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

EudraCT number: 2019-004961-42

3 Objective(s) of the study

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).
- To define the window of opportunity within which temporary treatment with bDMARDs might be more effective, by stratifying patients according to symptom duration: patients with shorter symptom duration (<3 months) versus those with more longstanding disease (between 3-12 months of symptom duration).

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. Differences between patients with very early disease (<3 months symptom duration) versus those with symptom duration between 3 and 12 months, will be evaluated.

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.

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), but the stratification of patients according to symptom duration (<3 months (identical to the CRESPA trial) versus between 3 and 12 months) will allow us to explore the exact time frame in which a window of opportunity is applicable. 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.

4 General information

4.1 National Coordinating Investigator(s)

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4.2 Sponsor

UZ Ghent
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9000 Ghent

4.3 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.

5 Introduction

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 compare groups with different symptom duration (<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.

6 The present study

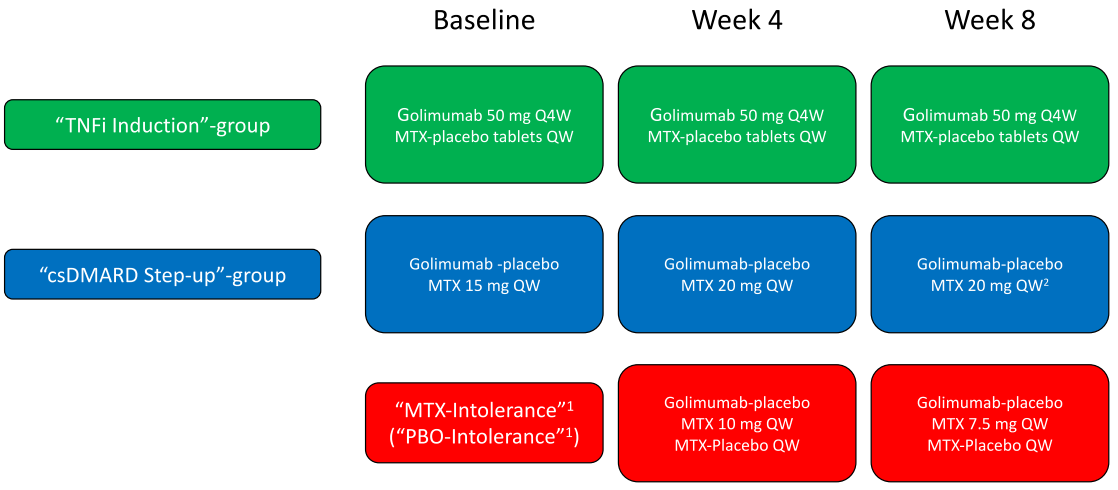
6.1 Study design

The SPARTACUS clinical trial 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=112) will be randomized (1:1) to either immediately receiving TNFi (golimumab) monotherapy ("TNFi Induction"-group) (n=56), or to the step-up regimen with csDMARDs ("csDMARD Step-up"-group) (n=56) (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 6.2.10 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

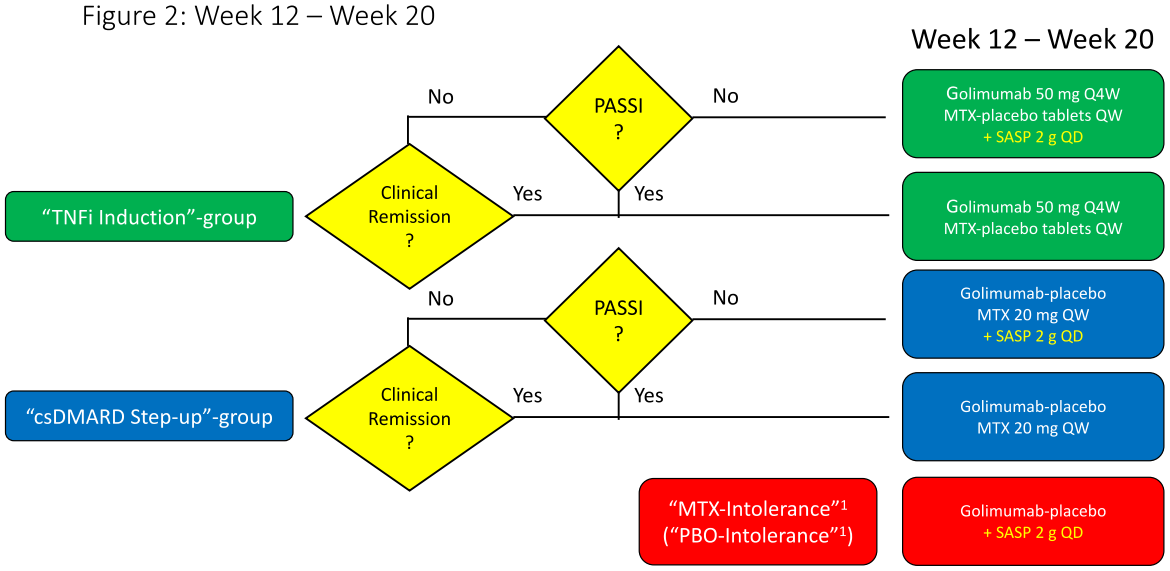


[1]"Blinded MTX-Intolerance"-regimen can be initiated from week 4, but also at later study visits.
[2]In case of intolerance to MTX(-Placebo) 20 mg QW, the previous dose (15 mg) can be used.

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 6.2.10 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



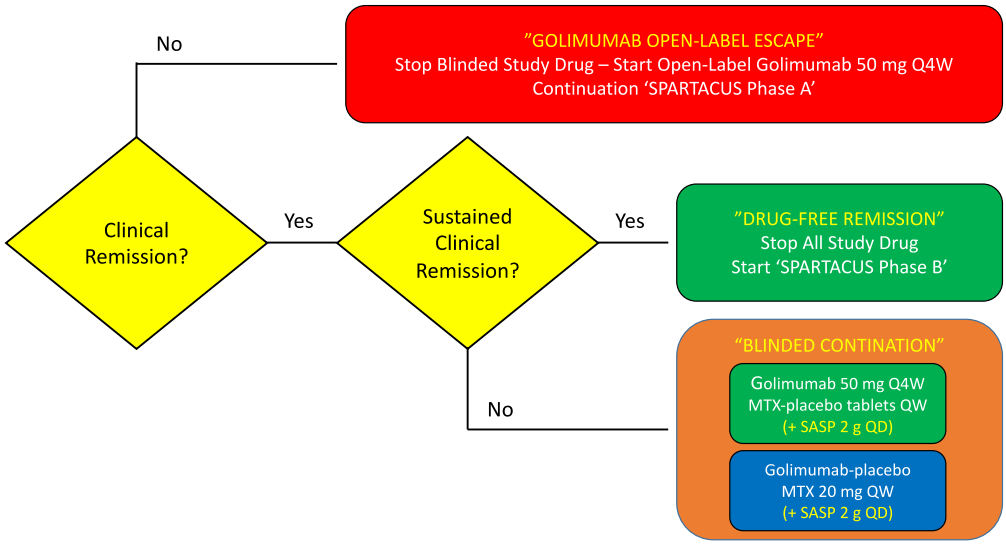
[1]Continued "MTX-Intolerance" after tapering to 7.5 mg QW results in MTX-discontinuation
'PASSI': Patient Acceptable Signs & Symptoms Improvement

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):

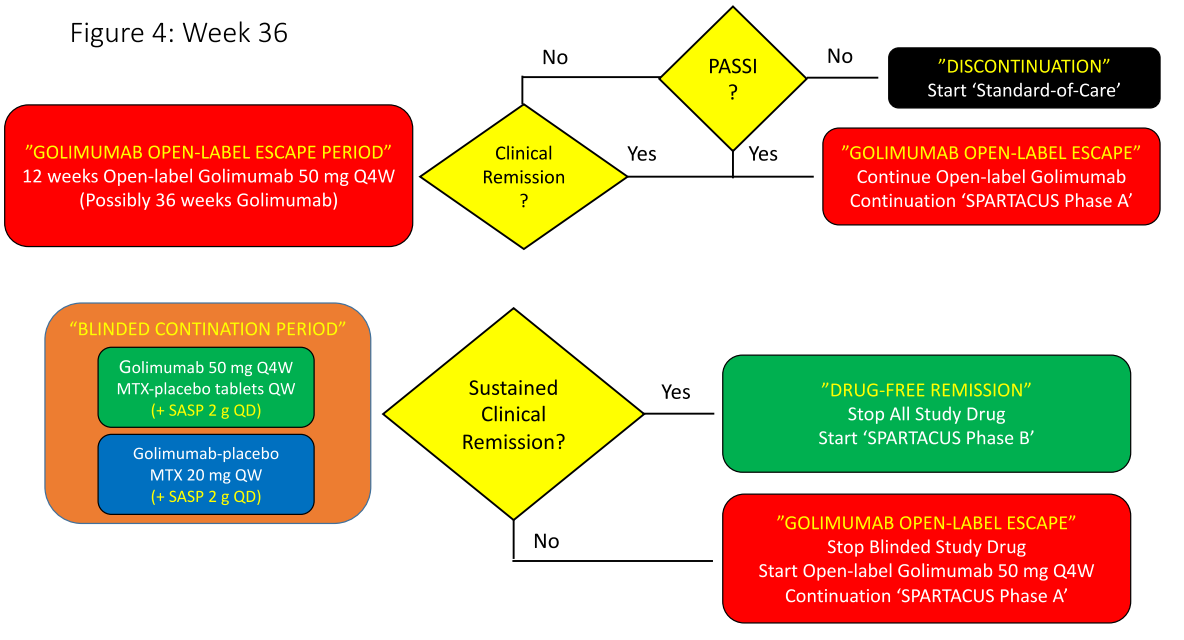
1. In patients that do not reach a state of clinical remission at week 24, blinded study medication will be interrupted and all patients will start open-label SC golimumab for an additional 36 weeks (up to max. week 60).
2. In patients that achieve sustained clinical remission at week 24, defined as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

