timepoints for entering phase B would be week 24, 36, 48 and 60 of

phase A); the last study visit of Phase A will become visit 1 in Phase B. In this prospective study, all patients will be systematically followed and data about disease activity will be collected at predefined timepoints (every 12 weeks in the first year; thereafter every 24 weeks). This will allow us to explore the possibility of maintaining drug-free remission. If a flare occurs within 144 weeks after medication withdrawal, standard-of-care treatment will be started at the discretion of the treating rheumatologist; at that time, phase B will end. Patients who are still in drug-free remission and reach the Phase B final study visit at week 144 will be prospectively followed in the Be-GIANT cohort allowing further long-term follow-up.

7.2 Start of the trial

The trial is considered started upon the first act of recruitment of a potential subject. For this trial this is considered as the first patient being informed about the study by his/her treating physician.
The start of the trial shall be notified to the RA within 15 calendar days.
The first visit of the first subject (i.e. when the first subject or his/her legally designated representative signs his/her first informed consent to participate in the trial) (FVFS) will also be notified to the RA within 15 calendar days.

7.3 End of the trial

7.3.1 For an individual subject

The subject has completed the trial when he or she has completed all phases of the study, including the last visit or the last scheduled procedures, as described in this protocol.

7.3.2 For the whole trial

The end of the recruitment of subjects shall be notified to the RA within 15 calendar days.
Overall, the end of the trial is reached 30 days after the last study procedure for the last subject has occurred (the last visit of the last subject, LVLS).
As soon as the whole trial has ended (cfr. the definition above), the RA shall be notified within 15 calendar days.
A summary of the results of the trial will be submitted to the RA within 1 year from the end of the trial, irrespective of the outcome of the trial.

7.4 Trial duration

7.4.1 For an individual subject

The on-study estimated total duration of the study, from the time the informed consent document is signed until the last visit or the last scheduled procedures is up to 60 week for phase A and up to 3 years for phase B.

7.4.2 For the whole trial

We estimate to recruit subjects for a period of 56 months, last subject last visit (LSLV) will be reached 51 months later. The total duration of the study will thus be 107 months.

8 Trial Population

8.1 Number of subjects and planned recruitment rate

In total it is expected to recruit 110 patients, of which 90 patients will be randomized in this trial and reach the primary endpoint timepoint (taking into account screen failures and drop outs) They will be recruited in rheumatology departments of different hospitals. At the UZ Ghent, the UZ Leuven and ZNA Jan Palfijn sites synovial biopsy sampling units are operational. The inclusion of patients is competitive, meaning that there are no minimum or maximum quota for inclusions per center.

8.2 Inclusion and exclusion criteria

8.2.1 Inclusion criteria

8.2.1.1 SPARTACUS Phase A: "Remission-Induction Phase"

A subject will be eligible for study participation if all of the following criteria are met:

- Subjects must be able and willing to provide written informed consent and comply with the requirements of this study protocol.
- Subjects must be between 18 and 65 years of age.
- Subjects must have been diagnosed with peripheral spondyloarthritis by the treating rheumatologist.
- Subjects must meet the ASAS classification criteria for peripheral spondyloarthritis (see addendum 1): subjects must have current arthritis (asymmetric or predominantly in the lower limbs) or current enthesitis (except for enthesitis only along the spine, sacroiliac joints and/or chest wall) or current dactylitis plus at least 1 of the following SpA features:
    - Anterior uveitis confirmed by an ophthalmologist (past or present)
    - Crohn's disease or ulcerative colitis diagnosed by a gastroenterologist (past or present).
    - Evidence of preceding infection (acute diarrhea or non-gonococcal urethritis or cervicitis 1 month before arthritis).
    - Psoriasis diagnosed by a dermatologist (past or present).
    - HLA B27 positivity
    - Sacroiliitis by imaging defined as bilateral grade 2–4 or unilateral grade 3–4 sacroiliitis on plain radiographs, according to the modified New York criteria or

active sacroiliitis on MRI according to the ASAS consensus definition (ref of addendum).

- Subjects must have had onset of peripheral SpA symptoms ≤12 months prior to the screening visit.
- Subjects must have active disease at screening defined by Patient Global Assessment of Disease Activity Numerical Rating Scale (NRS) ≥ 4 and Patient Global Assessment of Pain NRS ≥ 4. At the baseline visit patients will be clinically evaluated to exclude spontaneous clinical remission.
- In subjects with concurrent axial SpA symptoms, the peripheral SpA symptoms must be the predominant symptoms at study entry based on the Investigator's clinical judgment.
- Subjects must have a negative PPD test (or equivalent) and chest radiography (anteroposterior and lateral view) at screening. If the subject has a positive PPD test (or equivalent), has had a past ulcerative reaction following PPD placement and/or a chest radiography consistent with prior TB exposure, the subject must initiate, or have documented completion of a course of anti-TB therapy.
- Women of childbearing potential or men capable of fathering children must be using adequate birth control measures during the study and for 6 months after receiving the last administration of study agent (cfr. section 8.7).
- Subject is judged to be in good health as determined by the principal investigator based upon the results of medical history, physical examination, laboratory profile, and chest x-ray (CXR) performed during screening.
- Subjects must be able and willing to self-administer SC injections or have a qualified person available to administer SC injections.

8.2.1.2 SPARTACUS Phase B: "Drug-Free Remission Phase"

A subject will be eligible for phase B of the study if all of the following criteria are met:

- Subjects must have participated in SPARTACUS Phase A.
- Subjects must have reached a status of sustained clinical remission (defined as absence of clinical arthritis, enthesitis and dactylitis at 2 consecutive 'major' visits with an interval of 12 weeks).

8.2.2 Exclusion criteria

- Medical history of inflammatory arthritis of a different etiology than peripheral spondyloarthritis (e.g. rheumatoid arthritis, systemic lupus erythematosus, gout, …).
- Prior adequate treatment with methotrexate and/or sulphasalazine.
- Prior exposure to any biologic therapy with a potential therapeutic impact on SpA.
- Treatment with any investigational drug of chemical or biological nature within a minimum of 30 days or 5 half-lives of the drug (whichever is longer) prior to the Baseline Visit.
- Subject is taking or has taken prohibited medications as outlined in Table 1 without meeting the mandatory washout period(s) relative to the baseline visit.
- Infection(s) requiring treatment with intravenous (iv) anti-infective agents within 30 days prior to the Baseline visit or oral anti-infectives within 14 days prior to the baseline Visit.

- Have a known hypersensitivity to human immunoglobulin proteins or other components of golimumab.
- History of central nervous system (CNS) demyelinating disease or neurologic symptoms suggestive of CNS demyelinating disease.
- History of listeriosis, histoplasmosis, chronic or active Hepatitis B infection, Hepatitis C infection, human immunodeficiency virus (HIV) infection, immunodeficiency syndrome, chronic recurring infections or active TB.
- (History of) chronic heart failure (CHF), including medically controlled, asymptomatic CHF.
- History of malignancy (including lymphoma and leukemia) other than a successfully treated non-metastatic cutaneous squamous cell or basal cell carcinoma or localized carcinoma in situ of the cervix.
- Have received any live virus or bacterial vaccination within 3 months prior to the first administration of study agent; patients who are expected to receive such vaccinations during the trial, or within 3 months after the last administration of study agent.
- Positive serum pregnancy test at screening.
- Female subjects who are breast-feeding.
- Clinically significant abnormal screening laboratory results as evaluated by the Investigator.
- Positive anti-cyclic citrullinated peptide (anti-CCP) antibody at screening if the titers are crossing 3 times the upper limit of normal.
- Subject is considered by the investigator, for any reason, to be an unsuitable candidate for the study.
- Subject with current symptoms of fibromyalgia that would confound evaluation of the patient.

8.2.3 Justification of in- and exclusion criteria

Not applicable

8.3 Withdrawal and replacement of subjects

8.3.1 Withdrawal of subjects

Subjects are free to withdraw from participation in the trial at any time. A subject must be discontinued from the trial if *the subject* withdraws consent. The reason why a subject withdraws consent, if given, must be recorded in detail in the electronic Case Report Form (eCRF) and in the subject's medical records. The already gathered subject data should remain in the trial database.
However, subjects can choose to discontinue trial treatment or interventions, but remain in the trial for other assessments or data collection, if applicable. The reasons for a subject to withdraw from trial treatment, if given, must be recorded in detail in the electronic Case Report Form (eCRF) and in the subject's medical records. The subject data should be collected in the eCRF.
An investigator may discontinue trial treatment for a subject for the following reasons:

- Pregnancy;

- Significant trial intervention non-compliance;
- If any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the trial would not be in the best interest of the subject;
- Disease progression which requires discontinuation of the trial intervention;
- If the subject meets an exclusion criterion (either newly developed or not previously recognized) that precludes further trial participation;
- Subject unable to receive study intervention for a duration of at least 3 months

The reasons for withdrawing a subject from study treatment must be recorded in detail in the electronic Case Report Form (eCRF) and in the subject's medical records. However, even if trial treatment is discontinued, the subject will remain in the trial and other assessments or data collection should be done, if applicable. The subject data should be collected in the eCRF.
A subject will be considered lost to follow-up if he or she fails to return for *2* consecutive scheduled visits and is unable to be contacted by the trial site staff.
The following actions must be taken if a subject fails to return for a required trial visit:

- The site will attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain if the subject wishes to and/or should continue in the trial;
- Before a subject is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the subject (when possible, three telephone calls and if necessary a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record or study file;
- Should the subject continue to be unreachable, he or she will be considered to have withdrawn from the trial with a primary reason of lost to follow-up.

8.3.2 Replacement of subjects

Drop-out subjects that were randomized and have received at least one dose of study drug, will not be replaced.

8.3.3 Follow-up of withdrawn subjects

Regardless of the reason for withdrawal, the Principal Investigator (PI) must consider the following:

- Procedures for safe discontinuation of treatment;
- Retention and use of the data already collected.
- In case of withdrawing from study treatment, continue other assessments or data collection, if applicable.

8.4 Method of recruitment and compensation for subjects

Subjects are transferred by their rheumatologist or physician. An investigator trained on the study protocol will inform possible eligible subjects about the study. If a subject shows interest in participation the ICF is provided and subjects are given time to read the document, ask questions, and discuss participation with others as desired.
Based on the subjects history during anamnesis conducted by a staff member of the Department of Reumatology, subjects will be included in the study when they sign the study specific ICF and meet all the in- and exclusion criteria.
There will be no compensation for study participation.

8.5 Subject eligibility screening

Screen failures are subjects who consent to participate in the trial but do not meet one or more criteria required for participation in the trial during the screening procedures. Screen failures will not be enrolled in the trial. A minimal set of screen failure information will be kept to ensure transparent reporting of screen failure subjects.
Screen failures may be rescreened.

8.6 Subject follow-up after trial participation

No special care is needed after discontinuation of the trial. All patients that did not reach 'sustained clinical remission' will be treated with standard-of-care medication by their treating rheumatologist. After giving consent, all patients that leave the trial, regardless of outcome, can be prospectively followed in the Be-GIANT cohort allowing further long-term follow-up.

8.7 Restrictions and prohibitions for the subjects

- Patients should not donate blood at any time during the study or for 3 months after last dose of study drug.
- Adequate contraception* should be used during the study and for 6 months after the last dose by
    - Included women of childbearing potential and
    - Included men capable of fathering children and their fertile partners
- Female subjects must not donate eggs (ova, oocytes) during the study and for 6 months after the last dose of study drug.
- Male subjects must agree to no donate sperm while in the study and for 6 months after the last dose of study drug.

- There are no other restrictions except those specified in the exclusion criteria and the restrictions regarding the use of concomitant medications (see chapter 9).

* Adequate contraceptive methods are:
(1) Oral, injectable or implanted hormonal methods of contraception. Hormonal contraception exists in the form of (1) pills (which must be taken every day), (2) injections (which work for about 3 months) and (3) implanted devices that are inserted into the uterus and allowed to remain there for several years.

(2) Placement of an intrauterine device (IUD) or an intrauterine system (IUS) or
(3) Total abstinence (no sex/concourse) or
(4) Prior vasectomy or removal of the ovaries / ligature of the fallopian tubes (male/female sterilization)

9 Investigational Medicinal Product (IMP)

9.1 General information

CTU-1 of the University Hospital Ghent is responsible for the randomisation of the blinded study medication (secondary packaging).
In this study, the patients may also take NSAIDs and/or sulphasalazine which are registered drugs for the management of pSpA. All patients also take oral folic acid supplementation according to standard clinical practice.

9.1.1 Reporting requirements for investigational product complaints

The following could be considered potential product complaints that need to be reported to the sponsor. Should any such concerns or irregularities occur, the IMP will not be used and shall be kept in quarantine until confirms that it is permissible to use was received.

Examples of Product Complaints:
• Packaging: for example, broken container or cracked container
• Usage: for example, subject or healthcare provider cannot appropriately use the product
• Labeling: for example, missing labels, illegible labels, incorrect labels, and/or suspect labels
• Change in IMP appearance: for example color change or presence of foreign material
• Unexpected quantity in bottle: for example number of tablets or amount of fluid
• Evidence of tampering or stolen material

The report of a product complaint may be made by telephone, e-mail or facsimile (FAX).

Contact details of the National Coordinating Investigator:

Contact details of the producer of blinded methotrexate:

Contact details of the MAH/producer of methotrexate matching placebo:

Contact details of MAH/producer of Golimumab and matching placebo : [redacted]

9.1.2 Treatment compliance

The investigator or his/her designated and qualified representatives will administer/dispense study drug only to subjects enrolled in the study in accordance with the protocol. The study drug must not be used for reasons other than that described in the protocol.

Subject dosing will be recorded on a subject diary. Subjects will be instructed to return all drug containers (even if empty) to the study site personnel at each clinic visit. The study site personnel will document compliance in the study source documents and in the electronic CRF (eCRF).

9.1.3 Drug Accountability

The arrival of the study medication at the hospital pharmacy and the delivery to the study site will be documented.

The investigator or his/her representative will verify that study drug supplies are received intact and in correct amounts. To maintain transparency, the drug accountability will be documented in the eCRF REDCap with the description of the batch number, expiration date, date dispensed and subject number. Subjects will record the date of administration and the amount that is administered in a subject dosing diary. The dosing diary will be kept in de subject binder.

All empty/used study drug packaging will be inventoried by the site. Empty/used study drug packaging should be returned by the subject at each visit for accountability and compliance purposes and new packaging issued as necessary.

After drug accountability has been completed by the site, empty used packaging may be discarded with any subject identifiers removed.

Unused study drug and used packaging with remaining study drug will be destroyed on site according to local procedures or regulations. The destruction must be documented on the drug accountability log with the amount that was discarded and date of destruction.

9.1.4 Storage conditions

At the time of randomization and in alignment with the protocol, patient-specific study drug packages (containing golimumab/placebo and methotrexate/placebo) will be shipped from the pharmacy of the Ghent university hospital to the local study site under the respective temperature-controlled conditions described above conform good manufacturing practices (GMP).
The patient-specific packages will again be stored at the local study site under the same temperature-controlled conditions.

9.2 Golimumab (blinded)

9.2.1 General information

Also refer to	SmPC + IMPD
Name of the IMP	Blinded Golimumab
Qualitative and quantitative composition	Each pre-filled syringe of 1 mL contains 50 mg golimumab The substance has been registered with the EMA as = SUB25638
Pharmaceutical form	Solution for injection in pre-filled syringe (blinded)
Method of administration	Subcutaneous use
Authorised in the EU	Yes
Used within scope	No (blinded)
Marketing authorisation holder	Janssen Biologics B.V.
Marketing authorisation number(s)	Syringe: EU/1/09/546/003
Manufacturer	Janssen Biologics B.V., Einsteinweg 101, 2333 CB Leiden, Nederland
Distributor	Up until 30-Sep-2024:MSD Belgium, Lynx Binnenhof 5, B 1200 Brussel
Responsible for batch release	Janssen Biologics B.V., Einsteinweg 101, 2333 CB Leiden, Nederland

9.2.2 IMP rationale

Refer to Section 5, Objectives of the study

9.2.3 Preparation, administration, dosage and dose frequency of the IMP

Golimumab, which will be immediately used by patients randomized in the “TNFi-induction”-group, is a human monoclonal antibody (mab) with an IgG1 heavy chain isotype and a kappa light chain isotype that binds TNF-alfa with high affinity and specificity. The molecule is produced by a stable, recombinant murine cell line transfected with DNA coding for the heavy and light chains of the mab. Golimumab is supplied as a liquid in a prefilled syringe (PFS) for subcutaneous administration. Each prefilled syringe contains 50 mg (0.5 mL fill of liquid) golimumab, histidine, sorbitol and polysorbate 80 at pH 5.5. No preservatives are present. The prefilled syringe with golimumab will be administrated subcutaneously every 4 weeks. This is the standard dose/regimen recommended (and reimbursed in Belgium) for the indications psoriatic arthritis, ankylosing spondylitis and rheumatoid arthritis.

9.2.4 Permitted dose adjustments and interruption of treatment

[Fill in] The prefilled syringe with golimumab will be administrated subcutaneously every 4 weeks. In accordance with the visiting schedule, mentioned in section 11.4, there is a window of +/- 7 days.
In case of AE's the investigator can decide to interrupt or postpone the treatment.

9.2.5 Duration of treatment

Refer to Section 7, Study design to find detailed information about the Phase A and B treatment duration.

9.2.6 Packaging and labeling of the IMP

All blinded golimumab will be supplied as a sterile liquid in a 0.5 mL single-use prefilled syringe for subcutaneous administration.

Up until 30-Sep-2024, the prefilled syringes with blinded golimumab will be labelled by MSD.

9.2.7 Traceability, storage, return and destruction of the IMP

The UZ Ghent Pharmacy will store the prefilled syringes with golimumab until time of randomization in a locked refrigerator, which will be temperature-controlled by using a temperature logger (between 2°C and 8°C). The prefilled syringes will be protected from light.

9.2.8 Known side effects of the medication

Golimumab (SIMPONI®) is a prescription medicine. Common side effects of golimumab include: upper respiratory tract infection, viral infections such as flu, and reactions at site of injection.

SERIOUS INFECTIONS
Golimumab can lower the ability to fight infections. There are reports of serious infections caused by bacteria, fungi, or viruses that have spread throughout the body, including tuberculosis (TB) and histoplasmosis. Some of these infections have been fatal. TB should be tested before starting golimumab and signs of TB will be monitored during treatment.

CANCER
Some people treated with golimumab have developed certain kinds of (skin) cancer.

USE WITH OTHER DRUGS
People taking golimumab should not receive live vaccines or treatment with weakened bacteria (such as Bacillus Calmette-Guerin for bladder cancer).

HEPATITIS B INFECTION
Reactivation of hepatitis B virus has been reported in patients who are carriers of this virus and are taking TNF-blocker medicines, such as golimumab. Some of these cases have been fatal. Patients will be screened for hepatitis B infection prior to randomization.

HEART FAILURE
Heart failure can occur or get worse in people who use TNF blockers, including golimumab.

NERVOUS SYSTEM PROBLEMS
Rarely, people using TNF blockers, including golimumab, can have nervous system problems such as multiple sclerosis or Guillain-Barré syndrome.

IMMUNE SYSTEM PROBLEMS
Rarely, people using TNF blockers have developed lupus-like symptoms.

LIVER PROBLEMS
Serious liver problems can happen in people using TNF blockers, including golimumab.

BLOOD PROBLEMS
Low blood counts have been observed with people using TNF blockers, including golimumab.

ALLERGIC REACTIONS
Allergic reactions can happen in people who use TNF-blocker medicines, including golimumab. Some reactions can be serious and life-threatening.

9.3 Simponi® (open-label)

9.3.1 General information

Also refer to	SmPC
Name of the IMP	Simponi, active substance Golimumab
Qualitative and quantitative composition	Each pre-filled syringe of 1 mL contains 50 mg golimumab The substance has been registered with the EMA as = SUB25638
Pharmaceutical form	Solution for injection in pre-filled injector (open-label)
Method of administration	Subcutaneous use
Authorised in the EU	Yes
Used within scope	Yes
Marketing authorisation holder	Janssen Biologics B.V.
Marketing authorisation number(s)	Injector: EU/1/09/546/001 Syringe: EU/1/09/546/003
Manufacturer	Up until 30-Sep-2024, for open-label golimumab Simponi® Smartject™: MSD Belgium, Lynx Binnenhof 5, B 1200 Brussel
Distributor	Up until 30-Sep-2024: MSD Belgium, Lynx Binnenhof 5, B

	1200 Brussel
Responsible for batch release	Janssen Biologics B.V., Einsteinweg 101, 2333 CB Leiden, Nederland

9.3.2 IMP rationale

Refer to Section 5, Objectives of the study

9.3.3 Preparation, administration, dosage and dose frequency of the IMP

Golimumab, which will be immediately used by patients randomized in the “TNFi-induction”-group, is a human monoclonal antibody (mab) with an IgG1 heavy chain isotype and a kappa light chain isotype that binds TNF-alfa with high affinity and specificity. The molecule is produced by a stable, recombinant murine cell line transfected with DNA coding for the heavy and light chains of the mab. Golimumab is supplied as a liquid in a prefilled syringe (PFS) for subcutaneous administration. Each prefilled syringe contains 50 mg (0.5 mL fill of liquid) golimumab, histidine, sorbitol and polysorbate 80 at pH 5.5. No preservatives are present. The prefilled syringe with golimumab will be administrated subcutaneously every 4 weeks. This is the standard dose/regimen recommended (and reimbursed in Belgium) for the indications psoriatic arthritis, ankylosing spondylitis and rheumatoid arthritis.

9.3.4 Permitted dose adjustments and interruption of treatment

[Fill in] The prefilled syringe with golimumab will be administrated subcutaneously every 4 weeks. In accordance with the visiting schedule, mentioned in section 11.4, there is a window of +/- 7 days.
In case of AE’s the investigator can decide to interrupt or postpone the treatment.

9.3.5 Duration of treatment

Refer to Section 7, Study design to find detailed information about the Phase A and B treatment duration.

9.3.6 Packaging and labeling of the IMP

The open-label golimumab (Simponi®) will be supplied as a sterile liquid in a 0.5 mL single-use prefilled SmartJect autoinjector device or prefilled syringe for subcutaneous administration.

Simponi® that is already on site will be relabeled at the local hospital pharmacy. Open-label golimumab that will be supplied and distributed by UZ Gent pharmacy will also be labeled by the UZ Gent pharmacy.

9.3.7 Traceability, storage, return and destruction of the IMP

The Simponi® Smartject autoinjectors and syringes will be stored in a locked refrigerator at the participating centers, which will be temperature-controlled by using a temperature logger (between 2°C and 8°C) and protected from light.

9.3.8 Known side effects of the medication

Refer to Section 9.2.8.

9.4 Placebo Golimumab

9.4.1 General information

Also refer to	IMPD
Name of the IMP	Placebo
Qualitative and quantitative composition	/
Pharmaceutical form	Solution for injection in pre-filled syringe
Method of administration	Subcutaneous use
Authorised in the EU	NA
Used within scope	NA
Marketing authorisation holder	NA
Marketing authorisation number(s)	NA
Manufacturer	Janssen Biologics B.V., Einsteinweg 101, 2333 CB Leiden, Nederland
Distributor	Up until 30-Sep-2024: MSD Belgium, Lynx Binnenhof 5, B 1200 Brussel
Responsible for batch release	Janssen Biologics B.V., Einsteinweg 101, 2333 CB Leiden, Nederland

9.4.2 IMP rationale

Refer to Section 5, Objectives of the study.

9.4.3 Preparation of the IMP, administration, dosage and dose frequency of the IMP

For patients in the “csDMARD-Step-up”-group, placebo Golimumab injections will be administered, consisting of an aqueous medium of histidine, sorbitol, and polysorbate 80 at pH 5.5; this will be supplied as a sterile liquid for SC injection at a volume of 0.5 mL in single-use prefilled syringes.

The prefilled syringe with placebo golimumab will be administrated subcutaneously every 4 weeks.

9.4.4 Permitted dose adjustments and interruption of treatment

[Fill in] The prefilled syringe with golimumab will be administrated subcutaneously every 4 weeks. In accordance with the visiting schedule, mentioned in section 11.4, there is a window of +/- 7 days.
In case of AE's the investigator can decide to interrupt or postpone the treatment.

9.4.5 Duration of treatment

Refer to Section 7, Study design to find detailed information about the Phase A and B treatment duration.

9.4.6 Packaging and labeling of the IMP

Placebo Golimumab will be supplied as a sterile liquid in a 0.5 mL single-use prefilled syringe for subcutaneous administration.
Up until 30-Sep-2024, the prefilled syringes with placebo golimumab will be labelled by MSD.

9.4.7 Traceability, storage, return and destruction of the IMP

The UZ Ghent Pharmacy will store the prefilled syringes with placebo golimumab until time of randomization in a locked refrigerator, which will be temperature-controlled by using a temperature logger (between 2°C and 8°C). The prefilled syringes will be protected from light.

9.5 Ledertrexate

9.5.1 General information

Also refer to	Investigational Medicinal Product Dossier (IMPD)
Name of the IMP	Ledertrexate, active substance = Methotrexate
Qualitative and quantitative composition	Each tablet contains methotrexate sodium equivalent to 2.5 mg of methotrexate. The substance has been registered with the EMA as = SUB08856MIG
Pharmaceutical form	Capsule
Method of administration	Oral use
Authorised in the EU	Yes
Used within scope	Yes

Marketing authorisation holder	Pfizer NV/SA
Marketing authorisation number(s)	Pfizer: BE003446
Manufacturer	For blinded methotrexate: Ardena Drug Development & Manufacturing, Ardena Gent NV, Kleimoer 4, B 9030 Mariakerke. Contact persons: Annelies Paridaens, Director Project Management. [redacted]
Distributor	University Hospital Ghent pharmacy – clinical trials C. Heymanslaan 10, B 9000 Ghent
Responsible for batch release	University Hospital Ghent pharmacy

9.5.2 IMP rationale

Refer to Section 5, Objectives of the study.

9.5.3 Preparation of the IMP, administration, dosage and dose frequency of the IMP

In the “csDMARD-Step-up”-group, patients will start with oral methotrexate (MTX) capsules at a weekly dose of 15 mg for 4 weeks. In case of intolerance or toxicity to MTX, the weekly dose will be tapered to 10 mg at week 4 and if still problematic to 7,5 mg at week 8; in case of persisting intolerance/toxicity issues, MTX will be stopped at week 12. When there are no tolerability/toxicity issues, the weekly dose of MTX will be increased to 20 mg at week 4 (with a possibility to taper down if intolerance/toxicity would occur at this higher dose). Methotrexate 2,5 mg capsules contain the following supplements: lactose monohydrate, pre-gelled corn starch, magnesium stearate, sodium hydroxide, black iron oxide, titanium dioxide, yellow iron oxide and hypromellose.

The methotrexate capsules will be administered orally every week. The capsules should be swallowed whole and intact. They should not be opened or chewed or crushed.

9.5.4 Permitted dose adjustments and interruption of treatment

Patients will start with oral methotrexate (MTX) capsules at a weekly dose of 15 mg for 4 weeks. In case of intolerance or toxicity to MTX or MTX placebo, the weekly dose of MTX or MTX placebo can be tapered to 10 mg at week 4, with a further possible reduction to

7,5 mg at week 8; in case of persistent intolerance/toxicity, MTX or MTX placebo will be stopped at week 12. For safety reasons, the dose reduction rate can be adapted at the discretion of the investigator.

9.5.5 Duration of treatment

Refer to Section 7, Study design to find detailed information about the Phase A and B treatment duration.

9.5.6 Packaging and labeling of the IMP

Methotrexate will be supplied as capsules of 2.5 mg for oral administration packed in HDPE (high density polyethylene) bottle, 40 capsules per bottle.
CTU-1 of the University Hospital Ghent will label the bottles.

9.5.7 Traceability, storage, return and destruction of the IMP

The methotrexate capsules will be stored until time of randomization at the pharmacy of the Ghent university hospital; capsules will be stored in a locked room with a temperature logger (at a temperature between 15°C and 25°C).

9.5.8 Known side effects of the medication

Methotrexate (LEDERTREXATE®) is a prescription medicine.

VERY COMMON SIDE EFFECTS (≥ 10%)
Anorexia, nausea, vomiting, abdominal pain, ulcerations of the mucous membrane of mouth and throat (especially during the first 24 to 48 hours after administration), stomatitis, dyspepsia, increase in liver related enzymes (ALT, alkaline phosphatase, bilirubin, and LDH levels), decreased resistance to infection.

COMMON SIDE EFFECTS (≥ 1%)
Leukocytopenia, thrombocytopenia, anaemia, headache, pulmonary complications due to interstitial pneumonitis, diarrhoea, erythema, itching.

UNCOMMON SIDE EFFECTS (≥ 0.1%)
Severe anemia, allergic reactions, diabetes mellitus, depression, vertigo, confusion, convulsion, vasculitis, pulmonary fibrosis, gastro-intestinal bleeding and ulcers, development of liver fattening, liver fibrosis, exanthema, photosensitivity, poorly healing wounds, increase of rheumatic nodules, herpes zoster, skin ulcerations, arthralgia, myalgia, cystitis, haematuria.

RARE SIDE EFFECTS (≥ 0.01%)
Endocarditis, mood alterations, hypotension, thromboembolic events (e.g., arterial thrombosis, cerebral thrombosis, thrombophlebitis, deep vein thrombosis, retinal vein thrombosis, pulmonary embolism), sore throat, apnoea, discoloration or yellowing of the skin or the eyes indicating acute hepatitis, acne, gingival hyperplasia, renal failure, menstrual disorder, transient oligospermia.

9.6 Placebo Ledertrexate

9.6.1 General information

Also refer to	Investigational Medicinal Product Dossier (IMPD)
Name of the IMP	Placebo Ledertrexate
Qualitative and quantitative composition	A capsule will be filled with 292 mg lactose monohydrate as excipient
Pharmaceutical form	Capsule
Method of administration	Oral use
Authorised in the EU	NA
Used within scope	NA
Marketing authorisation holder	NA
Marketing authorisation number(s)	NA
Manufacturer	University Hospital Ghent pharmacy – CTU-1, C. Heymanslaan 10, B 9000 Ghent
Distributor	University Hospital Ghent pharmacy – clinical trials C. Heymanslaan 10, B 9000 Ghent
Responsible for batch release	University Hospital Ghent pharmacy

9.6.2 IMP rationale

Refer to Section 5, Objectives of the study.

9.6.3 Preparation of the IMP, administration, dosage and dose frequency of the IMP

In the “csDMARD-Step-up”-group, patients will start with oral methotrexate (MTX) capsules at a weekly dose of 15 mg for 4 weeks. In case of intolerance or toxicity to MTX, the weekly dose will be tapered to 10 mg at week 4 and if still problematic to 7,5 mg at week 8; in case of persisting intolerance/toxicity issues, MTX will be stopped at week 12. When there are no tolerability/toxicity issues, the weekly dose of MTX will be increased to 20 mg at week 4 (with a possibility to taper down if intolerance/toxicity would occur at this higher dose). Methotrexate 2,5 mg capsules contain the following supplements: lactose monohydrate, pre-gelled corn starch, magnesium stearate, sodium hydroxide, black iron oxide, titanium dioxide, yellow iron oxide and hypromellose.

In the “TNFi-induction”-group, matching placebo pills will be used looking identical to the methotrexate pills without the methotrexate active ingredient.

The methotrexate placebo capsules will be administered orally every week. The capsules should be swallowed whole and intact. They should not be opened or chewed or crushed.

9.6.4 Permitted dose adjustments and interruption of treatment

Patients will start with oral methotrexate (MTX) capsules at a weekly dose of 15 mg for 4 weeks. In case of intolerance or toxicity to MTX or MTX placebo, the weekly dose of MTX or MTX placebo can be tapered to 10 mg at week 4, with a further possible reduction to 7,5 mg at week 8; in case of persistent intolerance/toxicity, MTX or MTX placebo will be stopped at week 12. For safety reasons, the dose reduction rate can be adapted at the discretion of the investigator.

9.6.5 Duration of treatment

Refer to Section 7, Study design to find detailed information about the Phase A and B treatment duration.

9.6.6 Packaging and labeling of the IMP

Methotrexate placebo will be supplied as capsules of 2.5 mg for oral administration packed in HDPE (high density polyethylene) bottle, 40 capsules per bottle.

CTU-1 of the University Hospital Ghent will label the bottles.

9.6.7 Traceability, storage, return and destruction of the IMP

The methotrexate placebo capsules will be stored until time of randomization at the pharmacy of the Ghent university hospital; capsules will be stored in a locked room with a temperature logger (at a temperature between 15°C and 25°C).

9.7 Management of pSpA

In this study, the patients may also take NSAIDs and/or sulphasalazine which are registered drugs for the management of pSpA. All patients should take oral folic acid supplementation according to standard clinical practice.

10 Concomitant medication and treatment

The use of DMARDs (conventional synthetic, targeted synthetic or biological), NSAIDs and glucocorticoids, allowed prior to entry in the trial and/or during the trial (up to 3 months after last study drug administration) is summarized in table 1.

Table 1: Prior and concomitant use of DMARDs, NSAIDs and glucocorticoids.