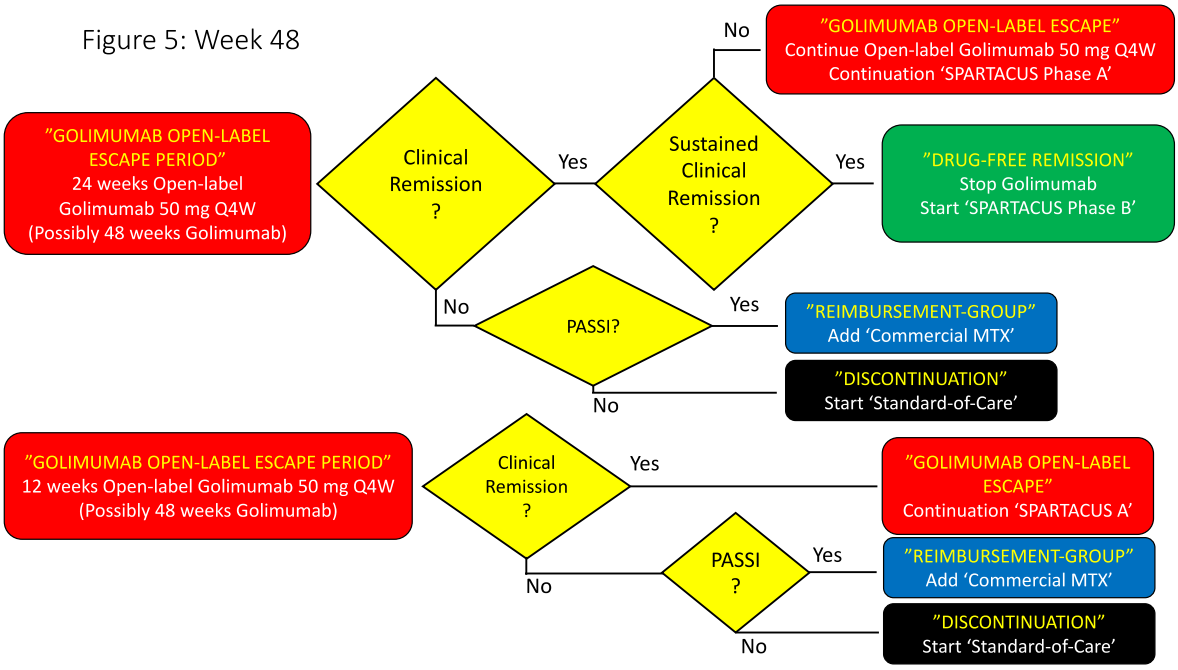


'PASSI': Patient Acceptable Signs & Symptoms Improvement

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:

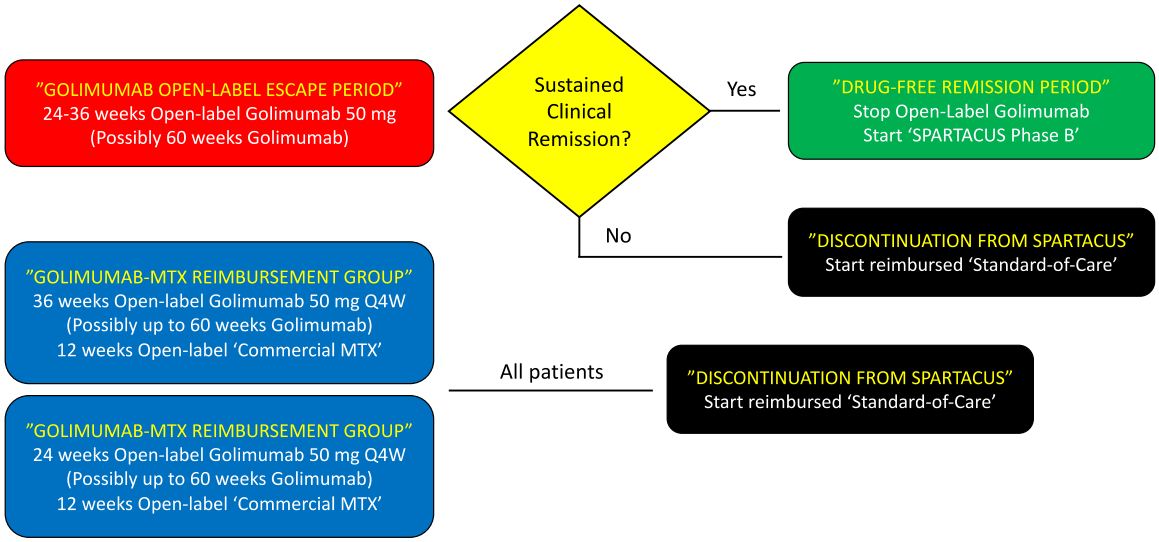
1. Patients reaching clinical remission for the first time at week 48 will continue without any change in the treatment schedule for another 12 weeks.
2. Patients with an inadequate response (based on the "PASSI"-question), will be discontinued from the study and will be treated with standard-of-care 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.

6.2 Medication

6.2.1 Composition and dosing

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.
For patients in the “csDMARD-Step-up”-group, placebo 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.

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.

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

6.2.2 Manufacturer

For blinded golimumab and matching placebo: Janssen Biologics B.V., Einsteinweg 101, 2333 CB Leiden, Nederland

For blinded methotrexate: Ardena Drug Development & Manufacturing, Pharmavize NV, Kleimoer 4, B 9030 Mariakerke.

Contact person: Lieven Van Vooren, Scientific Director.
E-mail: lieven.vanvooren@ardena.com
Ben Vermeulen, Project Manager
E-mail: ben.vermeulen@ardena.com
Telephone: +32 (0)9 267 65 00

For placebo (matching methotrexate): University Hospital Ghent pharmacy – CTU-1, C. Heymanslaan 10, B 9000 Ghent

CTU-1 of the University Hospital Ghent is also responsible for the randomisation of the blinded study medication (secondary packaging).

For open-label golimumab Simponi® Smartject™: MSD Belgium, Lynx Binnenhof 5, B 1200 Brussel

6.2.3 Distributor

For blinded golimumab and matching placebo: MSD Belgium, Lynx Binnenhof 5, B 1200 Brussel

For methotrexate and matching placebo: University Hospital Ghent pharmacy – clinical trials C. Heymanslaan 10, B 9000 Ghent

For open-label golimumab Simponi® Smartject autoinjector: MSD Belgium, Lynx Binnenhof 5, B 1200 Brussel

University Hospital Ghent pharmacy – clinical trials will distribute the blinded study medication to the participating sites.

MSD will distribute open-label Simponi® to the participating sites

6.2.4 Packaging

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

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

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

6.2.5 Administration way

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

The methotrexate and 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
The open-label golimumab (Simponi®) will be administrated subcutaneously every 4 weeks.

6.2.6 Labelling

The prefilled syringes with golimumab and matching placebo will be labelled by MSD.

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

Simponi® will be relabeled at the local hospital pharmacy.

6.2.7 Storage conditions

The UZ Ghent Pharmacy will store the prefilled syringes with golimumab/placebo 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.
The methotrexate/placebo capsules will also 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).

The Simponi® Smartject autoinjectors 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.

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.

6.2.8 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:
e-mail: dirk.elewaut@ugent.be or filip.vandenbosch@ugent.be
tel.: 09/332 2240 or 09/332 2863
fax: 09/332 4787

Contact details of the producer of blinded methotrexate:
e-mail: Lien.germonprez@ardena.com
Kleimoer 4
9030 Mariakerke

tel.: 09/267 65 00

Contact details of the MAH/producer of methotrexate matching placebo:
e-mail: pharmacy.clinicaltrials@UZGENT.be
tel : 09/332 29 73
fax: 09/332 3869

Contact details of MAH/producer of Golimumab and matching placebo :
Merck Global should be informed by email: dpoc_belux@merck.com

6.2.9 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).

6.2.10 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.

6.2.11 Known side effects of the medication

Golimumab

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.

Methotrexate
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, AST, 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.

6.3 The subjects

6.3.1 Number of subjects

In total 112 patients will be randomized in this study. 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.

6.3.2 Inclusion criteria

6.3.2.1 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 3 months after receiving the last administration of study agent.
- 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.

6.3.2.2 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).

6.3.3 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.

6.3.4 Replacement of subjects

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

6.3.5 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.
- Female subjects must agree to not donate eggs (ova, oocytes) during the study and for 3 months after last dose of study drug. Male subjects must agree to not donate sperm while in the study and for 3 months after 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).

6.3.6 Possible advantages and risks for the subjects

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 (and will be stratified at baseline according to symptom duration <3 vs. ≥3 months). 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.

7 Procedures and Study Flow-Chart

7.1 Procedures

7.1.1 '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 (AST, 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 (AST, 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 (AST, 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 (AST, 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 (AST, 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 (AST, 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 (AST, 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 (AST, 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

7.1.2 ‘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 (AST, 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 (AST, 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 (AST, ALT, GGT, AP, LDH), CK
At week 4, week 12, week 28: peripheral blood count, serum creatinine, ALT, AST
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 (AST; 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)

8 Randomisation / blinding / unblinding

All patients (n=112) will be randomized (1:1) to either immediately receiving golimumab monotherapy (n=56) (the "TNFi-induction"-group), or to the step-up regimen with csDMARDs (n=56) ("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 11). 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. Patients for whom the medication is unblinded will be discontinued from the clinical trial. The decision to unblind a patient will be extensively documented in the patient file.

9 Prior and concomitant therapy

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

<u>Non-steroidal anti-inflammatory drugs (NSAIDs)</u>

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 within 3 months of the first study drug administration, is not allowed.
- 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.

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

9.1 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.

10 End of study

End of study is 30 days after the patient's last study visit.