Drug	Prior Exposure	Concomitant use
Adequate dose of methotrexate	Not allowed	(Study medication)

Adequate dose of sulphasalazine	Not allowed	(Escape medication)
Other csDMARDs (e.g. hydroxychloroquine, …)	Allowed	Not allowed
tsDMARDs (with therapeutic effect on SpA)	Not allowed	Not allowed
bDMARDs (with therapeutic effect on SpA)	Not allowed	Not allowed, except golimumab (study drug)
NSAIDs	Stable ≤1 week before baseline	Allowed (incl. dose adjustment & stop)
Intra-articular glucocorticoid injection	Prior corticoid infiltrations are allowed provided that the necessary wash out (≥ 6 weeks) before biopsy is respected	Max. 2 injections between week 12 and 20
Short course oral glucocorticoids	Not allowed <6 weeks before baseline	Not allowed
Prolonged oral glucocorticoids	Not allowed	Not allowed
Intravenous or intramuscular glucocorticoids	Not allowed	Not allowed
Topical corticosteroid treatment for psoriasis	Allowed	Allowed
Topical treatment for uveitis	Allowed	Allowed

Non-steroidal anti-inflammatory drugs (NSAIDs)

All patients are allowed to be treated with NSAIDs provided that the dose is stable and not exceeding the maximum recommended dose. NSAID treatment should be stable for 1 week before the first study drug administration.

During the trial, NSAID intake should not exceed the maximum recommended dose; the dose can be adapted or even stopped at the discretion of the treating rheumatologist. The need for concomitant intake of NSAIDs, including changes in the dosing schedule, will be recorded (by calculating the NSAID-index). This index will be considered as a surrogate (in)efficacy marker.

From week 20, all concomitant oral medication should be kept stable until the assessment of the primary endpoint at week 24.

Intra-articular glucocorticoid injections

- Treatment with intra-articular glucocorticoid injection(s) for peripheral SpA symptoms are allowed provided that the necessary wash out (≥ 6 weeks) before biopsy is respected. In.
- In case of persistent severe arthritis, a maximum of 2 intra-articular glucocorticoid injections will be allowed (between week 12 (after the clinical evaluations) but before the week 20 assessment). The number of glucocorticoid injections will be considered as a surrogate (in)efficacy marker. When patients have received intra-articular injections, they will – by default – be considered as non-responders at week 24.

Investigational drugs

Prior use of any investigational drug of chemical or biological nature within a period of 30 days or 5 half-lives of the drug (whichever is longer) before the baseline visit is not allowed; concomitant use of these drugs is not allowed during the trial.

Vaccines:
Patient may not have received, or are expected to receive, any live virus or bacterial vaccination within 3 months prior to the first administration of study agent, during the trial, or within 3 months after the last administration of study agent.

In line with international management recommendations investigators should ensure that the vaccination status of patients with inflammatory rheumatic diseases is up to date; this would include booster vaccinations for influenza and Covid-19. At present there is no convincing evidence that these vaccines would interfere or create safety hazards in combination with the treatment strategies applied in the Spartacus trial.

All patients will receive oral folic acid according to standard clinical practice when using MTX.

Rescue therapy

There are essentially 3 types of “rescue therapy”:

- At week 12, a “Patient Acceptable Signs & Symptoms Improvement”-question (“PASSI”) will be asked. If the patient has not experienced an acceptable improvement of signs and symptoms, oral sulphasalazine at a dose of 2 g per day will be added to the blinded study medication.
- Between week 12 (after efficacy evaluation) and week 24, there is a possibility to inject a persistently swollen joint with glucocorticoids. This procedure can only be performed twice in this 12-week time-window.
- At week 24, there is an option to treat patients, that did not reach clinical remission with the blinded study medication, with open-label golimumab at the standard dose of 50 mg SC every 4 weeks. This option is also available at week 36 for patients that have remained on blinded study medication.

The use of concomitant medication will be recorded from screening until the patient’s last study visit. During the screening visit all current medication will be recorded on the concomitant medication log: Medication name, indication, dosage, frequence, start- and stop date. During each trial visit, the change in medication use will be registered in this log. Supplements are not considered as medication.

11 Procedures and Study Flow-Chart

11.1 Eligibility screening process

Refer to section 8.5.

11.2 Informed consent

Refer to section 17.2.

11.3 Measures taken to minimise bias

11.3.1 Randomisation/Blinding/Deblinding

All patients (n=97) will be randomized (1:1) to either immediately receiving golimumab monotherapy (n=48) (the "TNFi-induction"-group), or to the step-up regimen with csDMARDs (n=47) ("csDMARD-Step-up"-group) in a double-blind, double-dummy design.

The "TNFi-induction"-group will receive the standard golimumab dose of 50 mg subcutaneously (SC) every 4 weeks (with matching csDMARD-placebo capsules).
In the "csDMARD-Step-up" regimen, patients will start with oral methotrexate (MTX) capsules at a weekly dose of 15 mg for 4 weeks (with matching "golimumab"-placebo injections). In case of intolerance or toxicity to MTX or MTX placebo, the weekly dose of MTX or MTX placebo can be tapered to 10 mg at week 4, with a further possible reduction to 7,5 mg at week 8; in case of persistent intolerance/toxicity, MTX or MTX placebo will be stopped at week 12. When there are no tolerability/toxicity issues, the weekly dose of MTX or MTX placebo will be increased to 20 mg at week 4 (with an option to again reduce the dose in case of intolerance/toxicity).

At week 12, "Patient Acceptable Signs & Symptoms Improvement" ("PASSI") will be assessed (see Addendum 3) in order to determine the need for additional, open-label "escape" csDMARD treatment: in case of an acceptable improvement, blinded study medication will be continued until week 24; if there is no satisfactory response, oral sulphasalazine can be added to the blinded study medication at a dose of 2 g per day (escape medication).

The randomization to either the "TNFi induction"-group or the "csDMARD Step-up"-group will be done at the UZ Ghent Pharmacy and the randomization list will be kept there. If according to the data entered in the eCRF, the patient is eligible for randomization, the RedCap system will send a notification to the coordinating study team. Upon review of the screening visit data (including in- and exclusion criteria), the coordinating study team will approve randomization in the eCRF. This will trigger communication with the UZ Ghent pharmacy who will randomize the patient. The local site will be informed via an email and the eCRF system. The UZ Ghent Pharmacy will assemble patient-specific medication kits that will contain (according to the randomization list) the golimumab/placebo syringes for each individual patient. When a new patient is to be randomized, the kits will be sent to the site containing:

- 7 golimumab/placebo syringes:
    - 6 syringes for administration at baseline and weeks 4, 8, 12, 16 and 20.
    - 1 spare syringe:
        - To be used in case of a problem with the first 6 syringes.
        - This syringe will be administered at week 24 in case the patient would need to continue at week 24 for another 12 weeks with blinded study

drug. In that case 2 more golimumab/placebo syringes will be distributed for administration on weeks 28 and 32.

At the time of randomisation of a first patient the site will receive a number of methotrexate and placebo bottles provided with a randomisation number. This medication is not patient-specific and will be allocated per study visit.

At the start of the study, the UZ Ghent Pharmacy will send the unblinding information, in a sealed envelope, to the national coordinating investigator conform the GMP regulation. If the local investigator would feel that unblinding of study medication has become necessary, the national coordinating investigator at UZ Ghent should be contacted to discuss the case (see contact information paragraph 15.3). If necessary, the coordinating investigator at UZ Ghent can unblind the patient in question and send notification thereof to HIRUZ and the UZ Ghent Pharmacy.
The study code should only be broken for valid medical or safety reasons, e.g. in the case of a severe adverse event where it is necessary for the investigator or treating health care professional to know which treatment the subject is receiving before he or she can be treated. If possible, other study team members should remain blinded.
The code breaks for the trial are kept in a separate study binder. The binder is located in a locked cupboard that only the study staff have access to. In the event a code is required to be unblinded a formal request for unblinding will be made by the local PI to the Coordinating Investigator (CI).
The CI/PI documents the breaking of the code and the reasons for doing so on the eCRF/study documents, in the site file and medical notes. It will also be documented at the end of the trial in any final study report and/or statistical report.
The study team will notify the Sponsor in writing as soon as possible following the code break detailing the necessity of the code break.
As the investigator is responsible for the medical care of the individual study subject (Declaration of Helsinki §3 and ICH 4.3) the coding system should include a mechanism that permits rapid unblinding (ICH GCP 5.13.4). The investigator cannot be required to discuss unblinding if he or she feels that emergent unblinding is necessary.

Patients for whom the medication is unblinded will be discontinued from the clinical trial.

11.4 Study specific Procedures and Interventions

11.4.1 'SPARTACUS Phase A'

Phase A – Visit 1A: CLINICAL SCREENING (week -6 to -4 days)

- Informed consent.
- Check fulfilment of in- and exclusion criteria.
- Demographic data, symptom duration, medical history, incl. past anti-rheumatic treatment, smoking/alcohol status, and family history.
- Current medication (dose and duration).

- Latent Tuberculosis (TB) screening: chest X-ray (if not performed within the last 3 months), TB test (Mantoux PPD-test or Quantiferon), TB questionnaire (see Addendum 4).
- Patient reported outcomes:
  - Patient global assessment of disease activity (0-10 numerical rating scale).
  - Patient global assessment of pain (0-10 numerical rating scale).
- Physical examination.
- Vital signs (blood pressure, heart frequency).
- Weight, length.
- Rheumatological examination (see Addendum 5):
  - 78-Tender and 76-swollen joint count.
  - Dactylitis assessment.
  - Enthesitis assessment (SPARCC (SPondyloArthritis Research Consortium of Canada) Enthesitis Index).
  - Physician global assessment of disease activity (0-10 numerical rating scale).
- Laboratory investigation:
  - Diagnosis: HLA B27 (if not known), anti-CCP antibodies (if not determined within the last 12 months).
  - Screening: peripheral blood count, serum creatinine, uric acid, liver function tests (ALT, gamma-GT, Alkaline Phosphatase, LDH), Creatine Kinase. (laboratory evaluations considered "standard-of-care" daily practice for SpA patients treated with csDMARDs and TNFi). (the results of tests performed within the last month are allowed).
  -
  - Serum pregnancy test.
  - Screening for Hepatitis B, Hepatitis C, HIV and CMV IgG. (if not determined within the last 3 months).

  - Disease activity: inflammatory parameters: erthrocyte sedimentation rate (ESR), C-reactive protein (CRP).

Phase A – Visit 1B: SYNOVIAL BIOPSY SCREENING (week -6 to -4 days)

Performed in one of the synovial biopsy sampling units

- Ultrasound evaluation of clinically swollen joints identified at visit 1A.
- Ultrasound-guided synovial tissue sampling of a representative swollen joint (see Addendum 6 for list of joints that can be sampled). In case of multiple small joint involvement, a joint with a score of 2 or more on Grey Scale/Power Doppler ultrasound assessment will be chosen to sample.
- Laboratory investigation: Research samples (4 x 8ml blood-CPT (Cell Preparation Tube) and 10ml serum)
- Check fulfilment of in- and exclusion criteria.
- Post biopsy questionnaire (see Addendum 9)

Phase A – Visit 2: BASELINE (week 0)

- Check fulfilment of in- and exclusion criteria.
- Current medication (dose and duration).
- Patient reported outcomes (see Addendum 7):

    - Patient global assessment of disease activity (0-10 numerical rating scale).
    - Patient global assessment of pain (0-10 numerical rating scale).
    - Bath Ankylosing Spondylitis Disease Activity Index (BASDAI).
    - Bath Ankylosing Spondylitis Functional Index (BASFI).
    - Health Assessment Questionnaire (for SpA) (HAQ(-SpA)).
    - Assessment of SpondyloArthritis international Society (ASAS) Health Index (ASAS-HI).
    - "Health Economic Evaluation": EuroQoL 5 dimensions, co-morbidity Index (SCQ) and healthcare utilization and productivity (in the past 6 months), level of education
- Targeted physical examination.
- Follow-up upon the synovial biopsy if performed
- Rheumatological examination (see Addendum 5):
    - 78-Tender and 76-swollen joint count.
    - Dactylitis assessment.
    - Enthesitis assessment (SPARCC Enthesitis Index).
    - Bath Ankylosing Spondylitis Metrology Index (BASMI), including tragus-to-wall distance, lumbar flexion (Schöber index), lumbar lateroflexion, cervical rotation and intermalleolar distance; chest expansion.
    - Psoriasis skin evaluation (if applicable).
- Laboratory investigation:
    - Research samples (if not taken at Visit 1B 4 x 8ml blood-CPT + 10ml serum if treated in a synovial biopsy sampling unit)
- Assessment of adverse events after start of blinded study medication.
- Dispensation of study drug and treatment schedule education/diary:
    - Administration of Golimumab/Placebo injection at study site.
    - Dispensation of Placebo/Methotrexate capsules for weekly intake at home.

Phase A – Visit 3: WEEK 4 (+/- 1 week)

- Assessment of adverse events.
- Current medication (dose and duration).
- Study drug accountability.
- Patient reported outcomes (see Addendum 7):
    - Patient global assessment of disease activity (0-10 numerical rating scale).
    - Patient global assessment of pain (0-10 numerical rating scale).
    - Bath Ankylosing Spondylitis Disease Activity Index (BASDAI).
- Targeted physical examination.
- Rheumatological examination (see Addendum 5):
    - 78-Tender and 76-swollen joint count.
    - Dactylitis assessment.
    - Enthesitis assessment (SPARCC Enthesitis Index).
- Laboratory investigation:
    - Disease activity: ESR, CRP.
    - Safety: peripheral blood count, serum creatinine, liver function tests (ALT).
- Dispensation of study drug:
    - Administration of Golimumab/Placebo injection at study site.
    - Dispensation of Placebo/Methotrexate capsules for weekly intake at home. Dose according to tolerance (see Addendum 8).

Phase A – Visit 4: WEEK 8 (+/- 1 week)

- Assessment of adverse events.
- Current medication (dose and duration).
- Study drug accountability.
- Patient reported outcomes (see Addendum 7):
  - Patient global assessment of disease activity (0-10 numerical rating scale).
  - Patient global assessment of pain (0-10 numerical rating scale).
  - Bath Ankylosing Spondylitis Disease Activity Index (BASDAI).
- Targeted physical examination.
- Rheumatological examination (see Addendum 5):
  - 78-Tender and 76-swollen joint count.
  - Dactylitis assessment.
  - Enthesitis assessment (SPARCC Enthesitis Index).
- Laboratory investigation:
  - Disease activity: ESR, CRP.
  - Safety: at the discretion of the treating rheumatologist.
- Dispensation of study drug:
  - Administration of Golimumab/Placebo injection at study site.
  - Dispensation of Placebo/Methotrexate capsules for weekly intake at home. Dose according to tolerance (see Addendum 8).

Phase A – Visit 5: WEEK 12 (+/- 1 week)

- Assessment of adverse events.
- Tuberculosis Questionnaire.
- Current medication (dose and duration).
- Study drug accountability.
- Patient reported outcomes (see Addendum 7):
  - Patient global assessment of disease activity (0-10 numerical rating scale).
  - Patient global assessment of pain (0-10 numerical rating scale).
  - Bath Ankylosing Spondylitis Disease Activity Index (BASDAI).
  - Bath Ankylosing Spondylitis Functional Index (BASFI).
  - Assessment of SpondyloArthritis international Society (ASAS) Health Index (ASAS-HI).
  - “Health Economic Evaluation”: EuroQoL 5 dimensions, co-morbidity Index (SCQ) and healthcare utilization and productivity (in the past 3 months)
  - Patient Acceptable Signs & Symptoms Improvement (“PASSI”) question (See Addendum 3).
- Targeted physical examination.
- Vital signs (blood pressure, heart frequency).
- Weight.
- Smoking/alcohol status
- Rheumatological examination (see Addendum 5):
  - 78-Tender and 76-swollen joint count.
  - Dactylitis assessment.
  - Enthesitis assessment (SPARCC Enthesitis Index).

  - Bath Ankylosing Spondylitis Metrology Index (BASMI), including tragus-to-wall distance, lumbar flexion (Schöber index), lumbar lateroflexion, cervical rotation and intermalleolar distance; chest expansion.
  - Psoriasis skin evaluation (if applicable).
  - Physician global assessment of disease activity (0-10 numerical rating scale).
- Laboratory investigation:
  - Disease activity: ESR, CRP.
  - Safety: peripheral blood count, serum creatinine, liver function tests (ALT).
  - Research samples (only 10ml serum if treated in UZ Ghent or UZ Leuven)
- Dispensation of study drug and treatment schedule education:
  - Administration of Golimumab/Placebo injection at study site.
  - Dispensation of Placebo/Methotrexate capsules for weekly intake at home. Dose according to tolerance (see Addendum 8).
  - Depending on the response to the "PASSI"-question:
    - "PASSI"-Yes: continuation of blinded study medication
    - "PASSI"-No: prescription of Sulphasalazine open-label escape treatment.

Phase A – Visit 6: WEEK 16 (+/- 1 week)

- Assessment of adverse events.
- Current medication (dose and duration).
- Study drug accountability.
- Patient reported outcomes (see Addendum 7):
  - Patient global assessment of disease activity (0-10 numerical rating scale).
  - Patient global assessment of pain (0-10 numerical rating scale).
  - Bath Ankylosing Spondylitis Disease Activity Index (BASDAI).
- Targeted physical examination.
- Rheumatological examination (see Addendum 5):
  - 78-Tender and 76-swollen joint count.
  - Dactylitis assessment.
  - Enthesitis assessment (SPARCC Enthesitis Index).
- Laboratory investigation:
  - Disease activity: ESR, CRP.
  - Safety: at the discretion of the treating rheumatologist (depending on the use of e.g. sulphasalazine escape medication).
- Dispensation of study drug:
  - Administration of Golimumab/Placebo injection at study site.
  - Dispensation of Placebo/Methotrexate capsules for weekly intake at home. Dose according to tolerance (see Addendum 8).