11 Adverse Event reporting

List of abbreviations

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

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.

Definitions of Adverse Event (AE)

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

Serious Adverse Event (SAE)

Any untoward medical occurrence that at any dose:

- results in death
- is life-threatening
- requires inpatient hospitalization or prolongation of existing hospitalization,
- results in persistent or significant disability/incapacity,

or

- is a congenital anomaly/birth defect.

Note: Medical and scientific judgement should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the outcomes listed in the definition above.

Unexpected adverse event
An adverse event, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure for an unapproved investigational product or package insert/summary of product characteristics for an approved product).

Life-threatening
Any 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.

Associated with the use of the drug
An adverse event is considered associated with the use of the drug if the attribution is possible, probable or definitive.

Attribution definitions

Not related
An adverse event which is not related to the use of the drug.

Unlikely
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.

Possible
An adverse event which might be due to the use of the drug. An alternative explanation - e.g. concomitant drug(s), concomitant disease(s), - is inconclusive. The relationship in time is reasonable; therefore the causal relationship cannot be excluded.

Probable
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), concomitant disease(s).

Definitely
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), concomitant disease(s). The relationship in time is very suggestive (e.g. it is confirmed by dechallenge and rechallenge).

Reporting of adverse events

Adverse events will be reported between the first dose administration of trial medication and the last study visit.
All AEs and SAE's will be recorded in the patient's file and in the eCRF. All SAE's will be reported as described below.

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) and pregnancies occurring during clinical trials 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.

In case the investigator decides the SAE is a SUSAR (Suspected Unexpected Serious Adverse Reaction), HIRUZ will report the SUSAR to the Central EC and the CA within the timelines as defined in national legislation. The National Coordinating Investigator reports the SUSAR to all local Principal Investigators.

In case of a life-threatening SUSAR the entire reporting process must be completed within 7 calendar days. In case of a non-life-threatening SUSAR the reporting process must be completed within 15 calendar days.

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

Contact details of HIRUZ:
e-mail: hiruz.ctu@uzgent.be
tel.: 09/332 05 00

Contact details of the National Coordinating Investigator:
e-mail: dirk.elewaut@ugent.be or filip.vandenbosch@ugent.be
tel.: 09/332 2240 or 09/332 2863
fax: 09/332 4787

Contact details of the producer of blinded methotrexate:
e-mail: Lien.germonprez@ardena.com
Kleimoer 4
9030 Mariakerke
tel.: 09/267 65 00

Contact details of the MAH/producer of methotrexate matching placebo:
e-mail: pharmacy.clinicaltrials@UZGENT.be
tel : 09/332 29 73
fax: 09/332 3869

Contact details of MAH/producer of Golimumab and matching placebo :

- Merck Global Safety should be informed by fax using the 1301.10_IIS AE Fax Form and the Global Safety Intake Form

(see Addendum 10 -11).
fax: 02 332 13 79 email: dpoc_belux@merck.com

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.

Development Safety Update Report (DSUR)

The Coordinating Investigator will provide a DSUR once a year throughout the entire duration of the clinical study, or on request, to the CA, Central Ethics Committee and Sponsor. This DSUR will include all SAE's (who were not categorized as SAR's and were not immediately reported to the EC).

The report will be submitted 1 year (+ maximum 60 days) after the 'Development International Birth Date (DIBD)' , and will subsequently be submitted each year until the study is declared ended. This DIBD is the date of the sponsor's first overall authorisation to conduct the clinical trial in any country worldwide.

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12 Study analysis

12.1 Sample size calculation

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 45% difference in percentage of patients going into clinical remission between both groups (MTX versus TNFi): 20% versus 65%. A sample size of 28 patients in each group is sufficient to obtain 90% power to detect a difference in proportions of 45% (20% versus 65%) at the alpha level of 5% using a Fisher's exact test.

The comparison between the treatment groups will be made for the two symptom duration groups (<3 months and >3 months) separately. Thus, 112 patients will be included for the total study. To allow for some flexibility, it was decided to include 112 patients in total with a minimum of 44 patients per symptom group (yielding a minimum of 80% power per symptom group).

12.2 Analysis of the 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.

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.

12.3 Statistical analysis

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).
- 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).

13 Quality control and quality assurance

The investigator will maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents will be classified into two different categories: investigator's file, and subject clinical source documents.
The investigator's file will contain the documents as per Good Clinical Practice (GCP) and local regulations.
Regular monitoring will be performed by Hiruz CTU according to ICH-GCP. Data will be evaluated for compliance with the protocol and accuracy in relation to source documents. Following written standard operating procedures, the monitors will verify that the clinical trial is conducted and data are generated, documented and reported in compliance with the protocol, GCP and the applicable regulatory requirements. The monitor will provide a monitoring report after each visit for the coordinating- and the principle investigator.
More detailed information regarding the monitoring is described in the monitoring plan.

14 Indemnity insurance

An insurance with no fault responsibility has been foreseen by the sponsor in accordance with the Belgian law concerning experiments on humans, 7 May 2004.

15 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, …).

16 End of Study Notification

If all subjects have completed the study, a notification of the end of the study should be submitted to the (Central) Ethics Committee and the Federal Agency for Medicines and Health Products . This notification should be made within 90 days of the end of the clinical study. In case of early termination (definition in CT-1, 4.2), this is reduced to 15 days.

17 Final Study Report

Within one year after the final completion of the study, a full final study report will be written by the National Coordinating Investigator and submitted to the central ethical committee and competent authority (via Hiruz CTU).

Part II : General part of the Protocol

18 Independent Ethics Committee (IEC) / Institutional Review Bord (IRB)

This trial can only be undertaken after full approval of the protocol and addenda has been obtained from the IEC/IRB. This document must be dated and clearly identify the protocol, amendments (if any), the informed consent form and any applicable recruiting materials and subject compensation programs approved.
During the trial, the following documents will be sent to the IEC/IRB for their review:

- reports of adverse events that are serious, unexpected and associated with the investigational drug
- all substantial protocol amendments and revised informed consent form (if any).

Substantial amendments should not be implemented without prior review and documented approval / favorable opinion form the IEC/IRB except when necessary to eliminate an immediate hazard to trial subjects or when the change involves only logistical or administrative aspects of the trial.
Reports on, and reviews of the trial and its progress will be submitted to the IEC/IRB by the investigator at intervals stipulated in their guidelines.
At the end of the trial, the investigator will notify the IEC/IRB about the trial completion.

19 ICH/GCP Guidelines

This trial will be conducted in accordance with the protocol, current ICH-GCP guidelines and applicable law(s).
Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety and well-being of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible.

20 Competent Authority (CA)

This study must obtain approval from the competent authority (FAGG) prior to the start of the study. All substantial protocol amendments will be notified to the competent authorities during the course of the trial.
Reports on safety, and reviews of the trial and its progress will be submitted to the CA by the sponsor (via Hiruz CTU) at intervals stipulated in their guidelines.
At the end of the trial, the sponsor will notify the CA (via Hiruz CTU) about the trial completion as per regulatory requirements.

21 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.

22 Protocol compliance

Prospective, planned deviations or waivers to the protocol are not allowed. Under emergency circumstances, deviations from the protocol to protect the rights, safety or well-being of human subjects may proceed without prior approval of the sponsor and the EC. Such deviations shall be documented and reported to Hiruz CTU by email (hiruz.ctu@uzgent.be) and the EC as soon as possible. Accidental protocol deviations must be adequately documented and reported in the eCRF on the protocol deviation log. In case accidental protocol deviations are considered as critical issues that significantly affect patient safety, data integrity and/or study conduct these should be reported to Hiruz CTU immediately by email (hiruz.ctu@uzgent.be). Hiruz CTU will subsequently communicate and discuss this with the EC.

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.

23 Subject information and informed consent

Prior to entry in the trial, the investigator must explain to potential subjects the trial and the implication of participation. 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 authorized 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 are authorizing such access.
After this explanation and before entry to the trial, written, dated and signed informed consent should be obtained from the subject. The ICF should be provided in a language

sufficiently understood by the subject. Subjects must be given the opportunity to ask questions.
The subject 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 the subject'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 is unable to read, an impartial witness must attest the informed consent.

24 Case Report Forms

The source documents are to be completed at the time of the subject's visit. The eCRFs are to be completed within reasonable time after the subject's visit.
Patient reported outcomes will be available electronically. Subject must complete the PRO's during the study visits using the provided tablet. All records will be registered in the eCRF RedCap which is considered as source document.
The investigator must verify that all data entries in the eCRFs are accurate and correct. If certain information is Not Done, Not Available or Not Applicable, the investigator must enter "N.D." or "N.AV." or "N.AP", respectively in the appropriate space.

25 Direct access to source data / documents

The investigator will permit trial-related monitoring, audits, IRB/IEC review, and regulatory inspection(s), providing direct access to source data/documents.

26 Data handling and record keeping

All study data will be handled in accordance with the law on General Data Protection Regulation (GDPR) and institutional rules [Belgian law dated on 30 July 2018 and 22 Aug. 2002].

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 requirement(s).

Signature page

Investigator:

Name: Dr. Philippe Carron

Title: Coordinating Investigator

Signature:

Date: 18/8/2023

Investigator:

Name: Prof. Dr. Filip van den Bosch

Title: Coordinating Investigator

Signature:

Date: 18/AUG/2023

Investigator:

Name: Prof. Dr. Dirk Elewaut

Title: Coordinating Investigator

Signature:

Date: 21/08/23

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.