Phase A – Visit 7: WEEK 20 (+/- 1 week)

- Assessment of adverse events.
- Current medication (dose and duration).
- Study drug accountability.
- Patient reported outcomes (see Addendum 7):

    - Patient global assessment of disease activity (0-10 numerical rating scale).
    - Patient global assessment of pain (0-10 numerical rating scale).
    - Bath Ankylosing Spondylitis Disease Activity Index (BASDAI).
- Targeted physical examination.
- Rheumatological examination (see Addendum 5):
    - 78-Tender and 76-swollen joint count.
    - Dactylitis assessment.
    - Enthesitis assessment (SPARCC Enthesitis Index).
- Laboratory investigation:
    - Disease activity: ESR, CRP.
    - Safety: at the discretion of the treating rheumatologist (depending on the use of e.g. sulphasalazine escape medication).
- Dispensation of study drug:
    - Administration of Golimumab/Placebo injection at study site.
    - Dispensation of Placebo/Methotrexate capsules for weekly intake at home. Dose according to tolerance (see Addendum8).

Phase A – Visit 8: WEEK 24 (+/- 1 week)

- Assessment of adverse events.
- Tuberculosis Questionnaire.
- Current medication (dose and duration).
- Study drug accountability.
- Patient reported outcomes (see Addendum 7):
    - Patient global assessment of disease activity (0-10 numerical rating scale).
    - Patient global assessment of pain (0-10 numerical rating scale).
    - Bath Ankylosing Spondylitis Disease Activity Index (BASDAI).
    - Bath Ankylosing Spondylitis Functional Index (BASFI).
    - Health Assessment Questionnaire (for SpA) (HAQ(-SpA)).
    - Assessment of SpondyloArthritis international Society (ASAS) Health Index (ASAS-HI).
    - “Health Economic Evaluation”: EuroQoL 5 dimensions, co-morbidity Index (SCQ) and healthcare utilization and productivity (in the past 3 months)
- Targeted physical examination.
- Vital signs (blood pressure, heart frequency).
- Weight.
- Smoking/alcohol status
- Rheumatological examination (see Addendum 5):
    - 78-Tender and 76-swollen joint count.
    - Dactylitis assessment.
    - Enthesitis assessment (SPARCC Enthesitis Index).
    - Bath Ankylosing Spondylitis Metrology Index (BASMI), including tragus-to-wall distance, lumbar flexion (Schöber index), lumbar lateroflexion, cervical rotation and intermalleolar distance; chest expansion.
    - Psoriasis skin evaluation (if applicable).
    - Physician global assessment of disease activity (0-10 numerical rating scale).
- Laboratory investigation:
    - Disease activity: ESR, CRP.

    - Safety: peripheral blood count, serum creatinine, uric acid, liver function tests (ALT, gamma-GT, Alkaline Phosphatase, LDH), Creatine Kinase.
- Research samples (4 x 8ml blood-CPT and 10ml serum if treated in UZ Ghent or UZ Leuven)

- Trial continuation evaluation based on clinical remission (yes/no) at week 24 and potential sustained clinical remission (at week 12 and 24):

    - No clinical remission: stop blinded study medication; start open-label golimumab 50 mg SC every 4 weeks.
    - Clinical remission (but not sustained remission): continuation of the same blinded study medication.
    - Sustained clinical remission: stop blinded study medication; roll-over into SPARTACUS Phase B – visit 1.
- For patients continuing in SPARTACUS Phase A: dispensation of study drug and treatment schedule education:
    - Blinded continuation group:
        - Administration of Golimumab/Placebo injection at study site.
        - Dispensation of Placebo/Methotrexate capsules for weekly intake at home. Dose according to tolerance (see Addendum 8).
    - Open-label golimumab group:
        - Administration of Golimumab injection at study site.

Phase A – Visit 9: WEEK 28 (+/- 1 week)

- Assessment of adverse events.
- Current medication (dose and duration).
- Study drug accountability.
- Patient reported outcomes (see Addendum 7):
    - Patient global assessment of disease activity (0-10 numerical rating scale).
    - Patient global assessment of pain (0-10 numerical rating scale).
    - Bath Ankylosing Spondylitis Disease Activity Index (BASDAI).
- Targeted physical examination.
- Rheumatological examination (see Addendum 5):
    - 78-Tender and 76-swollen joint count.
    - Dactylitis assessment.
    - Enthesitis assessment (SPARCC Enthesitis Index).
- Laboratory investigation:
    - Disease activity: ESR, CRP.
    - Safety: peripheral blood count, serum creatinine, liver function tests (ALT).
- Dispensation of study drug:
    - Blinded continuation group:
        - Administration of Golimumab/Placebo injection at study site.
        - Dispensation of Golimumab/Placebo injection for week 32 administration at home. Education regarding self-injection.
        - Dispensation of Placebo/Methotrexate capsules for weekly intake at home. Dose according to tolerance (see Addendum 8).

- Open-label golimumab group:
  - Administration of Golimumab injection at study site.
  - Dispensation of Golimumab injection for week 32 administration at home. Education regarding self-injection.

Phase A – Visit 10: WEEK 36 (+/- 1 week)

- Assessment of adverse events.
- Tuberculosis Questionnaire.
- Current medication (dose and duration).
- Study drug accountability.
- Patient reported outcomes (see Addendum 7):
  - Patient global assessment of disease activity (0-10 numerical rating scale).
  - Patient global assessment of pain (0-10 numerical rating scale).
  - Bath Ankylosing Spondylitis Disease Activity Index (BASDAI).
  - Bath Ankylosing Spondylitis Functional Index (BASFI).
  - Assessment of SpondyloArthritis international Society (ASAS) Health Index (ASAS-HI).
  - "Health Economic Evaluation": EuroQoL 5 dimensions, co-morbidity Index (SCQ) and healthcare utilization and productivity (in the past 3 months)
  - Patient Acceptable Signs & Symptoms Improvement ("PASSI") question (see Addendum 3).
- Targeted physical examination.
- Vital signs (blood pressure, heart frequency).
- Weight.
- Smoking/alcohol status
- Rheumatological examination (see Addendum 5):
  - 78-Tender and 76-swollen joint count.
  - Dactylitis assessment.
  - Enthesitis assessment (SPARCC Enthesitis Index).
  - Bath Ankylosing Spondylitis Metrology Index (BASMI), including tragus-to-wall distance, lumbar flexion (Schöber index), lumbar lateroflexion, cervical rotation and intermalleolar distance; chest expansion.
  - Psoriasis skin evaluation (if applicable).
  - Physician global assessment of disease activity (0-10 numerical rating scale).
- Laboratory investigation:
  - Disease activity: ESR, CRP.
  - Safety: peripheral blood count, serum creatinine, uric acid, liver function tests (ALT, gamma-GT, Alkaline Phosphatase, LDH), Creatine Kinase.
- Trial continuation evaluation based on clinical remission (yes/no) at week 36 and potential sustained clinical remission (at week 24 and 36):
  - Blinded continuation group:
    - No clinical remission: stop blinded study medication; start open-label golimumab 50 mg SC every 4 weeks.
    - Sustained clinical remission: stop blinded study medication; roll-over into SPARTACUS Phase B – visit 1.

    - Open-label golimumab group: additional decision based upon “PASSI”-question (yes/no)
        - Clinical remission: continuation of open-label golimumab 50 mg SC every 4 weeks.
        - No clinical remission *and* “PASSI”-yes: continuation of open-label golimumab 50 mg SC every 4 weeks.
        - No clinical remission *and* “PASSI”-no: study discontinuation, further (standard-of-care) treatment at the discretion of the treating rheumatologist.
- For patients continuing in SPARTACUS Phase A: dispensation of study drug:
    - Administration of Golimumab injection at study site.
    - Dispensation of Golimumab injections for week 40 and week 44 administration at home. Education regarding self-injection.

Phase A – Visits 11: WEEK 48 (+/- 1 week)

- Assessment of adverse events.
- Tuberculosis Questionnaire.
- Current medication (dose and duration).
- Study drug accountability.
- Patient reported outcomes (see Addendum 7):
    - Patient global assessment of disease activity (0-10 numerical rating scale).
    - Patient global assessment of pain (0-10 numerical rating scale).
    - Bath Ankylosing Spondylitis Disease Activity Index (BASDAI).
    - Bath Ankylosing Spondylitis Functional Index (BASFI).
    - Health Assessment Questionnaire (for SpA) (HAQ(-SpA)).
    - Assessment of SpondyloArthritis international Society (ASAS) Health Index (ASAS-HI).
    - “Health Economic Evaluation”: EuroQoL 5 dimensions, co-morbidity Index (SCQ) and healthcare utilization and productivity (in the past 3 months)
    - Patient Acceptable Signs & Symptoms Improvement (“PASSI”) question (see Addendum 3).
- Targeted physical examination.
- Vital signs (blood pressure, heart frequency).
- Weight.
- Smoking/alcohol status
- Rheumatological examination (see Addendum 5):
    - 78-Tender and 76-swollen joint count.
    - Dactylitis assessment.
    - Enthesitis assessment (SPARCC Enthesitis Index).
    - Bath Ankylosing Spondylitis Metrology Index (BASMI), including tragus-to-wall distance, lumbar flexion (Schöber index), lumbar lateroflexion, cervical rotation and intermalleolar distance; chest expansion.
    - Psoriasis skin evaluation (if applicable).
    - Physician global assessment of disease activity (0-10 numerical rating scale).
- Laboratory investigation:
    - Disease activity: ESR, CRP.

    - Safety: peripheral blood count, serum creatinine, uric acid, liver function tests (ALT, gamma-GT, Alkaline Phosphatase, LDH), Creatine Kinase.
- Trial continuation evaluation based on clinical remission (yes/no) at week 48 and potential sustained clinical remission (at week 36 and 48):
    - Sustained clinical remission: stop open-label golimumab, roll-over into SPARTACUS Phase B – Visit 1
    - Clinical remission (but not yet sustained): continuation of open-label golimumab 50 mg SC every 4 weeks.
    - No clinical remission *and* "PASSI"-yes: continuation of open-label golimumab 50 mg SC every 4 weeks with the addition of "commercial methotrexate" (reimbursed, standard-of-care).
    - No clinical remission *and* "PASSI"-no: study discontinuation, further (standard-of-care) treatment at the discretion of the treating rheumatologist.
- For patients continuing in SPARTACUS Phase A: dispensation of study drug:
    - Administration of Golimumab injection at study site.
    - Dispensation of Golimumab injections for week 52 and week 56 administration at home. Education regarding self-injection.
    - Prescription of "commercial methotrexate" (dose at the discretion of the treating rheumatologist).

Phase A – Visits 12: WEEK 60 – END OF PHASE A VISIT or EARLY DISCONTINUATION VISIT (+/- 1 week)

- Assessment of adverse events.
- Tuberculosis Questionnaire.
- Current medication (dose and duration).
- Study drug accountability.
- Patient reported outcomes (see Addendum 7):
    - Patient global assessment of disease activity (0-10 numerical rating scale).
    - Patient global assessment of pain (0-10 numerical rating scale).
    - Bath Ankylosing Spondylitis Disease Activity Index (BASDAI).
    - Bath Ankylosing Spondylitis Functional Index (BASFI).
    - Assessment of SpondyloArthritis international Society (ASAS) Health Index (ASAS-HI).
    - "Health Economic Evaluation": EuroQoL 5 dimensions, co-morbidity Index (SCQ) and healthcare utilization and productivity (in the past 3 months)
- Targeted physical examination.
- Vital signs (blood pressure, heart frequency).
- Weight.
- Smoking/alcohol status
- Rheumatological examination (see Addendum 5):
    - 78-Tender and 76-swollen joint count.
    - Dactylitis assessment.
    - Enthesitis assessment (SPARCC Enthesitis Index).
    - Bath Ankylosing Spondylitis Metrology Index (BASMI), including tragus-to-wall distance, lumbar flexion (Schöber index), lumbar lateroflexion, cervical rotation and intermalleolar distance; chest expansion.

  - Psoriasis skin evaluation (if applicable).
  - Physician global assessment of disease activity (0-10 numerical rating scale).
- Laboratory investigation:
  - Disease activity: ESR, CRP.
  - Safety: peripheral blood count, serum creatinine, uric acid, liver function tests (ALT, gamma-GT, Alkaline Phosphatase, LDH), Creatine Kinase.
- Trial continuation evaluation:
  - Open-label golimumab monotherapy group (decision based on sustained clinical remission at week 48 and 60:
    - Sustained clinical remission: stop open-label golimumab, roll-over into SPARTACUS Phase B – Visit 1
    - No sustained clinical remission: study discontinuation, further (standard-of-care) treatment at the discretion of the treating rheumatologist.
  - Open-label golimumab with “commercial methotrexate” group: study discontinuation, further (standard-of-care) treatment at the discretion of the treating rheumatologist.

Phase A – UNSCHEDULED VISIT

- Assessment of adverse events.
- Current medication (dose and duration).
- Patient reported outcomes (see Addendum 7):
  - Patient global assessment of disease activity (0-10 numerical rating scale).
  - Patient global assessment of pain (0-10 numerical rating scale).
  - Bath Ankylosing Spondylitis Disease Activity Index (BASDAI).
- Targeted physical examination.
- Rheumatological examination (see Addendum 5) at the discretion of the investigator:
  - 78-Tender and 76-swollen joint count.
  - Dactylitis assessment.
  - Enthesitis assessment (SPARCC Enthesitis Index).
  - Bath Ankylosing Spondylitis Metrology Index (BASMI), including tragus-to-wall distance, lumbar flexion (Schöber index), lumbar lateroflexion, cervical rotation and intermalleolar distance; chest expansion.
  - Psoriasis skin evaluation (if applicable).
- Laboratory investigation at the discretion of the investigator

11.4.2 ‘SPARTACUS Phase B’

Systematic Follow-Up Visits

	Visit	Week	Window	Description
Phase B	1	0	-	Phase A “Roll-over” visite
Phase B	2	12	±1 week	Follow-Up Phase A adverse events
Phase B	3	24	±1 week	
Phase B	4	36	±1 week	

Phase B	5	48	±1 week	
Phase B	6	72	±2 weeks	
Phase B	7	96	±2 weeks	
Phase B	8	120	±2 weeks	
Phase B	9	144	±2 weeks	Final study visit

- Assessment of significant adverse events, extra-articular manifestations and / or relevant comorbidities.
- Current medication (dose and duration).
- Patient reported outcomes (See Addendum 7):
  - Patient global assessment of disease activity (0-10 numerical rating scale).
  - Patient global assessment of pain (0-10 numerical rating scale).
  - Bath Ankylosing Spondylitis Disease Activity Index (BASDAI).
  - Bath Ankylosing Spondylitis Functional Index (BASFI).
  - Health Assessment Questionnaire (for SpA) (HAQ(-SpA)).
  - Assessment of SpondyloArthritis international Society (ASAS) Health Index (ASAS-HI).
  - "Health Economic Evaluation": co-morbidity Index (SCQ), EuroQoL 5 dimensions and validated cost questionnaires (healthcare utilization in the past 6 months)
- Targeted physical examination.
- Weight.
- Smoking/alcohol status
- Rheumatological examination (see Addendum 5):
  - 78-Tender and 76-swollen joint count.
  - Dactylitis assessment.
  - Enthesitis assessment (SPARCC Enthesitis Index).
  - Bath Ankylosing Spondylitis Metrology Index (BASMI), including tragus-to-wall distance, lumbar flexion (Schöber index), lumbar lateroflexion, cervical rotation and intermalleolar distance; chest expansion.
  - Psoriasis skin evaluation (if applicable).
  - Physician global assessment of disease activity (0-10 numerical rating scale).
- Laboratory investigation:
  - Disease activity: ESR, CRP.
  - Safety (only at the Phase B – Visit 2 – Week 12 visit): peripheral blood count, serum creatinine, liver function tests (ALT, Gamma-GT, Alkaline Phosphatase, LDH), creatine kinase.
  - Research samples (Visit 1 and Visit 2)
- Flare vs. (sustained) drug-free remission evaluation:
  - Remission: continuation in SPARTACUS Phase B
  - Flare: discontinuation from SPARTACUS Phase B; start of (standard-of-care) treatment at the discretion of the treating rheumatologist.

Unscheduled Flare Identification Visit(s)

- Assessment of significant adverse events, extra-articular manifestations and / or relevant comorbidities.
- Current medication (dose and duration).
- Patient reported outcomes (see Addendum 7):

  - Patient global assessment of disease activity (0-10 numerical rating scale).
  - Patient global assessment of pain (0-10 numerical rating scale).
  - Bath Ankylosing Spondylitis Disease Activity Index (BASDAI).
  - Bath Ankylosing Spondylitis Functional Index (BASFI).
  - Health Assessment Questionnaire (for SpA) (HAQ(-SpA)).
  - Assessment of SpondyloArthritis international Society (ASAS) Health Index (ASAS-HI).
  - "Health Economic Evaluation": EuroQoL 5 dimensions, co-morbidity Index (SCQ) and healthcare utilization in the past 6 months
- Targeted physical examination.
- Weight.
- Rheumatological examination (see Addendum 5):
  - 78-Tender and 76-swollen joint count.
  - Dactylitis assessment.
  - Enthesitis assessment (SPARCC Enthesitis Index).
  - Bath Ankylosing Spondylitis Metrology Index (BASMI), including tragus-to-wall distance, lumbar flexion (Schöber index), lumbar lateroflexion, cervical rotation and intermalleolar distance; chest expansion.
  - Psoriasis skin evaluation (if applicable).
  - Physician global assessment of disease activity (0-10 numerical rating scale).
- Laboratory investigation:
  - Disease activity: ESR, CRP.
  - Safety: peripheral blood count, serum creatinine, liver function tests (ALT, Gamma-GT, Alkaline Phosphatase, LDH), creatine kinase.
- Flare vs. (sustained) drug-free remission evaluation:
  - Remission: continuation in SPARTACUS Phase B
  - Flare: discontinuation from SPARTACUS Phase B; start of (standard-of-care) treatment at the discretion of the treating rheumatologist.

Flare Follow-Up Visit/phone call (3 months after Flare ID visit +/-1 month)

- Current medication (dose and duration).

Flowchart

Schedule of planned study activities per visit for SPARTACUS Phase A

Protocol Activity	V1A	V1B	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	UNS
	scr	Biopt	W0	W4	W8	W12	W16	W20	W24	W28	W36	W48	W60	
Informed Consent	x													
Inclusion/Exclusion crit	x	x	x											
synovial biopsy & Ultrasound		x												
Anamnesis[a]	x													
Current Medication	x		x	x	x	x	x	x	x	x	x	x	x	X
Adverse Events			x	x	x	x	x	x	x	x	x	x	x	X
Latent TB screening[b]	x					x			x		x	x	x	
Patient disease activity & pain NRS	x		x	x	x	x	x	x	x	x	x	x	x	X
BASDAI			x	x	x	x	x	x	x	x	x	x	x	X
BASFI, ASAS-HI, Health economic evaluations			x			x			x		x	x	x	
HAQ-SpA			x						x			x		
Post biopsy questionnaire		x												
(Targeted) Physical examination[f]	x		x	x	x	x	x	x	x	x	x	x	x	X
Vital Signs	x					x			x		x	x	x	
Length (only at screening), weight	x					x			x		x	x	x	
Smoking/alcohol status	x					x			x		x	x	x	
76SJC/78TJC, dactylitis, enthesitis (SPARCC)	x		x	x	x	x	x	x	x	x	x	x	x	X
BASMI, chest expansion, Psoriasis assessment			x			x			x		x	x	x	X
Physician global NRS	x					x			x		x	x	x	
HLA B27[c], anti-CCP AB[d], HBV[i], HCV[i], HIV[i], CMV IgG[i]	x													
Safety Lab tests[e]	x[e]			x	x	x	x	x	x	x	x	x	x	X
ESR, CRP	x			x	x	x	x	x	x	x	x	x	x	X
Serum Pregnancy Testing	x													
Research samples[g]		x	x[h]			x			x					
PASSI						x					x	x		
Assessment of clinical remission status						x			x		x	x	x	
Study drug admin/dispensation			x	x	x	x	x	x	x	x	x	x	x	
Study drug accountability				x	x	x	x	x	x	x	x	x	x	

[a] Demographic data, symptom duration, medical history, past anti-rheumatic treatment, family history
[b] v1A: chest X-ray (if not performed within the last 3 months), TB test (Mantoux PPD-test or Quantiferon), TB questionnaire; other visits: only TB questionnaire
[c] If not known
[d] if not determined within the last 12 months
[e] At v1A (for visit 1A: results of tests performed within the last month are allowed), week 24, week 36, week 48, week 60: peripheral blood count, serum creatinine, uric acid, liver function tests (ALT, GGT, AP, LDH), CK
At week 4, week 12, week 28: peripheral blood count, serum creatinine, ALT
At week 8, week 16, week 20: at the discretion of the treating rheumatologist
At the unscheduled visit: at the discretion of the treating rheumatologist
[f] Full physical exam at screening, targeted physical exam at the other visits
[g] 4 x 8ml blood-CPT (the synovial biopsy sampling units will also collect 10ml serum; at week 12: only 10ml serum; ZNA Jan Palfijn will only collect serum at BL)
[h] Only if no samples taken at visit 1B
[i] if not determined within the last 3 months

Schedule of planned study activities per visit for SPARTACUS Phase B

Protocol Activity	V1[a] Week 0	V2 Week 12	V3-9 Every 12/24 weeks[d]	Unscheduled flare identification visit	Flare follow-up visit (phone call)
Inclusion/Exclusion	x				
Current Medication		x	x	x	x
Adverse Events		x	x	x	
Patient Reported Outcomes[b]		x	x	x	
Targeted physical exam		x	x	x	
Weight		x	x	x	
Smoking/alcohol status		x	x		
76SJC/78TJC		x	x	x	
Dactylitis		x	x	x	
Enthesitis (SPARCC)		x	x	x	
BASMI, chest expansion		x	x	x	
Psoriatic skin evaluation (if applicable)		x	x	x	
Physician global NRS		x	x	x	
Lab tests: ESR, CRP		x	x	x	
Safety Lab tests[c]		x		x	
Research samples[e]	x	x			
Determination of Flare versus remission status		x	x	x	

[a] V1 = phase A 'Roll-over' visit, combined with the phase A visit in which sustained remission was obtained

[b] Patient global assessment of disease activity NRS, patient global assessment of pain NRS, BASDAI, BASFI, HAQ-SpA, ASAS-HI, Health economic evaluations

[c] peripheral blood count, serum creatinine, liver function tests (ALT, GGT, AP, LDH), creatinine kinase

[d] at year 1 every 12 weeks: week 24, week 36, week 48

at years 2-3 every 24 weeks: week 72, week 96, week 120, week 144

[e] 4 x 8ml blood-CPT (UZ Ghent and UZ Leuven also collect 10ml serum)

12 Biological samples

Laboratory tests as indicated in the trial protocol will be performed by the local laboratory of the trial site. As patients will be treated with active medication in both trial arms during SPARTACUS Phase A, all efficacy and safety laboratory samples are considered to be standard-of-care (from screening until 12 weeks after last study administration); they will be performed according to (inter)national clinical practice guidelines. At SPARTACUS Phase A – Visit 1 (screening), there will also be a standard-of-care analysis of HLA B27 (if not known), anti-CCP antibodies (if not determined in the last 12 months), and if not determined in the last 3 months: Hepatitis B, Hepatitis C,HIV and CMV IgG.

During SPARTACUS Phase B ("drug-free remission period") efficacy laboratory samples will be collected at the designated timepoints; they will also be analysed at the local laboratory.

During the Spartacus trial, research samples (i.e. synovial tissue samples, blood-CPT and serum samples) will be collected, pseudonimized and stored in the "SPARTACUS Biobank".

The synovial tissue samples taken at UZ Ghent and UZ Leuven will be processed and stored at MRB Ghent and the Translational Cell & Tissue Research Lab KU Leuven respectively according to the Spartacus LAB SOP: 'Synovial biopsy tissue Freezing' and the Spartacus LAB SOP: 'Synovial tissue_FFPE'. The synovial tissue samples taken at the ZNA Jan Palfijn Hospital will be sent immediately to MRB Ghent to be processed and stored according to the above-mentioned SOPs. Afterwards the synovial tissue samples will be shipped in batch to the VIB Inflammation Research Center Ghent for further downstream analysis.

The blood-CPT samples taken at UZ Ghent and UZ Leuven will be processed in MRB Ghent and the Translational Cell & Tissue Research Lab KU Leuven respectively, according to the Spartacus LAB SOP: 'CPT Protocol for isolation of PBMC' and afterwards prepared for storage according to the Spartacus LAB SOP: 'PBMC Freezing'. These samples will then be stored at MRB Ghent and the Translational Cell & Tissue Research Lab KU Leuven respectively. The blood-CPT samples taken at the other participating centers will be processed at the local lab according to the Spartacus LAB SOP: 'Preparing CPT blood tubes for shipping' and shipped to MRB Ghent. They will be further processed in MRB Ghent according to the Spartacus LAB SOP: 'CPT Protocol for isolation of PBMC' and afterwards prepared for storage according to the Spartacus LAB SOP: 'PBMC Freezing'. For the further downstream analysis, the required fraction will be shipped in batch from MRB Ghent to the VIB center in Ghent and Translational Cell & Tissue Research Lab KU Leuven. The remainder of the PBMCs (i.e., the fraction that is left after analysis in the Translational Cell & Tissue Research Lab KU Leuven and VIB) will be shipped (back) to MRB Ghent.

The blood serum samples taken at UZ Ghent and UZ Leuven will be processed in MRB Ghent and the Translational Cell & Tissue Research Lab KU Leuven respectively according to the Spartacus LAB SOP: 'Serum collection and storage'. Afterwards these samples will be shipped in batch to the MRB Ghent for further downstream analysis by

VIB. For the patients that undergo a synovial biopsy at the ZNA Jan Palfijn Hospital, blood serum samples will also be taken during this biopsy visit and shipped to MRB Ghent for further processing and downstream analysis by VIB as described above.

Samples will be stored for max. 10 years upon collection of each individual sample until downstream analyses (as defined in the protocol) are performed.

Unused, leftover material will be transferred to the “Biobank van menselijk lichaamsmateriaal van patiënten met reumatische en/of musculoskeletale aandoeningen en gezonde controles” (under supervision of Prof. Dr. Dirk Elewaut) upon appropriate written informed consent.

13 Statistical considerations

13.1 Sample size calculation, power calculation, significance level

The primary end point of SPARTACUS is the percentage of patients going into remission.
The sample size for SPARTACUS was calculated based on the percentage of patients that went into clinical remission (TNFi versus placebo) in the CRESPA trial: 75% in the TNFi group versus 20% in the placebo group. Currently, there are no data in peripheral Spondyloarthritis regarding the percentage of patients going into clinical remission under a treatment with Methotrexate. There are also no data regarding differences in treatment effect regarding symptom duration: <3 months versus >3 months. Therefore, we estimated an expected 30% difference in percentage of patients going into clinical remission between both groups (MTX versus TNFi): 20% versus 50%. A sample size of at least 45 patients in each group is sufficient to obtain 80% power or more to detect a difference in proportions of 30% (20% versus 50%) at the alpha level of 5% using a Fisher's exact test.

13.2 Type of statistical methods and team

The primary endpoint of SPARTACUS is to compare the proportion of patients achieving clinical remission, defined as absence of arthritis, enthesitis and dactylitis at week 24, in the “TNFi induction”-group versus the “csDMARD Step-up” group. This will be done using appropriate statistical methods. Statistical tests and evaluations will be performed by Philippe Carron and Filip Van den Bosch (Ghent University Hospital, Department of Rheumatology); where appropriate, expert statistical advice will be sought (Roos Colman, Ghent University Hospital, Department of Medical Statistics).

In addition to this, several secondary endpoints will be evaluated:

- Comparison between the “TNFi induction” group and the “csDMARD Step-up” group regarding:

    - Achievement of “sustained clinical remission” at week 24 (and week 36 for the patients remaining on blinded study medication).
    - Improvement from baseline to week 12 and 24 in individual clinical assessments (78-Tender Joint Count, 76-Swollen Joint Count, Dactylitis Count, SPARCC Enthesitis Score) and composite scores (ASDAS: Axial Spondyloarthritis Disease Activity Score).
    - Improvement from baseline to week 12 and 24 in patient-reported outcomes (Patient global assessment of disease activity and pain, BASDAI, BASFI, ASAS Health Index.
    - Improvement from baseline to week 12 and 24 in inflammatory parameters (ESR, CRP).
    - Changes in concomitant NSAID intake (NSAID-index) and “escape” intra-articular glucocorticoid injections between baseline and week 24
- Difference in occurrence of (serious) adverse events (AEs) and AEs of specific interest between the 2 treatment strategies from baseline to week 24 (and week 36 for patients remaining on blinded study medication). Descriptive analysis of the number and type of adverse events between both strategies
- Percentage of patients achieving (sustained) clinical remission with open-label golimumab treatment after failure of the initial randomized, blinded treatment strategy.
- Exploration of difference in percentage of patients that reach (sustained) clinical remission according to symptom duration (<3 months versus ≥3 month and <12 months). The interaction between treatment group and symptom duration as a continuous predictor will also be analyzed to investigate the effect of symptom duration with regard to reaching the specified primary and secondary outcomes.
- For patients in SPARTACUS Phase B (drug-free remission period):
    - Exploration of the duration of drug-free remission.
    - Time to (documented) pSpA disease flare.
    - Time to restart of “standard-of-care” pSpA treatment.
    - Exploration of clinical parameters that could be predictive for reaching (sustained) clinical remission and/or flare.
- Correlation between the “Patient Acceptable Signs & Symptoms Improvement” (“PASSI”) and different clinical assessments, laboratory values and patient-reported outcomes (or combinations thereof).

14 Data handling

14.1 Method of data collection

An electronic data capture (EDC) system, i.e. REDCap, will be used for data collection. REDCap is provided and maintained by Vanderbilt University; a license for use was granted to the Health, Innovation and Research Institute (HIRUZ). REDCap is a web-based system.

14.1.1 Case Report Form (CRF)

Only the data required by the protocol are captured in the eCRF. The eCRFs and the database will be developed, based on the protocol. The final eCRF design will be approved by the CI.
The study site staff is responsible for data entry in REDCap.
Subjects that are included in the trial, will be assigned a unique study number upon their registration in REDCap. On all documents submitted to the sponsor or CI, subjects will pseudonomised. REDCap has built-in options for univariate alerts, such as valid-value, valid-range, and missing-value alerts.
Data reported on each eCRF should be consistent with the source data. If information is not known, this must be clearly indicated on the eCRF. All missing and ambiguous data will be clarified.
All data entries and corrections will only be performed by study site staff, authorised by the Investigator. Data will be reviewed by trained personnel (monitor, data manager) and any errors or inconsistencies will be clarified.

14.1.2 Data directly collected in the eCRF (no source available)

For this trial, we use ePRO's where the participants complete surveys in the hospital on a tablet of the hospital and connected to a secured hospital network. The ePRO can be opened by using a survey link that is unique per participant and per visit.
The participant will need to log in to the survey before he/she can complete the survey.

14.2 Data storage

The data is accessed through a web browser directly on the secure REDCap server. The server is hosted within the Ghent University Hospital campus and meets hospital level security and back-up requirements.

Privacy and data integrity between the user's browser and the server is provided by mandatory use of Transport Layer Security (TLS), and a server certificate issued by TERENA (Trans-European Research and Education Networking Association). All trial sites will have access to REDCap. Site access is controlled with IP restriction.

14.3 Archiving of data

The investigator and sponsor specific essential documents will be retained for at least 25 years. At that moment, it will be judged whether it is necessary to retain them for a longer period, according to applicable regulatory or other requirements.

Once all subjects have completed the study visits and the study was closed the study documents will be archived. Documents will be stored at MERAK N.V. BELGIE Steenhoevestraat 6 - 2800 Mechelen - tel. +32 (0)15 28 40 60

14.4 Access to data

The investigators and institutions involved in the trial will permit clinical trial-related monitoring, audits and regulatory inspections (including provision of direct access to source data and documents).

Login in REDCap is password controlled. Each user will receive a personal login name and password and will have a specific role which has predefined restrictions on what is allowed in REDCap. Furthermore, users will only be able to see data of subjects of their own site. Any activity in the software is traced and transparent via the audit trail.

15 Safety

15.1 Definitions

Adverse Events and Adverse Reactions	
Term	**Definition**
Adverse Event (AE)	Any untoward medical occurrence in a subject to whom a medicinal product is administered and which does not necessarily have a causal relationship with this treatment.
Unexpected Adverse Event	An adverse event of which the nature or severity is not consistent with the Reference Safety Information (RSI) of the product (i.e. the applicable information in the Investigator's Brochure (IB) for an investigational medicinal product which is not authorised or in the Summary of Product Characteristics (SmPC) for an authorised investigational medicinal product).
Adverse Reaction (AR)	An untoward and unintended response in a subject to an investigational medicinal product which is related to any dose administered to that subject. The phrase "response to an investigational medicinal product" means that a causal relationship between a study medication and an AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out. All cases judged by either the reporting medically qualified professional or the Sponsor as having a reasonable suspected causal relationship to the study medication qualify as adverse reactions.
Serious Adverse Event (SAE)	Any untoward medical occurrence that: • requires inpatient hospitalisation or prolongation of existing hospitalisation; • results in persistent or significant disability/incapacity; • results in a congenital anomaly or birth defect; • is life-threatening; *or* • results in death. Other important medical events may also be considered serious if they jeopardise the subject or require an intervention to prevent one of the above consequences. NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
Suspected Unexpected Serious Adverse Reaction (SUSAR)	A serious adverse reaction, the nature, severity or outcome of which is not consistent with the Reference Safety Information (RSI).