ASAS Classification Criteria for Peripheral Spondyloarthritis (SpA)

Arthritis or enthesitis or dactylitis

plus

≥ 1 SpA feature
- uveitis
- psoriasis
- Crohn‘s/colitis
- preceding infection
- HLA-B27
- sacroiliitis on imaging

OR

≥ 2 other SpA features
- arthritis
- enthesitis
- dactylitis
- IBP (ever)
- family history for SpA

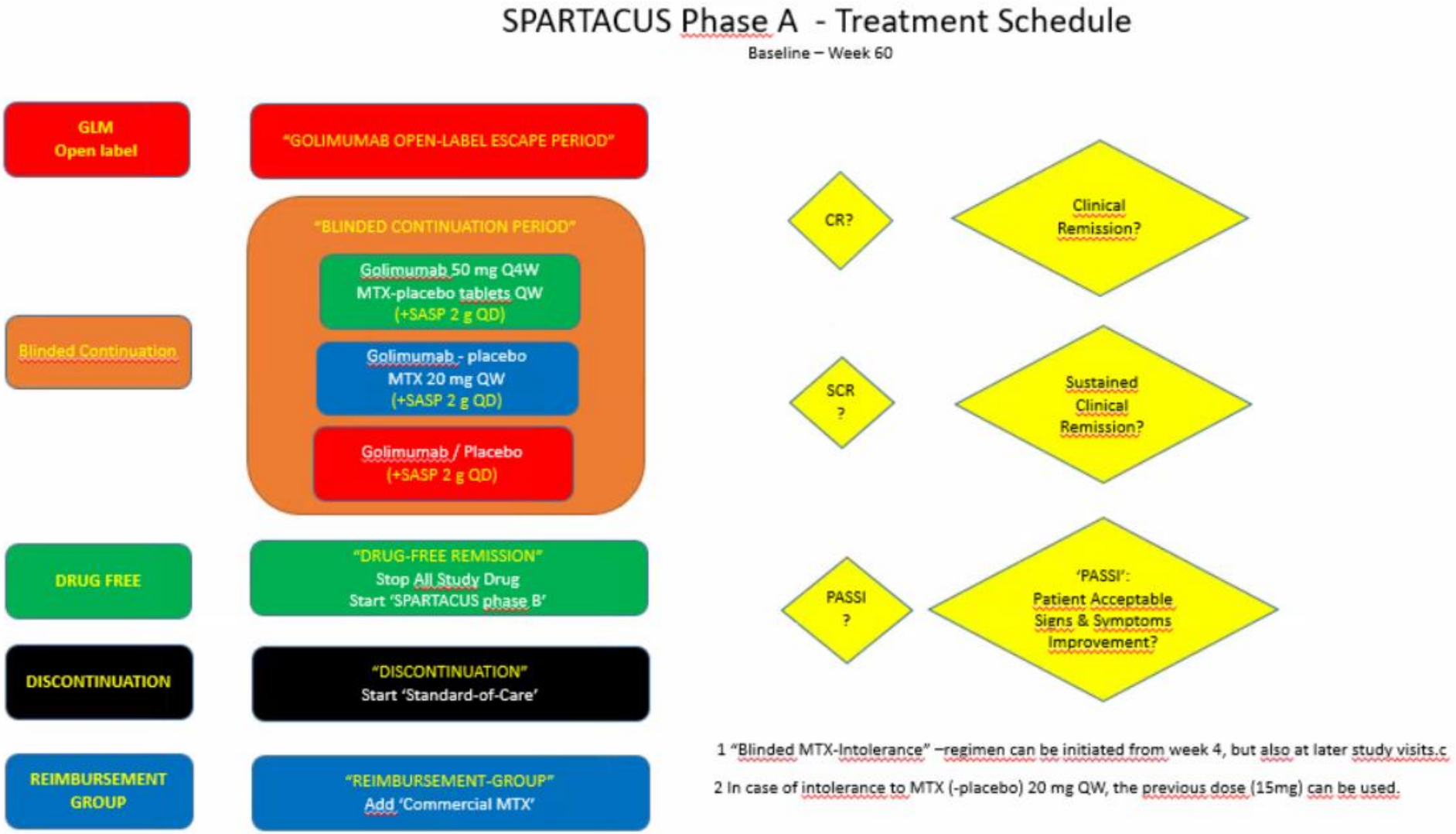
Peripheral arthritis: usually predominantly lower limbs and/or asymmetric arthritis
Enthesitis: clinically assessed
Dactylitis: clinically assessed

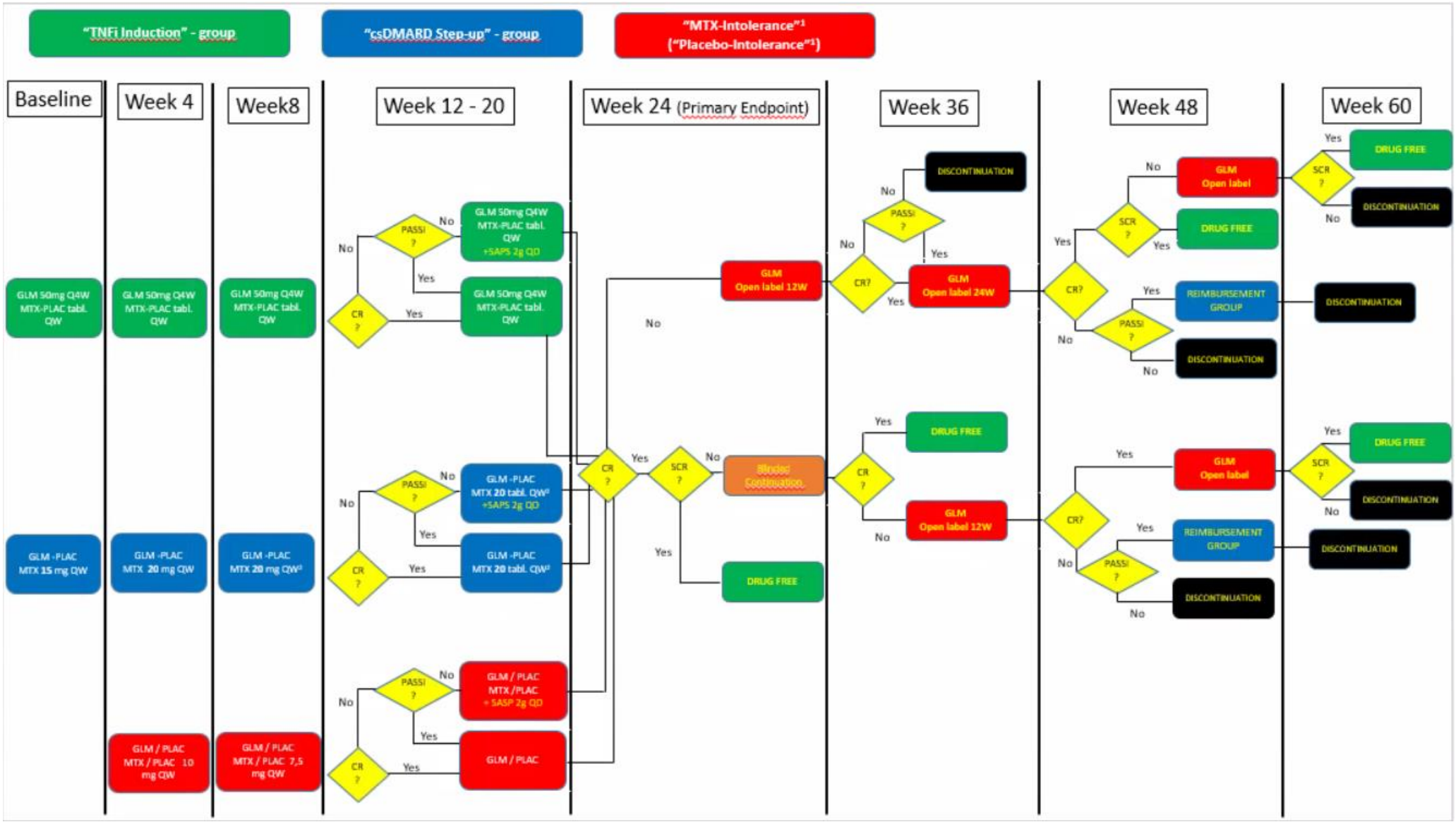
IBP: Inflammatory back pain

Sensitivity: 77.8%, Specificity: 82.2%; n=266

Rudwaleit M et al. Ann Rheum Dis 2011;70:25-31 (with permission)

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

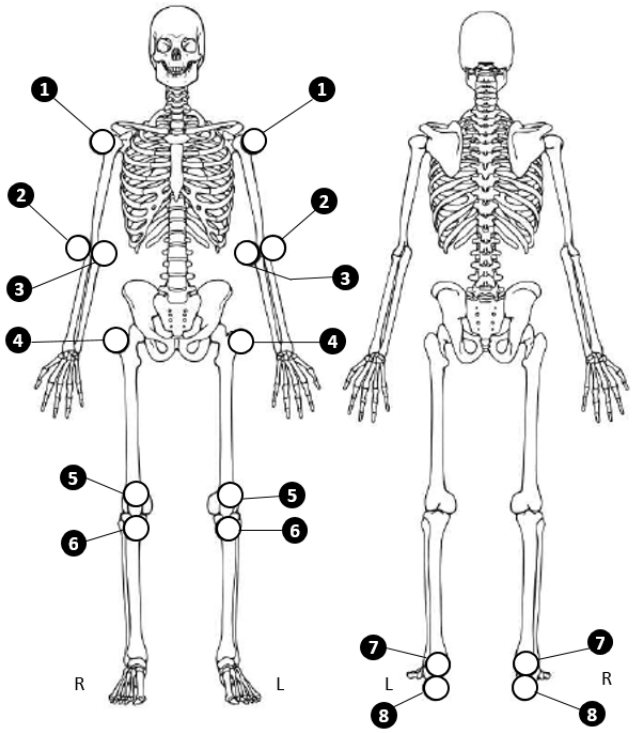
	Right						Left					
Joint	**Pain/tenderness**			**Swelling**			**Pain/tenderness**			**Swelling**		
Temporomandibular	0	1	NA	0	1	NA	0	1	NA	0	1	NA
Sternoclavicular	0	1	NA	0	1	NA	0	1	NA	0	1	NA
Acromio-clavicular	0	1	NA	0	1	NA	0	1	NA	0	1	NA
Shoulder	0	1	NA	0	1	NA	0	1	NA	0	1	NA
Elbow	0	1	NA	0	1	NA	0	1	NA	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)