NB: to avoid confusion or misunderstanding of the difference between the terms "serious" and "severe", the following note of clarification is provided: "Severe" is often used to describe intensity of a specific event, which may be of relatively minor medical significance. "Seriousness" is the regulatory definition supplied above.

Attributions	
Term	**Definition**
Not related	An adverse event which is not related to the use of the drug.
Unlikely related	An adverse event for which an alternative explanation is more likely - e.g. concomitant drug(s), concomitant disease(s), and/or the relationship in time suggests that a causal relationship is unlikely.
Possibly related	An adverse event which might be due to the use of the drug. An alternative explanation - e.g. concomitant drug(s) or concomitant disease(s) - is inconclusive. The relationship in time is reasonable; therefore the causal relationship cannot be excluded.
Probably related	An adverse event which might be due to the use of the drug. The relationship in time is suggestive (e.g. confirmed by dechallenge). An alternative explanation is less likely - e.g. concomitant drug(s) or concomitant disease(s).
Definitely related	An adverse event which is listed as a possible adverse reaction and cannot be reasonably explained by an alternative explanation - e.g. concomitant drug(s) or concomitant disease(s). The relationship in time is very suggestive (e.g. it is confirmed by dechallenge and rechallenge).

An adverse event is considered associated with the use of the drug if the attribution is 'possibly', 'probably' or 'definitely related'.

15.2 Reporting requirements

List of abbreviations

AE	Adverse Event
CA	Competent Authority
EC	Ethics Committee
RA	Regulatory authorities
SAE	Serious Adverse Event
SSAR	Suspected Serious Adverse Reaction
SUSAR	Suspected Unexpected Serious Adverse Reaction

15.2.1 AE reporting

Adverse events (AE)
The following information will be recorded:

- nature of adverse event
- date and time of occurrence and disappearance
- intensity: mild, moderate or severe
- frequency: once, continuous or intermittent
- decision regarding study: continuation or withdrawal
- relation to the study medication (see below)

AE's will be recorded from the first drug administration until the patient's last study visit. Special attention will be given to those subjects who have discontinued the trial for an AE, or who experienced a severe or a serious AE.

15.2.2 SAE reporting

Medical events that occur between signing of the Informed Consent and the first intake of trial medication will be documented on the medical and surgical history section and concomitant diseases page of the eCRF.
SAE's occurring within a period of 30 days following the last intake of trial medication will also be handled as such if spontaneously reported to the investigator.

All serious adverse events (SAE) (initial and follow up information – except for those, described in 15.5 and events, described in section 15.2.4, and pregnancies occurring during clinical trial must be reported by the local Principal Investigator within 24 hours after becoming aware of the SAE to:

- The national coordinating Investigator
- HIRUZ of the University Hospital Ghent who report to the central EC
- The designated contact person of the Marketing Authorisation Holder (MAH) or producer of the medicinal (investigational) product

This reporting is done by using the appropriate SAE form. For the contact details, see below.

It is the responsibility of the local Principal Investigator to report the local SAE's to the local EC.

15.2.3 SUSAR reporting

In case the Coordinating Investigator/sponsor, in consultation with HIRUZ CTU, decides the SAE is a SUSAR (considering the seriousness, probability of harmfulness and unexpectedness), HIRUZ CTU will report the SUSAR to the EMA, through the Eudravigilance (EV) database within the timelines as defined in European legislation. In case of a life-threatening SUSAR the sponsor should report at least the minimum information as soon as possible and in any case no later than 7 calendar days after being made aware of the case. In case of a non-life-threatening SUSAR the reporting process must be completed within 15 calendar days.

Coordinating Investigator informs local PIs of safety profile changes, not of individual SUSAR reports. For example, information derived from SUSAR reports could be

provided via investigators' letters including both an updated benefit-risk evaluation and risk mitigation measures.

15.2.4 Other reporting requirements

NA

15.3 List of contact details for safety reporting

The first report of a serious adverse event may be made by telephone, e-mail or facsimile (FAX).

Contact details of HIRUZ:

[redacted]

Contact details of the National Coordinating Investigator:

[redacted]

Contact details of the producer of blinded methotrexate:

[redacted]

Contact details of the MAH/producer of methotrexate matching placebo:

[redacted]

Contact details of MAH/producer of open label and blinded Golimumab and matching placebo :

- Up until 30-Sep-2024: Merck Global Safety should be informed by fax using the 1301.10_IIS AE Fax Form and the Global Safety Intake Form

  [redacted]

The investigator must provide the minimal information: i.e. trial number, subject's initials and year of birth, medication code number, period of intake, nature of the adverse event and investigator's attribution.
This report of a serious adverse event by telephone must always be confirmed by a written, more detailed report. For this purpose the appropriate SAE form will be used. Pregnancies occurring during clinical trials are considered immediately reportable events. They must be reported as soon as possible using the same SAE form. The outcome of the pregnancy must also be reported.

If the subjects are not under 24-hour supervision of the investigator or his/her staff (out-patients, volunteers), they (or their designee, if appropriate) must be provided with a "trial card" indicating the name of the investigational product, the trial number, the investigator's name and a 24-hour emergency contact number.

15.4 Flowchart reporting

Type of Adverse Event	Action(s) be taken
AE	List all relevant AEs per subject in the patient's file and add this information to the CRF.
SAE	• Notify to HIRUZ CTU and CI within 24 hours after becoming aware of the SAE; • Add the SAE to a list that will be reported yearly (see section 15.7); • Add the SAE in the CRF (please take into account section 15.5).
SUSAR	• Notify to HIRUZ CTU and CI within 24 hours after becoming aware of the SAE; • The CI/sponsor will assess the causality and unexpectedness of the SAE to determine if it qualifies as a SUSAR. • HIRUZ CTU submits the SUSAR to the EMA (through EV database) after communication with the CI; • Study team of CI informs company that provides the IMP (as stipulated in the agreement). • Coordinating Investigator informs local PIs of safety profile changes.

Reporting to the local ethics committee of SAEs and SUSARs remains the responsibility of the PI and should be done in accordance with the requirements of the local institution's procedure.

15.5 Events excluded from reporting

NA

15.6 Data Safety Monitoring Board (DSMB)

All IMP is authorised and used in current practice. Considering the known safety profile of the IMP and trial design, a DSMB is not foreseen.

15.7 Annual Safety Report (ASR)

The Coordinating Investigator will provide an ASR once a year throughout the entire duration of the clinical study, or on request, to the EMA.. This ASR will include all SAEs and relevant safety information regarding all investigational medicinal products, used in this trial.

The report will be submitted no later than 60 calendar days after the ASR Data Lock Point (DLP). The first DLP is 1 year after the first date of the sponsor's authorisation to conduct the clinical trial. Subsequently, the ASR will be submitted each year (+ maximum 60 days) until the trial is declared ended.

The Coordinating Investigator provides the ASR to all local PIs.

15.8 Follow-up after an adverse reaction

After the initial AE/SAE report, the investigator must proactively follow each participant at subsequent visits/contacts. The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested to elucidate the nature and/or causality of the AE or SAE as fully as possible. All SAEs as defined in Section 15.1, will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost for follow-up (defined in Section 8.3)

16 Monitoring, audits and inspections

16.1 Monitoring

16.1.1 General

Monitoring of the trial will be performed in compliance with GCP E6(R2) and the applicable regulatory requirements. The study team will be trained during an initiation visit by the monitor. A detailed description of the monitoring tasks can be found in the latest version of the (study-specific) 'Clinical Trial Monitoring Plan'.

16.1.2 Monitoring team

Monitoring services will be provided by HIRUZ CTU. All relevant contact details (e.g. primary contact person) can be found in the 'Clinical Trial Monitoring Plan'.

16.1.3 Scope

Monitoring services will consist of the following (non-exhaustive list):

- review of informed consents and the followed process;
- check on recruitment status;
- checking for protocol deviations/violations;
- checking GCP compatibility;
- check on safety reporting compliance;
- IMP handling and storage;
- review of study data.

More information can be found in the Clinical Trial Monitoring Plan.

16.2 Inspection

This trial can be inspected at any time by regulatory agencies during or after completion of the trial. Therefore access to all study records, including source documents, must be accessible to the inspection representatives. Subject privacy must be respected at all times, in accordance to GDPR, GCP and all other applicable local regulations.
The investigator/study team should immediately notify the sponsor if (s)he has been contacted by a regulatory agency concerning an upcoming inspection.

16.3 Deviation policy

Sponsor and all investigators agree to take any reasonable actions to correct protocol or other deviations/violations noted during monitoring/inspection, in consultation with the monitoring team. All deviations must be documented on the correct deviation log by the study team that is kept available at any time for monitoring/inspection purposes. Subject deviations must be reported in the eCRF. Site deviations and sponsor deviations must be reported on the paper Site Deviation Log and Sponsor Deviation Log, respectively, and each deviation has to be signed off. Under emergency circumstances, deviations from the protocol to protect the rights, safety or well-being of human subjects may take place without prior approval of the sponsor and the RA.

16.4 Serious breach to GCP and/or the protocol

A ‘serious breach’ means a breach likely to affect to a significant degree the safety and rights of a subject or the reliability and robustness of the data generated in the clinical trial.
Any deviation of the approved protocol version or the CTR that is likely to affect subject safety, data integrity and/or study conduct should be clearly documented on the applicable deviation log and will be communicated with the Coordinating Investigator, HIRUZ CTU and possibly the RA.
Please contact HIRUZ CTU immediately in case of a potential serious breach: [redacted]
The sponsor shall notify the RA about a serious breach of the CTR or of the version of the protocol applicable at the time of the breach through the EU portal without undue delay but not later than seven days of becoming aware of that breach.

Early termination of the trial (in a specific center or overall) may be necessary in case of major non-compliance.

The following items will be documented on the protocol deviation log: date of deviation, description of deviation, actions taken and classification of deviation. Deviations will be classified as minor or major. A minor protocol deviation is a deviation that does not affect the safety, rights or well-being of subjects or the quality of their data. A major protocol deviation is a deviation that affects safety, rights or well-being of subjects or quality of their data.

Any deviation that potentially interferes with and/or affects the efficiency and/or quality conduct of the study will be discussed by the monitor with the PI and will be documented on the monitoring report including a proposed plan of action for resolution if applicable.

16.5 Early termination

Early termination or suspension of the study or an investigational site may be necessary in case of major non-compliance, critical safety issues or premature trial discontinuation. This can occur at any time by the sponsor, principal investigator of the local site, EC or regulatory authority. In the event that the clinical investigation would be discontinued prematurely, all clinical investigation products will be retained, the terminating party shall justify its decision in writing and the sponsor will communicate (via Hiruz CTU) early termination, including the reason for early termination, to the EC and regulatory authority.

17 Ethical and legal aspects

17.1 Good Clinical Practice

The trial will be conducted in accordance with the latest version of the ICH E6 (R2) GCP guidelines, creating a standard for the design, conduct, performance, monitoring, auditing, recording, analyses and reporting of clinical studies that provides assurance that the data and reported results are accurate and that the rights, integrity and confidentiality of study subjects are protected.

17.2 Informed consent

Eligible subjects may only be included in the trial after providing written (witnessed, if needed) IEC-approved informed consent, or, if incapable of doing so, after such consent has been provided by a legally acceptable representative(s) of the subject. Informed consent must be obtained before conducting any study-specific procedures (as described in this protocol).
Prior to entry in the trial, the investigator must explain the trial and the implication(s) of participation to potential subjects and/or their legal representatives. Subjects will be informed that their participation is voluntary and that they may withdraw consent to participate at any time. Participating subjects will be told that their records may be accessed by competent authorities and by authorised persons without violating the confidentiality of the subject, to the extent permitted by the applicable law(s) and/or regulations. By signing the Informed Consent Form (ICF), the subjects or legally acceptable representatives are authorising such access.
After this explanation and before entry to the trial, written, dated and signed informed consent should be obtained from the subject or legally acceptable representative. The ICF should be provided in a language sufficiently understood by the subject. Subjects must be given the opportunity to ask questions.

The subject or legally acceptable representative will be given sufficient time to read the ICF and to ask additional questions. After this explanation and before entry to the trial, consent should be appropriately recorded by means of either the subject's or his/her legal representative's dated signature or the signature of an independent witness who certifies the subject's consent in writing. After having obtained the consent, a copy of the ICF must be given to the subject.

In case the subject or legally acceptable representative is unable to read, an impartial witness must attest the informed consent.
Subjects who are unable to comprehend the information provided can only be enrolled after consent of a legally acceptable representative.
The following information should be added to the electronic patient dossier (EPD):

- which version of the ICF was obtained;
- who signed the ICF;
- if sufficient time has been given to consider participation into the trial;
- which investigator obtained ICF with the date of signature;
- if a copy was provided to the subject;
- start and end of participation in the trial.

17.3 Approval of the study protocol

17.3.1 General

The protocol has been reviewed and approved by the RA. This trial cannot start before their approval has been obtained, a site initiation visit has been performed by the monitor and, if applicable, all necessary agreements are finalized.

17.3.2 Protocol modifications and urgent safety measures

Any substantial change or addition to the protocol can only be made in a written protocol modification that must be approved by the RA.
Only modifications that are intended to eliminate an apparent immediate safety threat to the participants may be implemented immediately.
Notwithstanding the need for approval of formal protocol modifications, the investigators are expected to take any immediate action, required for the safety of any subject included in this trial, even if this action represents a deviation from the protocol. These actions should always be notified to the sponsor without undue delay, in order for the sponsor to notify the RA.

17.4 Confidentiality and data protection

All study data will be handled in accordance with the law on General Data Protection Regulation (GDPR) and institutional rules (i.e. in accordance with the Belgian laws dated on 30-JUL-2018 and 22-AUG-2002).

The collection and processing of personal data from subjects enrolled in this trial will be limited to those data that are necessary to fulfill the objectives of the trial. These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations.
Appropriate technical and organisational measures to protect the personal data against unauthorised disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place. Sponsor and site personnel whose responsibilities require access to personal data agree to keep the identity of subjects confidential. In case of data security breach, local institution's procedures will be followed.
Site personnel informs the subject about the the processing of personal data and direct access for the investigator/institution to his or her original medical records (source data/documents) for trial-related monitoring, audit, Ethics Committee review and regulatory inspection. The subject is also informed about the data to other entities, if applicable.

All data will be Pseudonymised. Pseudonymisation *i*s the responsibility of the PI. Pseudonymisation can be done by the PI or any other medical practitioner–investigator appointed by the PI and legally authorised to do so (therapeutic relationship with the participant). The key for encryption and decryption of pseudonymised data is kept by the PI and other investigators authorised by the PI. Data is processed in an electronic, secure database (REDCap), in accordance with the technical and organisational security measures of the Ghent University Hospital.

Privacy and confidentiality of data generated in the future on stored samples will be protected by the same standards applicable to all other clinical data.
Stored samples will be [Choose from the list] throughout the sample storage and analysis process and will not be labeled with personal identifiers.

17.5 Liability and insurance

This study protocol is without prejudice to national and European Union law on the civil and criminal liability of the Sponsor, Coordinating Investigator, Principal Investigator(s) and other parties concerned.
The sponsor has entered into a no-fault insurance policy for this trial, in accordance with the relevant legislation (article 12 of the Belgian Law of 7 May 2017 and article 76 of the EU Regulation 536/2014).

18 Publication policy

The results of this study will be reported and published at conferences and in peer-reviewed clinical journals. The privacy of the subjects will be respected at all times. Authorship publications will follow the Uniform Requirement for Manuscripts Submitted to Biomedical Journals (International Committee of Medical Journal Editors, 2009), which states:

“Authorship credit should be based on (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; (3) final approval of the version to be published and (4) Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Authors should meet conditions 1, 2, 3 and 4.”

For further details , see http://www.icmje.org/recommendations/browse/roles-and-responsibilities/defining-the-role-of-authors-and-contributors.html.

For the SPARTACUS-trial the following additional criteria will be applicable with regard to publications concerning the clinical outcomes of the study:

- An investigator from a trial site that has included at least 1 (randomized) patient will be listed under the ”SPARTACUS-consortium” and in the acknowledgment section of the publication: their name will appear upon searching for publications in “Pubmed”.
- An investigator from a trial site that has included at least 5 (randomized) patients will be mentioned as co-author on the publications.
- A trial site that has included more than 10 (randomized) patients will be allowed to have 2 co-authors on the main publication.

Concerning the publication of the translational / basic science results, trial sites that have included more than 10 (randomized) patients will have 1 co-author on these publications.