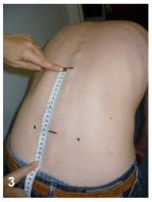
- Heels and back rest against the wall
- Chin at usual carrying level
- Maximal effort to move the head (occiput) against the wall
- Report the best of two tries (in cm) for the occiput to wall distance and the mean of left and right for the tragus to wall distance

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



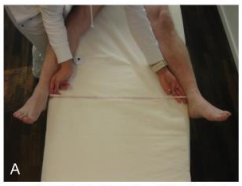




- Heels and back rest against the wall. No flexion in the knees, no bending forward
- Place a mark on the thigh (1), bend sidewards without bending knees or lifting heels (2), and without moving the shoulders or hips, place a second mark and record the difference (3)
- The best of two tries is recorded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

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Intermalleolar Distance

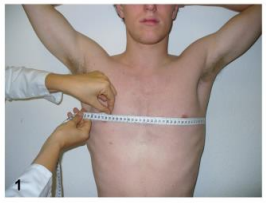


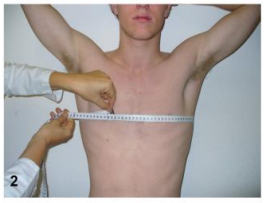


- The patient is lying down (A) with the legs separated as far as possible with knees straight and toes pointing upwards (preferred method).
- Alternatively, the patient stands (B) and separates the legs as far as possible.
- The distance between the medial malleoli is measured.

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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

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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

Voorbereidingsfase:
Afhankelijk van het te onderzoeken en biopseren gewricht wordt de patiënt in liggende of zittende houding geïnstalleerd. Het hoogste comfort van de patiënt wordt hierbij nagestreefd. De procedure verloopt in strikt aseptische condities (d.w.z. steriel) en de vereiste voorzorgen worden hiervoor genomen (gebruik van steriele doeken rond het betreffende gewricht, brede ontsmetting, mondmasker, handschoenen, steriele bescherming van de echografiesonde).
Een uitgebreid echografie onderzoek van het betreffende gewricht vindt eerst plaats om de juiste structuren te identificeren en de beste plaats voor weefselafname te lokaliseren.

Eigenlijke procedure:
Het traject dewelke de biopsienaald zal volgen van het uitwendige huidoppervlak tot het te biopseren weefsel zal worden verdoofd door middel van een injectie met lidocaïne. Dit dient een 3 tot 5 minuten in te werken alvorens de eigenlijke weefselafname zal gebeuren. In tussentijd zal de onderzoeker en het assisterend personeel het biopsiemateriaal voorbereiden.
De echografiesonde wordt steriel verpakt en geplaatst op het gewricht alwaar de biopsie zal plaatsvinden. De onderzoeker kan op het scherm een goed beeld vormen van waar de biopsie zal plaatsvinden. De tip van de naald zal eerst onderhuids worden ingebracht en deze kan worden gevisualiseerd door de onderzoeker. Deze naald wordt verder opgeschoven langs het traject tot het weefsel dan men wil biopseren. Wanneer de onderzoeker zeker is van de juiste locatie in het gewricht zullen verschillende biopsieën (10-12) van het weefsel worden afgenomen terwijl de naald ter plaatse blijft. Nadat voldoende weefselstalen zijn afgenomen zal overtollig vocht worden geaspireerd.

Nabehandeling:
De injectieplaats wordt opnieuw ontsmet en afgedekt met een pleister of verband.
De patiënt dient tot 30 minuten na de biopsie op de afdeling te blijven ter observatie. Geen specifieke monitoring is vereist.
De patiënt wordt gevraagd contact op te nemen met de verantwoordelijke of behandelende arts in geval van pijn, zwelling of roodheid van het gebiopseerde gewricht in de 5-7 dagen na de procedure. Zo gewenst kunnen pijnstillers worden ingenomen (paracetamol, onstekingsremmers) doch dit is niet verplicht. Ook lokale ijsapplicatie mag gebeuren indien de patiënt dit genoodzaakt vindt.

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:
Patient-Reported Outcomes

BASDAI

Kruis a.u.b. het blokje aan dat uw antwoord het best weergeeft, b.v. ☒
Alle vragen hebben betrekking op **de voorafgaande week**.

1. Hoe moe was u?

0	1	2	3	4	5	6	7	8	9	10

niet heel erg

2. Hoeveel pijn in de nek, rug of heup had u als gevolg van uw aandoening?

0	1	2	3	4	5	6	7	8	9	10

geen zeer veel

3. Hoeveel pijn en zwelling had u in andere gewrichten dan de nek, rug en heupen?

0	1	2	3	4	5	6	7	8	9	10

geen zeer veel

4. Hoeveel last had u van plaatsen op uw lichaam die gevoelig zijn bij aanraken of druk?

0	1	2	3	4	5	6	7	8	9	10

geen zeer veel

5. Hoeveel last had u van ochtendstijfheid vanaf het moment dat u opstond?

0	1	2	3	4	5	6	7	8	9	10

geen zeer veel

6. Hoe lang duurde de ochtendstijfheid vanaf het moment dat u opstond?

0	1	2	3	4	5	6	7	8	9	10

0 uur 1 uur 2 of meer uren

Addendum 7b:
Patient-Reported Outcomes

BASFI

Kruis a.u.b. een blokje aan om aan te geven in welke mate u in staat was de onderstaande activiteiten uit te voeren **gedurende de laatste week** b.v. ☒

1. Uw kousen of panty's aantrekken zonder hulp of hulpmiddelen (b.v. kousentrekker)

0	1	2	3	4	5	6	7	8	9	10

gemakkelijk onmogelijk

2. Vanuit de heup naar voren buigen om zonder hulp een pen van de grond te rapen.

0	1	2	3	4	5	6	7	8	9	10

gemakkelijk onmogelijk

3. Aan een hoge plank kunnen zonder hulp of hulpmiddelen (b.v. helpende hand).

0	1	2	3	4	5	6	7	8	9	10

gemakkelijk onmogelijk

4. Rechtkomen uit een eetkamerstoel zonder armleuning, zonder uw handen of andere hulp te gebruiken.

0	1	2	3	4	5	6	7	8	9	10

gemakkelijk onmogelijk

5. Zonder hulp van de grond komen als u op uw rug ligt..

0	1	2	3	4	5	6	7	8	9	10

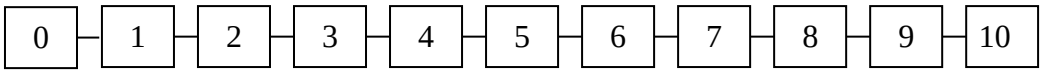
gemakkelijk onmogelijk

6. Gedurende 10 minuten zonder steun blijven staan zonder ongemakken.

0	1	2	3	4	5	6	7	8	9	10

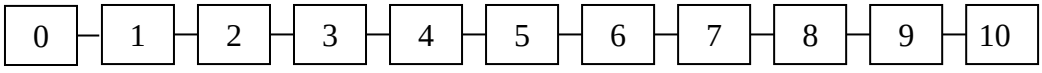
gemakkelijk onmogelijk

7. Een trap van 12-15 treden opgaan zonder een leuning of wandelstok of dergelijke te gebruiken. Eén voet op elke trede.



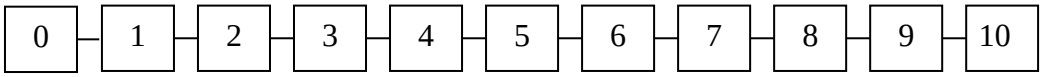
gemakkelijk onmogelijk

8. Over uw schouder kijken zonder uw lichaam te draaien.



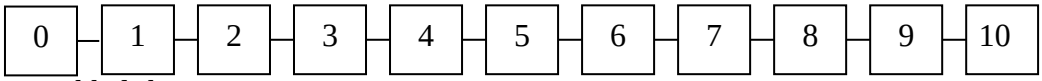
gemakkelijk onmogelijk

9. Fysiek zware activiteiten uitvoeren (b.v. fysiotherapie oefeningen, tuinieren, sport).



gemakkelijk onmogelijk

10. Een volledige dagtaak thuis of op het werk uitvoeren.

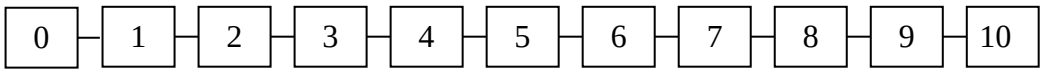


gemakkelijk onmogelijk

Addendum 7c:
Patient-Reported Outcomes

PATIENT GLOBAL (ZIEKTE-ACTIVITEIT)

Kruis een blokje aan, om aan te geven in welke mate uw ziekte actief was gedurende **de afgelopen week**.



niet actief zeer actief

Addendum 7d:
Patient-Reported Outcomes

PIJN

Kruis het blokje aan dat uw antwoord het best weergeeft, b.v. ☒ 10

1. Hoe erg was de pijn over het algemeen gemiddeld de afgelopen week?

0	1	2	3	4	5	6	7	8	9	10

geen pijn ondraaglijke pijn

2. Hoeveel rugpijn had u **'s nachts** gedurende de afgelopen week?

0	1	2	3	4	5	6	7	8	9	10

geen pijn ondraaglijke pijn

3. Hoeveel rugpijn (**dag en nacht**) had u gemiddeld gedurende afgelopen week?

0	1	2	3	4	5	6	7	8	9	10

geen pijn ondraaglijke pijn

Addendum 7e:
Patient-Reported Outcomes

Vragenlijst Dagelijks Functioneren: HAQ (Nederlandse Health Assessment Questionnaire)