A publication steering committee will be formed, consisting of Prof. Dr. Dirk Elewaut (VIB Ghent), Prof. Dr. Rik Lories (KU Leuven), Dr. Philippe Carron and Prof. Dr. Filip Van den Bosch (Ghent University hospital – coordinating clinical trial center). The steering committee will be in charge of the global publication strategy. After publication of the main study results, investigators from the different participating centers that have included at least 1 (randomized) patient will have the opportunity to submit proposals to the steering committee for ancillary analyses; this will be done via the standardized form in addendum 12. Ancillary analysis requests will be reviewed by the steering committee, which may ask for additional information or suggest alternative analyses. For specific research questions, the steering committee may decide to ask an additional review by external referees (e.g. for health economic analyses, …).

Signature page

SPondyloArthritis: inducing drug-free Remission by early TNF-Alpha bloCkade Under guidance of Single cell RNA sequencing and epigenetic profiling.

I certify that I will conduct the trial in compliance with the protocol, any modifications, GCP and the declaration of Helsinki, the CTR and all other applicable regulatory requirements.

Investigator:

Name:

Title:

Signature:

Date: _____

Investigator:

Name:

Title:

Signature:

Date: _____

Investigator:

Name:

Title:

Signature:

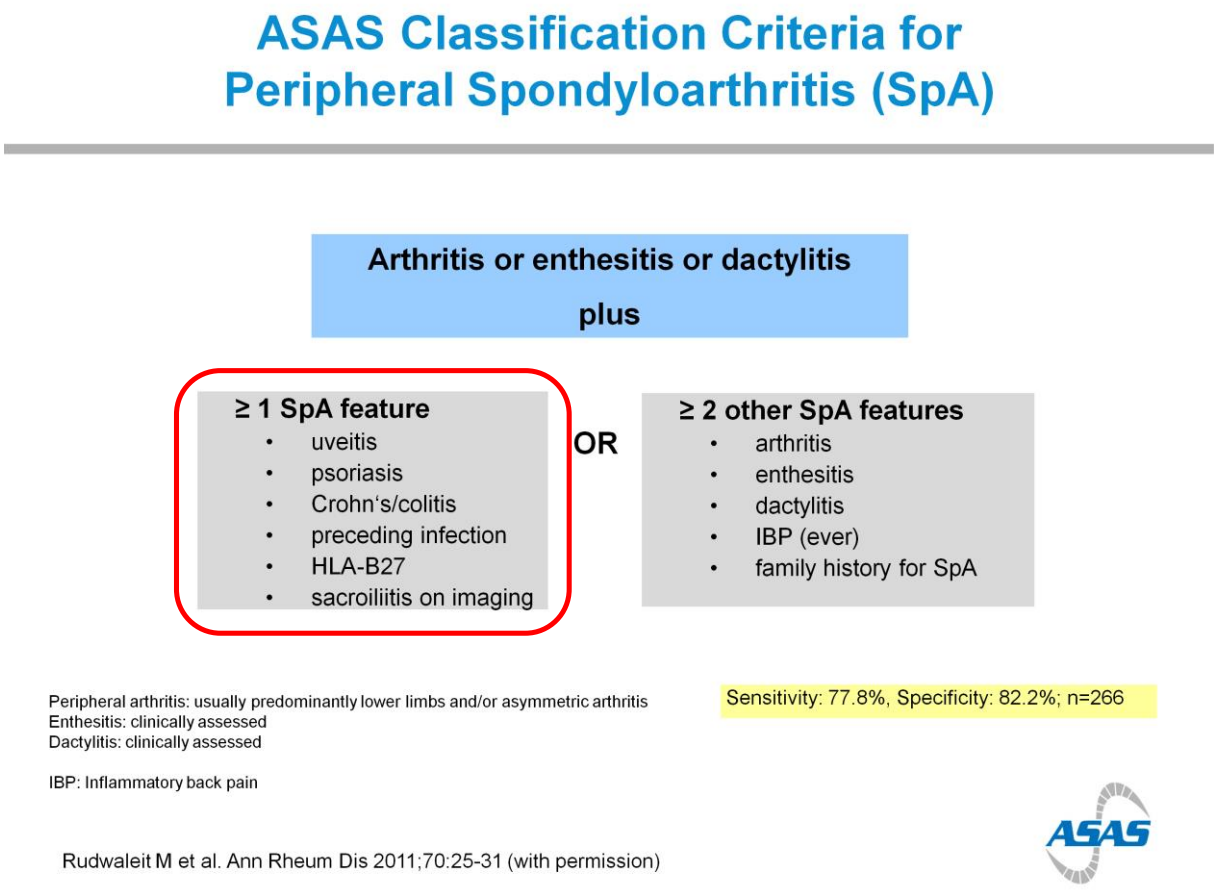
Date: _____

19 Addenda

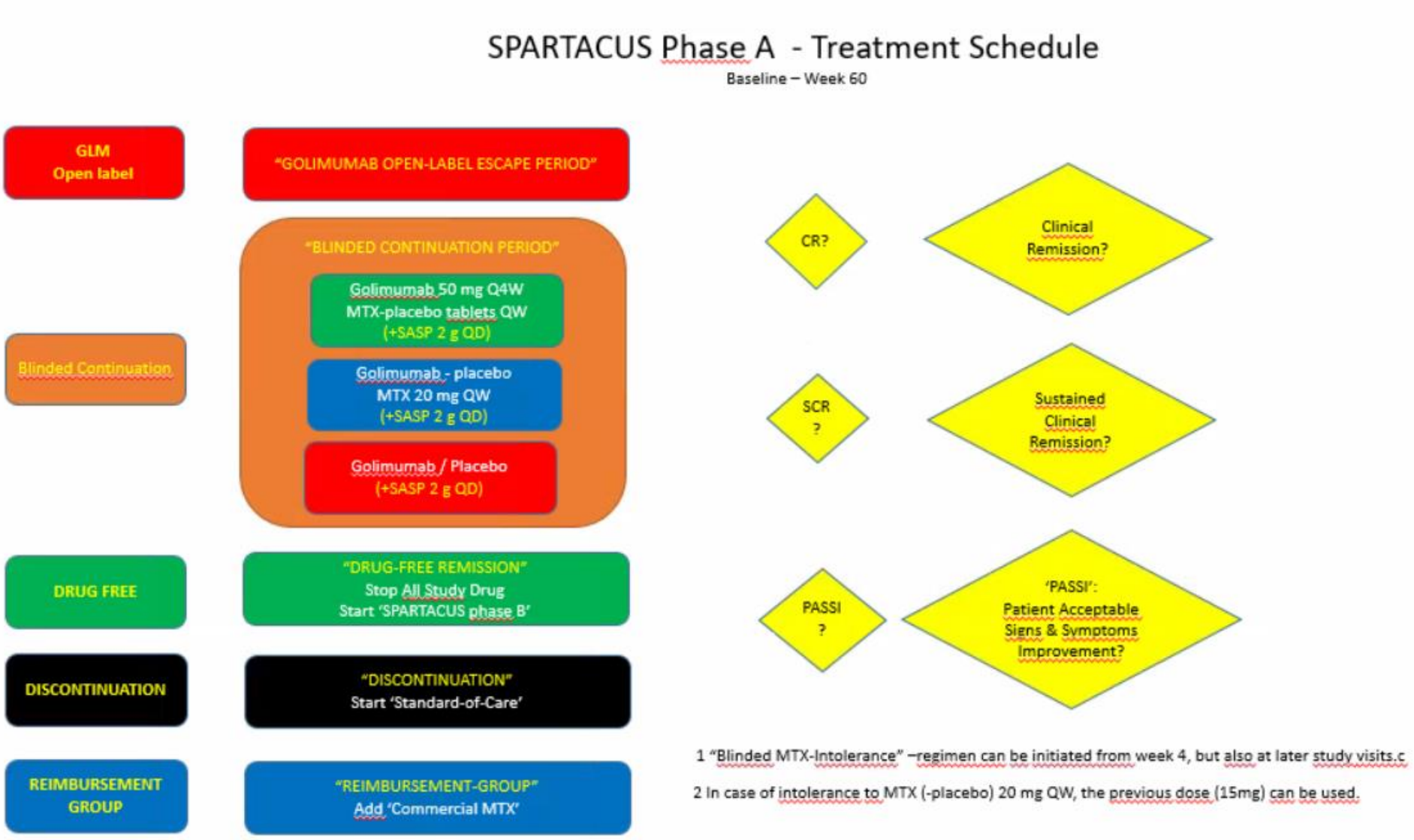
Addendum 1: ASAS (Assessment in SpondyloArthritis international Society) Classification Criteria

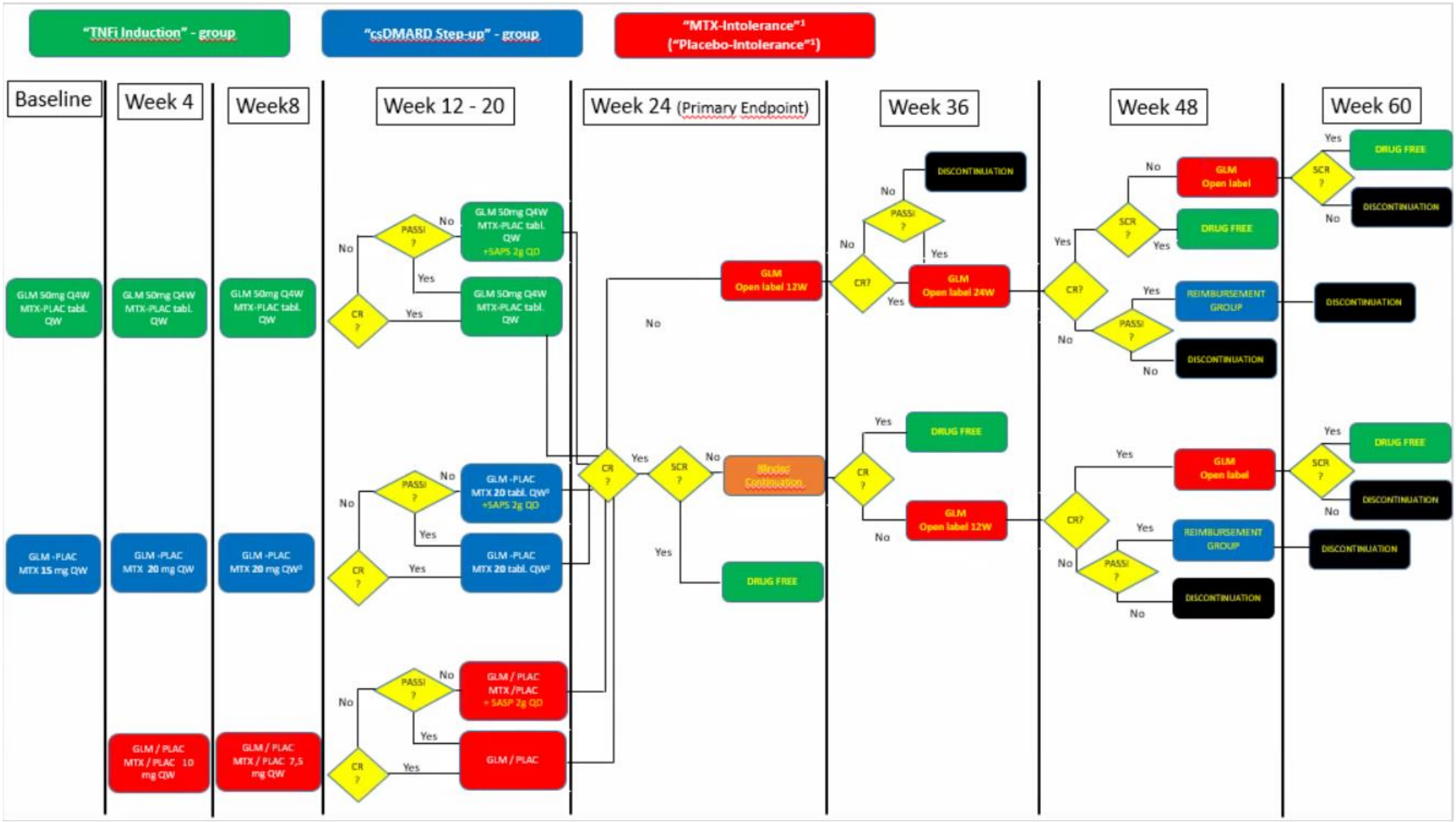
For SPARTACUS inclusion-purposes, classification of peripheral SpA patients will be done using the “left arm” of the criteria, requiring “arthritis or enthesitis or dactylitis” plus ≥1 specific SpA feature.

Patients only fulfilling the “right arm” of the criteria can be discussed with a coordinating investigator of UZ Ghent on an individual basis.



Addendum 2:
SPARTACUS Phase A (Remission Induction) Study Design




"TNFi Induction" - group
"csDMARD Step-up" - group
"MTX-Intolerance"[1]
("Placebo-Intolerance"[1])
Baseline
Week 4
Week8
Week 12 - 20
Week 24 (Primary Endpoint)
Week 36
Week 48
Week 60
GLM 50mg Q4W MTX-PLAC tabl. QW
GLM -PLAC MTX 15 mg QW
GLM / PLAC MTX / PLAC 10 mg QW
GLM -PLAC MTX 20 mg QW
GLM / PLAC MTX / PLAC 7,5 mg QW
PASS! ?
CR ?
SCR ?
CR?
GLM 50mg Q4W MTX-PLAC tabl. QW +SAPS 2g QD
GLM -PLAC MTX 20 tabl. QW[2] +SAPS 2g QD
GLM / PLAC MTX /PLAC + SASP 2g QD
GLM / PLAC
Blinded Continuation
GLM Open label 12W
GLM Open label 24W
DISCONTINUATION
DRUG FREE
GLM Open label
REIMBURSEMENT GROUP
Yes
No

Addendum 3:
Patient Acceptable Signs & Symptoms Improvement ("PASSI") Questionnaire

- Taking into account both efficacy and side effects, did you experience over the past 12 weeks enough improvement in signs and symptoms of your arthritis-enthesitis-dactylitis to consider continuation of the same treatment schedule for the next 12 weeks?"

- "Als u rekening houdt met zowel het effect als de bijwerkingen van het behandelingsschema dat u de voorbije 12 weken heeft gekregen, hebt u dan voldoende verbetering ervaren in de symptomen van uw artritis-enthesitis-dactylitis om de volgende 12 weken hetzelfde behandelingsschema aan te houden?"

Addendum 4:
Tuberculosis Questionnaire

1. Have you or an immediate family member or other close contact ever been diagnosed or treated for tuberculosis? □ No □ Yes

2. Have you lived in or had prolonged travels to countries in the following regions: □ No □ Yes

   - Africa
   - Eastern Europe
   - Asia
   - Russia
   - Latin America
   - Caribbean Islands

3. Have you lived or worked in a prison, refugee camp, homeless shelter, immigration center, or nursing home? □ No □ Yes

4. Have you, or an immediate family member, had any of the following problems for the past 3 weeks or longer: □ No □ Yes

   - Chronic Cough
   - Production of Sputum
   - Blood-Streaked Sputum
   - Unexpected Weight Loss
   - Fever
   - Fatigue/Tiredness
   - Night Sweats
   - Shortness of Breath

Addendum 5a:
Rheumatological Examinations
78-Tender and 76-Swollen Joint Count

Joint Count : Worksheet (Tender & Swollen Joint Count) : 1 = present,0 = absent, ND/NA