	Zonder enige moeilijkheid	Met enige moeilijkheid	Zeer moeilijk	On-mogelijk
1. ***AANKLEDEN EN KLAARMAKEN***: Bent u in staat				
A Zich aan te kleden, veters te knopen en kleding dicht te knopen?	☐	☐	☐	☐
B Uw haar te wassen?	☐	☐	☐	☐
2. ***OPSTAAN:*** Bent u in staat				
A Van een stoel op te staan?	☐	☐	☐	☐
B In en uit bed te komen?	☐	☐	☐	☐
3. ETEN: Bent u in staat				
A Uw vlees te snijden?	☐	☐	☐	☐
B Een vol kopje of glas naar uw mond te brengen ?	☐	☐	☐	☐
C Een karton melk of fruitsap te openen?	☐	☐	☐	☐
4. STAPPEN: Bent u in staat				
A Buiten op vlak terrein te stappen?	☐	☐	☐	☐
B 5 treden op te stappen?	☐	☐	☐	☐
5. HYGIENE:				
Bent u in staat	☐	☐	☐	☐
A Zich volledig te wassen en af te drogen?	☐	☐	☐	☐
B Een bad te nemen?	☐	☐	☐	☐
C Op en van het toilet te gaan?	☐	☐	☐	☐
6. GRIJPEN:				
Bent u in staat	☐	☐	☐	☐
A Een voorwerp van 2,5 kg boven uw hoofd vast te nemen?	☐	☐	☐	☐
B Zich te bukken om een kledingstuk op te rapen?				
7. ***HET GEBRUIK VAN DE HANDEN:***				
Bent u in staat				
A Een autodeur te openen?	☐	☐	☐	☐
B Het deksel los te schroeven van een pot die reeds werd geopend?	☐	☐	☐	☐
C Een kraan open en dicht te draaien?	☐	☐	☐	☐
8. ***ANDERE ACTIVITEITEN:***				
Bent u in staat				
A Uw boodschappen te doen?	☐	☐	☐	☐
B In en uit een auto te stappen?	☐	☐	☐	☐
C Huishoudelijke taken te verrichten zoals stofzuigen of een beetje in de tuin werken?	☐	☐	☐	☐
Score toegekend aan elke kolom →	0	1	2	3
TOTAAL	……	……	……	……

EXTRA : Vragenlijst Dagelijks Functioneren: HAQ Spondyloarthropathie

1. **ACTIVITEITEN**: Bent u in staat				
A Zware pakken te dragen, zoals zakken met boodschappen?	☐	☐	☐	☐
B Gedurende lange perioden te zitten, zoals op uw werk?	☐	☐	☐	☐
C Aan een tafel of bureau met vlak werkoppervlak te werken?	☐	☐	☐	☐
2. **MET DE AUTO RIJDEN**: **Hier aankruisen _____ als u GEEN rijbewijs of een auto hebt** Bent u in staat:				
A Om in de achteruitkijkspiegel te kijken?	☐	☐	☐	☐
B Om uw hoofd te draaien om achteruit te rijden?	☐	☐	☐	☐

Addendum 7f:
Patient-Reported Outcomes

ASAS- Health Index

Beantwoord aub elk van de onderstaande uitspraken door het antwoord te markeren dat **op dit ogenblik** het best bij u past wanneer u denkt aan uw reumatische ziekte (elke vorm van spondyloarthritis, zoals de ziekte van Bechterew)

1. Pijn verstoort soms mijn dagelijkse activiteiten.
   - □ Mee eens
   - □ Mee oneens

2. Ik heb moeite met lang staan.
   - □ Mee eens
   - □ Mee oneens

3. Ik heb moeite met hardlopen (rennen).
   - □ Mee eens
   - □ Mee oneens

4. Ik heb moeite met het gebruiken van een toilet.
   - □ Mee eens
   - □ Mee oneens

5. Ik ben vaak uitgeput.
   - □ Mee eens
   - □ Mee oneens

6. Ik ben minder gemotiveerd dan voorheen om iets te doen dat lichamelijke inspanning kost.
   - □ Mee eens
   - □ Mee oneens

7. Ik heb geen zin meer in seks.
   - □ Mee eens
   - □ Mee oneens
   - □ Niet van toepassing, ik wil deze vraag niet beantwoorden

8. Ik heb moeite met het bedienen van de pedalen in de auto.
   - □ Mee eens
   - □ Mee oneens
   - □ Niet van toepassing / ik kan niet rijden / ik rijd nooit

9. Ik heb moeite met het in contact komen met mensen.
   - □ Mee eens
   - □ Mee oneens

10. Ik kan buiten niet op een vlakke ondergrond wandelen.
    - □ Mee eens
    - □ Mee oneens

11. Ik heb moeite om me te concentreren.
    - □ Mee eens
    - □ Mee oneens

12. Ik kan minder goed reizen door mijn beperkte beweeglijkheid.

□ Mee eens
□ Mee oneens

13. Ik raak vaak gefrustreerd.
□ Mee eens
□ Mee oneens

14. Ik heb moeite met het wassen van mijn haren.
□ Mee eens
□ Mee oneens

15. Ik heb financiële veranderingen ervaren door mijn reumatische aandoening.
□ Mee eens
□ Mee oneens

16. Ik slaap 's nachts slecht.
□ Mee eens
□ Mee oneens

17. Ik heb het gevoel dat ik mijn problemen niet kan overwinnen.
□ Mee eens
□ Mee oneens

Addendum 7g:
Patient-Reported Outcomes

EQ-5D

Zet bij iedere groep in de lijst hieronder een kruisje in het hokje dat het best past bij uw gezondheid VANDAAG.

MOBILITEIT

Ik heb geen problemen met lopen ❑
Ik heb een beetje problemen met lopen ❑
Ik heb matige problemen met lopen ❑
Ik heb ernstige problemen met lopen ❑
Ik ben niet in staat om te lopen ❑

ZELFZORG

Ik heb geen problemen met mijzelf wassen of aankleden ❑
Ik heb een beetje problemen met mijzelf wassen of aankleden ❑
Ik heb matige problemen met mijzelf wassen of aankleden ❑
Ik heb ernstige problemen met mijzelf wassen of aankleden ❑
Ik ben niet in staat mijzelf te wassen of aan te kleden ❑

DAGELIJKSE ACTIVITEITEN *(bijv werk, studie, huishouden, gezins- en vrijetijdactiviteiten)*

Ik heb geen problemen met mijn dagelijkse activiteiten ❑
Ik heb een beetje problemen met mijn dagelijkse activiteiten ❑
Ik heb matige problemen met mijn dagelijkse activiteiten ❑
Ik heb ernstige problemen met mijn dagelijkse activiteiten ❑
Ik ben niet in staat mijn dagelijkse activiteiten uit te voeren ❑

PIJN/ ONGEMAK

Ik heb geen pijn of ongemak ❑
Ik heb een beetje pijn of ongemak ❑
Ik heb matige pijn of ongemak ❑
Ik heb ernstige pijn of ongemak ❑
Ik heb extreme pijn of ongemak ❑

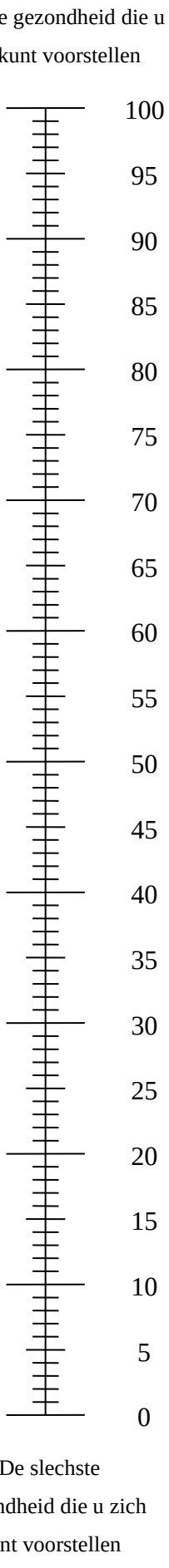
ANGST / SOMBERHEID

Ik ben niet angstig of somber ❑
Ik ben een beetje angstig of somber ❑
Ik ben matig angstig of somber ❑
Ik ben erg angstig of somber ❑
Ik ben extreem angstig of somber ❑

- We willen weten hoe goed of slecht uw gezondheid VANDAAG is.
- Deze meetschaal loopt van 0 tot 100.
- 100 staat voor de <u>beste</u> gezondheid die u zich kunt voorstellen.

  0 staat voor de <u>slechtste</u> gezondheid die u zich kunt voorstellen.
- Markeer een X op de meetschaal om aan te geven hoe uw gezondheid VANDAAG is.
- Noteer het getal waarbij u de X heeft geplaatst in onderstaand vakje.

UW GEZONDHEID VANDAAG = ☐



Addendum 7h:
Patient-Reported Outcomes

Co-morbidity index

De vragenlijst bijkomende ziektebeelden (SCQ)

Het volgende is een lijst van veelvoorkomende ziektebeelden. Wilt u aangeven (d.m.v. omcirkelen van het antwoord dat op u van toepassing is), of u op dit moment lijdt aan één van de ziektebeelden in de eerste kolom. Zo niet, dan kunt U verder gaan met het volgende ziektebeeld. Als u wel bekend bent met dit ziektebeeld, wilt u dan in de tweede kolom aangeven of u hiervoor medicijnen gebruikt of een andere behandeling krijgt. In de derde kolom kunt u aangeven of de ziekte u beperkt in één van uw activiteiten.
Tot slot kunt u maximaal drie ziektebeelden aangeven waar u wel aan lijdt, maar die niet in deze lijst zijn opgenomen.

	HEBT U DIT ZIEKTEBEELD ?		**WORDT U VOOR DIT ZIEKTEBEELD BEHANDELD?**		**BEPERKT DIT ZIEKTEBEELD UW ACTIVITEITEN ?**	
Ziektebeeld	**Nee**	**Ja**	**Nee**	**Ja**	**Nee**	**Ja**
Aandoening van het hart	N	J	N	J	N	J
Hoge bloeddruk.....	N	J	N	J	N	J
Longaandoening	N	J	N	J	N	J
Diabetes (suikerziekte).....	N	J	N	J	N	J
Maagzweer of een andere maagaandoening.	N	J	N	J	N	J
Nieraandoening.....	N	J	N	J	N	J
Leveraandoening	N	J	N	J	N	J
Bloedarmoede of een andere bloedziekte	N	J	N	J	N	J
Kanker.....	N	J	N	J	N	J
Depressie.....	N	J	N	J	N	J
Andere medische problemen (vult u deze hieronder in):						
1.....	N	J	N	J	N	J
2.....	N	J	N	J	N	J
3.....	N	J	N	J	N	J

Addendum 7i:
Patient-Reported Outcomes

Vragenlijst zorgconsumptie en productiviteit (baseline)

Vragenlijst over uw gebruik van gezondheidszorg: in de afgelopen 6 maanden (bij start van de studie (week 0) en Fase B week 72, 96, 120, 144)

Met deze vragenlijst willen we al uw zorggebruik vastleggen. Dus niet alleen uw zorggebruik voor uw reumatische aandoening.

Vraag 1. Hoe vaak bent u in de afgelopen 6 maanden bij deze zorgverlener(s) geweest?
OPGELET ! Visites in het kader van deze studie dient u NIET te noteren TENZIJ een extra visite moest worden ingepland omwille van gezondheidsredenen.
('0' invullen als u er niet geweest bent)

Type zorgverlener	***Aantal daadwerkelijke bezoeken***
voorbeeld cardioloog	*voorbeeld* 2 keer
huisarts	… keer
reumatoloog	… keer
andere specialist	… keer
arts eerste hulp (spoedgevallen)	… keer
psychotherapeut of psychiater	… keer
bedrijfsarts	… keer
gespecialiseerde verpleegkundige	… keer
Kinesitherapeut of ergotherapeut	… keer
andere*: ……..	… keer

*: Zoals psycholoog, chiropractor, medisch diëtist, medisch pedicure,…
Alternatieve gezondheidszorgverleners (acupuncturist, homeopaat, etc.) hoeft u NIET te vermelden.

Vraag 2. Hoe vaak had u in de afgelopen 6 maanden een van de onderstaande onderzoeken ?
OPGELET ! Geplande onderzoeken in het kader van deze studie dient u NIET te noteren TENZIJ een extra onderzoek moest worden ingepland omwille van gezondheidsredenen.
(a.u.b.'0' invullen als u geen onderzoek heeft gehad)

Type onderzoek	***Aantal keer dat het onderzoek gebeurde***
Laboratorium test (bloed)	… keer
MRI	… keer
Echo	… keer
Röntgen onderzoek (dit is een gewone RX)	… keer
Ander onderzoek:	… keer

Vraag 3. Bent u in de afgelopen 6 maanden overdag in het ziekenhuis geweest voor een behandeling? OPGELET ! De biopsie uitgevoerd in kader van deze studie moet u niet noteren.
U bleef hierbij niet slapen. U kwam bijvoorbeeld naar het infuuscentrum of dagcentrum.

Soort dagbehandeling	***Aantal dagbehandelingen***
bloedtransfusie	… keer
infuus biological (bijv. infliximab)	… keer
revalidatie dagbehandeling	… keer
dialyse	… keer
pijnbehandeling	… keer
Operatie / ingreep in dagbehandeling	… keer
andere: ……..	… keer

Vraag 4. Heeft u in de afgelopen 6 maanden dagen doorgebracht in de volgende zorginstellingen? U bleef hierbij slapen.

Soort zorginstelling	***Hoeveel dagen verbleef u de afgelopen 6 maanden in zulke instelling?***
ziekenhuis	… dagen
revalidatiecentrum	… dagen
psychiatrische instelling	… dagen
verpleeghuis	… dagen
bejaardenhuis	… dagen

Vraag 5. Hoeveel uren per week heeft u in de afgelopen 6 maanden gebruik gemaakt van volgende diensten?

Type dienstverlening	***Gemiddeld aantal uren per week***
professionele thuiszorg (betaalde huishoudhulp)	… uren
hulp van familie of vrienden in verband met uw gezondheid (onbetaalde hulp)	… uren
andere: ……..	… uren

Vragen over uw werk

Vraag 6. Hebt u momenteel betaald werk? Met betaald werk bedoelen we beroepsmatige werkzaamheden van minsten 8 uur per week. Studenten job zijn daarbij uitgesloten. Kruis het goede antwoord aan.

- ❑ Ja, ik heb momenteel betaald werk.
- ❑ Nee, ik heb momenteel geen betaald werk: ga dan naar vraag 12

Vraag 7. Indien u momenteel betaald werk hebt

a. Wanneer startte u met uw eerste betaalde werk

In het jaar ..…... (maand: ……..)

b. Hoeveel uur per week werkt u momenteel?

Tel alleen de uren waarvoor u betaald wordt. Werkt u niet elke week evenveel uren, neem dan het gemiddelde.

…… uren per week

b. Op hoeveel dagen in de week werkt u momenteel?

Werkt u niet elke week evenveel dagen, neem dan het gemiddelde.

…… dagen per week

c. Welk type beroepsomschrijving (in uw huidige werk) past best bij u ?

- ☐ landbouwer
- ☐ ambachts man (tuinonderhoud, schoenmaker, etc)
- ☐ Bediende, leerkracht,
- ☐ Dienstverlenend (verkoop, horeca, conciërge, verpleging, etc)
- ☐ arbeider
- ☐ Thuiszorg, onderhoudswerk, bejaardenhulp
- ☐ Hoger kader, leidinggevend, universitair beroep
- ☐ overig: ……

Is dit een beroep als zelfstandige

- ❑ Ja, .
- ❑ nee

Vraag 8. **a. Hoeveel keer (periodes) heeft u verzuimd de <u>afgelopen 6 maanden</u>, ten gevolge van uw gezondheid?**
…… keer.

b. Per verzuimperiode: hoeveel werkdagen verzuimde u? *Opgelet: indien u een halve dag miste, tel dit dan als '0,5'. Graag '0,0' invullen als u geen dagen afwezig was.*

	Aantal werkdagen
1ste verzuim periode	. . . , . . .
2e verzuimperiode	. . . , . . .
3e verzuimperiode	. . . , . . .
4e verzuimperiode	. . . , . . .
5e verzuimperiode	. . . , . . .
6e verzuimperiode	. . . , . . .
Overige periode (totaal)	. . . , . . .

Vraag 9. **Waren er dagen waarop u wel gewerkt heeft, maar tijdens uw werk last had van uw lichamelijke of psychische problemen?** Het gaat om dagen in de <u>afgelopen 4 weken</u>.
☐ Ja
☐ Nee

Heeft u "Ja" aangekruist? Beantwoord dan vraag 10 en 11.
Ga anders verder met vraag 12.

Vraag 10. **Op hoeveel werkdagen had u tijdens uw werk last van gezondheids-problemen?** Tel alleen de werkdagen in de <u>afgelopen 4 weken</u>.
…… werkdagen.

Vraag 11. **Op de dagen dat u last had, kon u misschien niet zoveel werk doen als normaal. Hoeveel werk kon u op deze dagen gemiddeld doen?** Kijk naar de cijfers hieronder. Een 10 betekent dat u op deze dagen net zoveel kon doen als normaal. Een 0 betekent dat u op deze dagen niets kon doen. Zet een cirkel om het goede cijfer.

Ik kon op deze dagen niets doen				Ik kon onge-veer de helft doen					Ik kon net zoveel doen als normaal	
0	1	2	3	4	5	6	7	8	9	10

Vraag 12. **Waren er dagen waarop u thuis minder kon doen door uw lichamelijke of psychische problemen?** Het gaat om dagen in de <u>afgelopen 4 weken</u>.
☐ Ja
☐ Nee
Heeft u "Ja" aangekruist? Beantwoord dan vraag 13 en 14.

Vraag 13. **Op hoeveel dagen was dit zo?** Tel alleen de dagen in de afgelopen 4 weken.
…… dagen.

Vraag 14. **Stel dat een familielid of buurvrouw/kennis u op deze dagen had geholpen. En alles wat u thuis niet kon doen, voor u had gedaan. Hoeveel uur was uw familielid of buurvrouw/kennis hier op deze dagen dan gemiddeld mee bezig geweest?**

Gemiddeld …… uur op deze dagen.

Vraag 15. De volgende vragen lijken erg op de voorgaande vragen. Omwille van wetenschappelijke redenen willen we de twee verschillende manieren vergelijken om het effect van gezondheid op werk te meten
Met de volgende vragen wil men bepalen wat de **invloed is van uw gezondheid op uw vermogen om te werken en om uw dagelijkse bezigheden** uit te voeren.

a. Hebt u op dit moment een baan (werkt u tegen betaling)?

   Nee:□
   Ja: □
   Indien NEEN, Zet een kruisje bij Nee en ga verder **naar vraag f**.

De volgende vragen hebben betrekking op de **afgelopen zeven dagen**, vandaag niet inbegrepen

b. Hoeveel uur was u tijdens de afgelopen zeven dagen afwezig van uw betaalde werk vanwege problemen i.v.m. uw gezondheid? Reken hierbij de uren die u gemist hebt op dagen waarop u ziek was, later op het werk kwam, vroeger wegging enz. i.v.m. uw gezondheid. Reken hier de tijd die u gemist hebt omdat u aan deze studie deelneemt niet bij.

   _____ UUR

c. Hoeveel uur bent u tijdens de afgelopen zeven dagen afwezig geweest van uw betaalde werk vanwege een andere reden, zoals vakantie, feestdagen, tijd die u vrij hebt genomen, om aan deze studie deel te nemen?