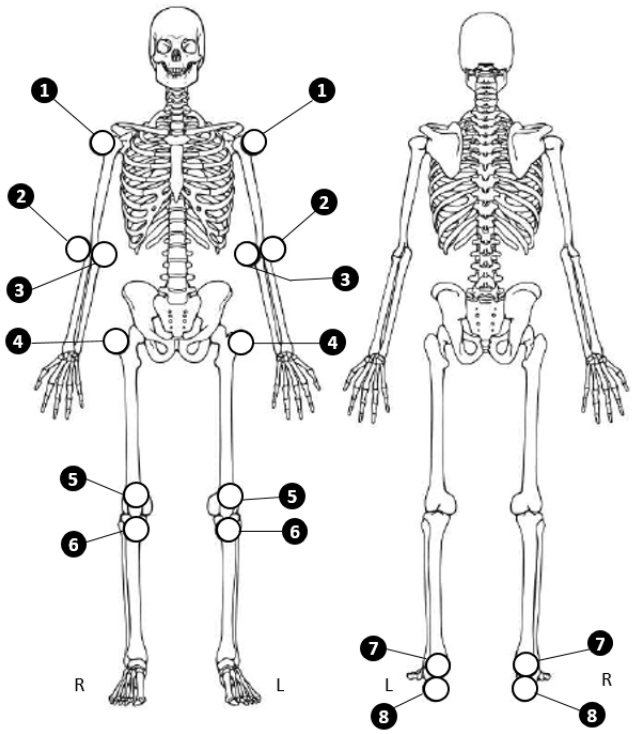
	Right						Left					
Joint	**Pain/tenderness**			**Swelling**			**Pain/tenderness**			**Swelling**		
Temporomandibular	0	1	NA	0	1	NA	0	1	NA	0	1	NA
Sternoclavicular	0	1	NA	0	1	NA	0	1	NA	0	1	NA
Acromio-clavicular	0	1	NA	0	1	NA	0	1	NA	0	1	NA
Shoulder	0	1	NA	0	1	NA	0	1	NA	0	1	NA
Elbow	0	1	NA	0	1	NA	0	1	NA	0	1	NA
Wrist	0	1	NA	0	1	NA	0	1	NA	0	1	NA
CMC1	0	1	NA	0	1	NA	0	1	NA	0	1	NA
Metacarpophalangeal 1	0	1	NA	0	1	NA	0	1	NA	0	1	NA
Metacarpophalangeal 2	0	1	NA	0	1	NA	0	1	NA	0	1	NA
Metacarpophalangeal 3	0	1	NA	0	1	NA	0	1	NA	0	1	NA
Metacarpophalangeal 4	0	1	NA	0	1	NA	0	1	NA	0	1	NA
Metacarpophalangeal 5	0	1	NA	0	1	NA	0	1	NA	0	1	NA
Thumb Interphalangeal	0	1	NA	0	1	NA	0	1	NA	0	1	NA
Prox. Interphalangeal 2	0	1	NA	0	1	NA	0	1	NA	0	1	NA
Prox. Interphalangeal 3	0	1	NA	0	1	NA	0	1	NA	0	1	NA
Prox. Interphalangeal 4	0	1	NA	0	1	NA	0	1	NA	0	1	NA
Prox. Interphalangeal 5	0	1	NA	0	1	NA	0	1	NA	0	1	NA
Dist. Interphalangeal 2	0	1	NA	0	1	NA	0	1	NA	0	1	NA
Dist. Interphalangeal 3	0	1	NA	0	1	NA	0	1	NA	0	1	NA
Dist. Interphalangeal 4	0	1	NA	0	1	NA	0	1	NA	0	1	NA
Dist. Interphalangeal 5	0	1	NA	0	1	NA	0	1	NA	0	1	NA
Hip	0	1	NA				0	1	NA			
Knee	0	1	NA	0	1	NA	0	1	NA	0	1	NA
Ankle	0	1	NA	0	1	NA	0	1	NA	0	1	NA
Tarsus	0	1	NA	0	1	NA	0	1	NA	0	1	NA
Metatarsophalangeal 1	0	1	NA	0	1	NA	0	1	NA	0	1	NA
Metatarsophalangeal 2	0	1	NA	0	1	NA	0	1	NA	0	1	NA
Metatarsophalangeal 3	0	1	NA	0	1	NA	0	1	NA	0	1	NA
Metatarsophalangeal 4	0	1	NA	0	1	NA	0	1	NA	0	1	NA
Metatarsophalangeal 5	0	1	NA	0	1	NA	0	1	NA	0	1	NA
Great Toe/Hallux	0	1	NA	0	1	NA	0	1	NA	0	1	NA
Interphalangeal 2	0	1	NA	0	1	NA	0	1	NA	0	1	NA
Interphalangeal 3	0	1	NA	0	1	NA	0	1	NA	0	1	NA
Interphalangeal 4	0	1	NA	0	1	NA	0	1	NA	0	1	NA
Interphalangeal 5	0	1	NA	0	1	NA	0	1	NA	0	1	NA
DIP 2	0	1	NA	0	1	NA	0	1	NA	0	1	NA
DIP 3	0	1	NA	0	1	NA	0	1	NA	0	1	NA
Dip 4	0	1	NA	0	1	NA	0	1	NA	0	1	NA
Dip 5	0	1	NA	0	1	NA	0	1	NA	0	1	NA

Addendum 5b:
Rheumatological Examinations
Dactylitis Count / Score

DACTYLITIS (Code: 0 = Absent, 1 = Present)

Joint	Right	Left
Finger 1 = thumb		
Finger 2		
Finger 3		
Finger 4		
Finger 5		
Toe 1 = big toe		
Toe 2		
Toe 3		
Toe 4		
Toe 5		

Addendum 5c:
Rheumatological Examinations
SPondyloArthritis Research Consortium of Canada (SPARCC) Enthesitis Index



- 16 sites
- Easy to locate
- No grading
- Score from 0 to 16

1	Supraspinatus insertion
2	Lateral epicondyle humerus
3	Medial epicondyle humerus
4	Greater trochanter
5	Quadriceps insertion into superior border of patella
6	Patellar tendon insertion inferior pole of patella OR tibial tubercle*
7	Achilles tendon
8	Insertion plantar fascia

* For scoring purposes, the inferior patella and tibial tuberosity are considered 1 site because of their anatomical proximity.

Maksymowych WP et al. Ann Rheum Dis 2009;68:948-953

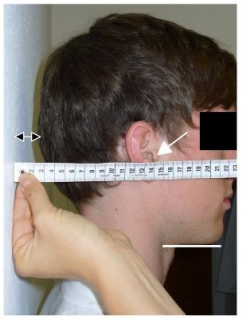
Addendum 5d:
Rheumatological Examinations
Bath Ankylosing Spondylitis Metrology Index (BASMI)

Spinal Mobility – Cervical Rotation

- The patient sits straight on a chair, chin at usual carrying level, hands on the knees.
- The assessor places a goniometer at the top of the head in line with the nose (1.)
- The assessor asks to rotate the neck maximally to the left, follows with the goniometer, and records the angle between the sagital plane and the new plane after rotation (2.)
- A second reading is taken and the best of the two is recorded for the left side
- The procedure is repeated for the right side.
- The mean of left and right is recorded in degrees (0-90 Degree).

ASAS handbook, Ann Rheum Dis 2009; 68 (Suppl II) (with permission)

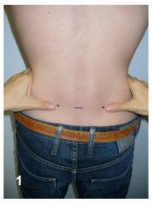
Spinal Mobility - Occiput to Wall (black arrow) and Tragus to Wall (white arrow)

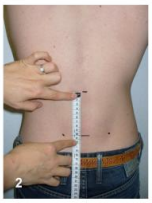


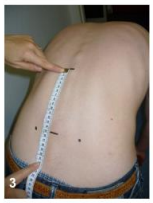
- Heels and back rest against the wall
- Chin at usual carrying level
- Maximal effort to move the head (occiput) against the wall
- Report the best of two tries (in cm) for the occiput to wall distance and the mean of left and right for the tragus to wall distance

Adapted from: ASAS handbook, Ann Rheum Dis 2009; 68 (Suppl II)

Spinal Mobility – Modified Schober



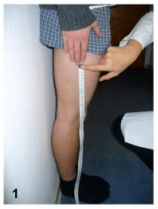


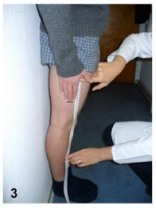


- Patient standing erect
- Mark an imaginary line connecting both posterior superior iliac spines (close to the dimples of Venus) (1)
- A next mark is placed 10 cm above (2)
- The patient bends forward maximally, measure the difference between the two marks (3)
- Report the increase (in cm to the nearest 0.1 cm)
- The best of two tries is recorded.

ASAS handbook, Ann Rheum Dis 2009; 68 (Suppl II) (with permission)

Spinal Mobility – Lateral Spinal Flexion

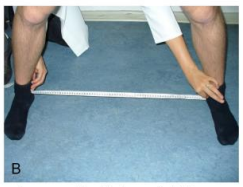




- Heels and back rest against the wall. No flexion in the knees, no bending forward
- Place a mark on the thigh (1), bend sidewards without bending knees or lifting heels (2), and without moving the shoulders or hips, place a second mark and record the difference (3)
- The best of two tries is recorded for left and right separately.
- Finally, the mean of left and right is calculated (in cm to the nearest 0.1 cm).

ASAS handbook, Ann Rheum Dis 2009; 68 (Suppl II) (with permission)

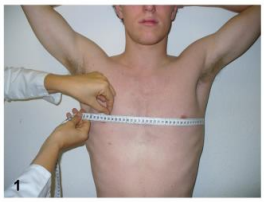
Intermalleolar Distance

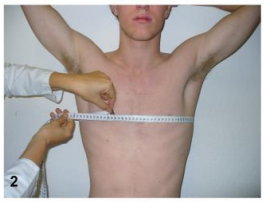


- The patient is lying down (A) with the legs separated as far as possible with knees straight and toes pointing upwards (preferred method).
- Alternatively, the patient stands (B) and separates the legs as far as possible.
- The distance between the medial malleoli is measured.

ASAS handbook, Ann Rheum Dis 2009; 68 (Suppl II) (with permission)

Spinal Mobility – Chest Expansion





- Hands resting on - or behind the head
- Measure at 4th intercostal level anteriorly
- Difference between maximal inspiration (1) and exspiration (2) in cm (eg. 4.3 cm) is recorded
- Report the best of two tries

ASAS handbook, Ann Rheum Dis 2009; 68 (Suppl II) (with permission)

Table 3 Equations proposed for the conversion of the assessments *A* into scores *S* for the five components of the $BASMI_{lin}$

	$S = 0$ if:	Between 0 and 10:	$S = 10$ if:
Lateral lumbar flexion* (cm)	$A \geqslant 21.1$	$S = (21.1 - A)/2.1$	$A \leqslant 0.1$
Tragus-to-wall distance* (cm)	$A \leqslant 8$	$S = (A - 8)/3$	$A \geqslant 38$
Lumbar flexion (modified Schober) (cm)	$A \geqslant 7.4$	$S = (7.4 - A)/0.7$	$A \leqslant 0.4$
Intermalleolar distance (cm)	$A \geqslant 124.5$	$S = (124.5 - A)/10$	$A \leqslant 24.5$
Cervical rotation angle* (°)	$A \geqslant 89.3$	$S = (89.3 - A)/8.5$	$A \leqslant 4.3$

*For lateral lumbar flexion, tragus-to-wall distance, and cervical rotation the average of right and left should be taken.
If a score lies beyond the range 0–10, the values 0 or 10 have to be used, respectively. For facilitating computer calculations with "if ... then ... else" fields in a table calculation program such as Microsoft Excel, the limits of the linear ranges are also given. The $BASMI_{lin}$ is the mean of the five scores.
BASMI, Bath Ankylosing Spondylitis Metrology Index.

Addendum 5e:
Rheumatological Examinations
Skin Assessment

Investigator Global Assessment for overall psoriatic disease

Score	Description
□ Clear	- No signs of psoriasis (post-inflammatory hyperpigmentation may be present)
□ Almost clear	- Normal to pink coloration of lesions - No thickening - No to minimal focal scaling
□ Mild disease	- pink to light red coloration - Just detectable to mild thickening - Predominantly fine scaling
□ Moderate disease	- Dull bright red, clearly distinguishable erythema - Clearly distinguishable to moderate thickening - Moderate scaling
□ Severe disease	- Bright to deep dark red coloration - Severe thickening with hard edges - Severe / coarse scaling covering almost all or all lesions

Addendum 6a:
Protocol: Synovial biopsies

Preparation phase:
Depending on the joint to be examined and biopsied, the patient is positioned lying down or sitting. The highest comfort of the patient is pursued. The procedure is carried out under strict aseptic conditions (i.e., sterile) and the necessary precautions are taken for this (use of sterile drapes around the relevant joint, thorough disinfection, face mask, gloves, sterile covering of the ultrasound probe). A comprehensive ultrasound examination of the relevant joint is first conducted to identify the correct structures and locate the best site for tissue sampling.

Actual procedure:
The trajectory that the biopsy needle will follow from the external skin surface to the tissue to be biopsied will be anesthetized using an injection of lidocaine. This should take effect for 3 to 5 minutes before the actual tissue collection will occur. In the meantime, the researcher and the assisting personnel will prepare the biopsy material. The ultrasound probe is sterilely packaged and placed on the joint where the biopsy will take place. The researcher can form a clear image on the screen of where the biopsy will take place. The tip of the needle will first be inserted subcutaneously and this can be visualized by the researcher. This needle is then advanced along the trajectory until it reaches the tissue that one wants to biopsy. When the researcher is certain of the correct location in the joint, several biopsies (10-12) of the tissue will be taken while the needle remains in place. After sufficient tissue samples have been taken, excess fluid will be aspirated.

Aftercare:
The injection site is to be disinfected again and covered with a plaster or bandage. The patient must remain in the department for observation for up to 30 minutes after the biopsy. No specific monitoring is required. The patient is advised to contact the responsible or treating physician in case of pain, swelling, or redness of the biopsied joint within 5-7 days after the procedure. If desired, pain relievers (paracetamol, anti-inflammatories) can be taken, but this is not mandatory. Local ice application may also be done if the patient finds it necessary.

Addendum 6b:

Joints accessible for synovial tissue sampling

(Provided there has not been a steroid injection the last 6 weeks)

- Wrist
- Elbow
- Metacarpophalangeal joints (MCP)
- Proximal Interphalangeal joints (PIP)
- Knee
- Ankle
- Metatarsophalangeal joints (MTP)

Addendum 7a – 7k:
Patient-Reported Outcomes

a) BASDAI

b) BASFI

c) PATIENT GLOBAL DISEASE-ACTIVITY

d) PATIENT GLOBAL PAIN

e) HAQ (Health Assessment Questionnaire)

HAQ Spondyloarthropathie

f) ASAS- Health Index

g) EQ-5D

h) Co-morbidity index

i) CARE CONSUMPTION AND PRODUCTIVITY QUESTIONNAIRE (baseline)

j) CARE CONSUMPTION AND PRODUCTIVITY QUESTIONNAIRE (Follow-up)

k) EDUCATION AND WORKING STATUS (Baseline)

EDUCATION AND WORKING STATUS (Follow-up)

Questionnaires can be obtained upon request.

Addendum 8a:
Medication Schedules: Methotrexate/Placebo

Standard step-up schedule in case of good tolerance to Methotrexate/Placebo

Week	Dose
Baseline	15mg
Week 4	20mg
Week 8	20mg
Week 12 until sustained remission	20mg
Sustained remission	STOP

Standard step-down schedule in case of immediate intolerance and / or toxicity to Methotrexate/Placebo

Week	Down titration
Baseline	15mg
Week 4	10mg
Week 8	7.5 mg
Week 12	STOP

In case of intolerance and / or toxicity occurring at a certain dose of methotrexate / placebo at any time point during Phase A, the previous tolerated dose will be used.

Addendum 8b:
Medication Schedules: NSAIDs

Dosage of NSAIDs Used to Treat Ankylosing Spondylitis

drug	half-life (hours)	approved maximal daily dosage -normally for arthritis- (mg)
Aceclofenac#	about 4	200
Celecoxib	8-12	400
Diclofenac*	about 2	125-150
Etoricoxib#	about 22	90
Ibuprofen	1.8-3.5	2400-3200
Indomethacin*	about 2	150-200
Ketoprofen	1.5-2.5	200-300
Meloxicam	about 20	15
Naproxen	10-18	1000
Phenylbutazone#	50-100	600
Piroxicam	30-60	20

*retard formula available
not approved in the US

Adapted from Song IH et al. Arthritis Rheum 2008;58:929-38

Addendum 9

Post Biopsy Questionnaire

Questionnaire can be obtained upon request.

Addendum 10

CIOMS FORM

I. REACTION INFORMATION
II. SUSPECT DRUG(S) INFORMATION
III. CONCOMITANT DRUG(S) AND HISTORY
IV. MANUFACTURER INFORMATION

Applicable up until 30 September 2024.

GCD-SOP-601.4
Intake Form Instructio

Addendum 11

Applicable up until 30 September 2024.

Investigator Initiated Studies
Program

FAX

Date:

Number of pages including cover sheet:

To:	MSD Global Pharmacovigilance*	**From:**	_____
Fax:	02 332 13 79	**Phone No.:**	_____
Email:	dpoc_belux@merck.com	**Fax No.:**	_____
		Email:	_____

SERIOUS ADVERSE EVENT REPORT COVER PAGE

Protocol Title: SPondyloArthritis: inducing drug-free Remission by early TNF-Alpha bloCkade Under guidance of Single cell RNA sequencing and epigenetic profiling. "The SPARTACUS trial"

Study Drug:	Golimumab/ Methotrexate	**MSD Protocol Number or MISP 5 digit identifier:**	58652
Principal Investigator:	Filip Van den Bosch	**Site Investigator:**	
Serious Event:		**Patient (Screening/ Randomization No.):**	
Country of Incidence	Belgium	**Type of Report:**	☐ Initial ☐ Follow-up

PLEASE ATTACH YOUR COMPLETED ADVERSE EVENT REPORTING FORM (MEDWATCH FORM 3500 or EQUIVALENT)

***Investigator-Sponsor may report directly to the local Country Operations office if preferred by MSD. Fax numbers for local Country Operations can be substituted for Headquarter numbers.**

Addendum 12

SPARTACUS Ancillary Research Project Proposal

Title of the project:
Date of submission:
Investigator: Name: …… First name: …… e-mail address: ……..
Rationale of this research proposal:
Objectives:
Statistical analysis plan:
Time frame for this analysis :