   ……. UUR

d. Hoeveel tijd hebt u in de afgelopen zeven dagen daadwerkelijk (betaald) gewerkt?

(Indien “0” ga door naar vraag 6)

……. UUR

e. Hoezeer heeft uw gezondheid tijdens de afgelopen zeven dagen uw productiviteit beïnvloed terwijl u op het werk was? Denk aan de dagen waarop u beperkt werd in de hoeveelheid of het soort werk dat u kon doen, minder bereikte dan u gewild had of niet zo zorgvuldig kon werken als gewoonlijk. Indien uw gezondheid weinig invloed op uw werk had, kies dan een laag getal. Kies een hoog getal indien uw gezondheid veel invloed had op uw werk.

Mijn gezondheid had geen invloed op mijn werk	0	1	2	3	4	5	6	7	8	9	10	Mijn gezondheid heeft mij volledig belet mijn werk te doen

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f. Hoezeer heeft uw gezondheid tijdens de afgelopen zeven dagen uw vermogen beïnvloed uw normale dagelijkse bezigheden, buiten uw baan, uit te voeren? Met normale bezigheden bedoelen we de activiteiten die u gewoonlijk uitvoert zoals huishoudelijk werk, winkelen, voor de kinderen zorgen, lichaamsbeweging, studeren enz. Denk aan de momenten waarop u beperkt werd in de hoeveelheid of soort activiteiten die u kon doen of minder bereikte dan u gewild had. Indien de gezondheid weinig invloed had op uw activiteiten, kies dan een laag getal. Kies een hoog indien de gezondheid veel invloed had op uw activiteiten.

Mijn gezondheid had geen invloed op mijn dagelijkse activiteiten	0	1	2	3	4	5	6	7	8	9	10	Mijn gezondheid heeft mij volledig belet mijn dagelijkse activiteiten uit te voeren

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Addendum 7j:
Patient-Reported Outcomes

Vragenlijst zorgconsumptie en productiviteit (Follow-up)

Vragenlijst over uw gebruik van gezondheidszorg in de afgelopen 3 maanden (Fase A week 12, 24, 36, 48 en 60 en Fase B 12, 24, 36 en 48)

Met deze vragenlijst willen we al uw zorggebruik vastleggen. Dus niet alleen uw zorggebruik voor uw reumatische aandoening.

Vraag 1. Hoe vaak bent u in de afgelopen 3 maanden bij deze zorgverlener(s) geweest? OPGELET! Visites in het kader van deze studie dient u NIET te noteren TENZIJ een extra visite moest worden ingepland omwille van gezondheidsredenen.
('0' invullen als u er niet geweest bent)

Type zorgverlener	*Aantal daadwerkelijke bezoeken*
voorbeeld cardioloog	*voorbeeld* 2 keer
huisarts	…… keer
reumatoloog	… keer
andere specialist	… keer
arts eerste hulp (spoedgevallen)	… keer
Psychotherapeut of psichiater	… keer
bedrijfsarts	… keer
gespecialiseerde verpleegkundige	… keer
Kinesitherapeut of ergotherapeut	… keer
andere*: ……	… keer

*: Zoals psycholoog, chiropractor, medisch diëtist, medisch pedicure,… Alternatieve gezondheidszorgverleners (acupuncturist, homeopaat, etc.) hoeft u NIET te vermelden.

Vraag 2. Hoe vaak had u in de afgelopen 3 maanden een van de onderstaande onderzoeken ? OPGELET ! Geplande onderzoeken in het kader van deze studie dient u NIET te noteren TENZIJ een extra onderzoek moest worden ingepland omwille van gezondheidsredenen.
(a.u.b.'0' invullen als u geen onderzoek heeft gehad)

Type onderzoek	*Aantal keer dat het onderzoek gebeurde*
Laboratorium test (bloed)	… keer
MRI	… keer
Echo	… keer
Röntgen onderzoek (dit is een gewone RX)	… keer
Ander onderzoek:	… keer
Ander onderzoek	… keer

Vraag 3. Bent u in de afgelopen 3 maanden overdag in het ziekenhuis geweest voor een behandeling? U bleef hierbij niet slapen. U kwam bijvoorbeeld naar het infuuscentrum of dagcentrum.

Soort dagbehandeling	***Aantal dagbehandelingen***
bloedtransfusie	… keer
infuus biological (bijv. infliximab)	… keer
revalidatie dagbehandeling	… keer
dialyse	… keer
pijnbehandeling	… keer
Operatie / ingreep in dagbehandeling	… keer
andere: ……..	… keer

Vraag 4. Heeft u in de afgelopen 3 maanden dagen doorgebracht in de volgende zorginstellingen? U bleef hierbij slapen.

Soort zorginstelling	***Hoeveel dagen verbleef u de afgelopen 6 maanden in zulke instelling?***
ziekenhuis	… dagen
revalidatiecentrum	… dagen
psychiatrische instelling	… dagen
verpleeghuis	… dagen
bejaardenhuis	… dagen

Vraag 5. Hoeveel uren per week heeft u in de afgelopen 6 maanden gebruik gemaakt van volgende diensten?

Type dienstverlening	***Gemiddeld aantal uren per week***
professionele thuiszorg (betaalde huishoudhulp)	… uren
hulp van familie of vrienden in verband met uw gezondheid (onbetaalde hulp)	… uren
andere: ……..	… uren

Vragen over uw werk

Vraag 6. Hebt u momenteel betaald werk? Met betaald werk bedoelen we beroepsmatige werkzaamheden van minsten 8 uur per week. Studenten job zijn daarbij uitgesloten. Kruis het goede antwoord aan.

- ❑ Ja, ik heb momenteel betaald werk.
- ❑ Nee, ik heb momenteel geen betaald werk: ga dan naar vraag 12

Vraag 7. Indien u momenteel betaald werk hebt

a. Wanneer startte u met uw eerste betaalde werk

In het jaar ..…... (maand: ……..)

b. Hoeveel uur per week werkt u momenteel?

Tel alleen de uren waarvoor u betaald wordt. Werkt u niet elke week evenveel uren, neem dan het gemiddelde.

…… uren per week

b. Op hoeveel dagen in de week werkt u momenteel?

Werkt u niet elke week evenveel dagen, neem dan het gemiddelde.

…… dagen per week

c. **Welk type beroepsomschrijving (in uw huidige werk) past best bij u ?**

- ☐ landbouwer
- ☐ ambachts man (tuinonderhoud, schoenmaker, etc)
- ☐ Bediende, leerkracht,
- ☐ Dienstverlenend (verkoop, horeca, conciërge, verpleging, etc)
- ☐ arbeider
- ☐ Thuiszorg, onderhoudswerk, bejaardenhulp
- ☐ Hoger kader, leidinggevend, universitair beroep
- ☐ overig: ……

Is dit een beroep als zelfstandige

- ❑ Ja, .
- ❑ nee

Vraag 8. **a. Hoeveel keer (periodes) heeft u verzuimd de <u>afgelopen 3 maanden</u>, ten gevolge van uw gezondheid?**
…… keer.

b. Per verzuimperiode: hoeveel werkdagen verzuimde u?
Opgelet: indien u een halve dag miste, tel dit dan als '0,5'.
Graag '0,0' invullen als u geen dagen afwezig was.

	Aantal werkdagen
1ste verzuim periode	. . . , . . .
2e verzuimperiode	. . . , . . .
3e verzuimperiode	. . . , . . .
4e verzuimperiode	. . . , . . .
Overige periode (totaal)	. . . , . . .

Vraag 9. **Waren er dagen waarop u wel gewerkt heeft, maar tijdens uw werk last had van uw lichamelijke of psychische problemen?** Het gaat om dagen in de <u>afgelopen 4 weken</u>.
☐ Ja
☐ Nee

Heeft u "Ja" aangekruist? Beantwoord dan vraag 10 en 11.
Ga anders verder met vraag 12.

Vraag 10. **Op hoeveel werkdagen had u tijdens uw werk last van gezondheids-problemen?** Tel alleen de werkdagen in de <u>afgelopen 4 weken</u>.
…… werkdagen.

Vraag 11. **Op de dagen dat u last had, kon u misschien niet zoveel werk doen als normaal. Hoeveel werk kon u op deze dagen gemiddeld doen?** Kijk naar de cijfers hieronder. Een 10 betekent dat u op deze dagen net zoveel kon doen als normaal. Een 0 betekent dat u op deze dagen niets kon doen. Zet een cirkel om het goede cijfer.

Ik kon op deze dagen niets doen				Ik kon onge-veer de helft doen					Ik kon net zoveel doen als normaal	
0	1	2	3	4	5	6	7	8	9	10

Vraag 12. **Waren er dagen waarop u thuis minder kon doen door uw lichamelijke of psychische problemen?** Het gaat om dagen in de afgelopen 4 weken.

☐ Ja
☐ Nee

Heeft u "Ja" aangekruist? Beantwoord dan vraag 13 en 14.

Vraag 13. **Op hoeveel dagen was dit zo?** Tel alleen de dagen in de afgelopen 4 weken.
…… dagen.

Vraag 14. **Stel dat een familielid of buurvrouw/kennis u op deze dagen had geholpen. En alles wat u thuis niet kon doen, voor u had gedaan. Hoeveel uur was uw familielid of buurvrouw/kennis hier op deze dagen dan gemiddeld mee bezig geweest?**

Gemiddeld …… uur op deze dagen.

Vraag 15. De volgende vragen lijken erg op de voorgaande vragen. Omwille van wetenschappelijke redenen willen we de twee verschillende manieren vergelijken om het effect van gezondheid op werk te meten
Met de volgende vragen wil men bepalen wat de **invloed is van uw gezondheid op uw vermogen om te werken en om uw dagelijkse bezigheden** uit te voeren.

g. Hebt u op dit moment een baan (werkt u tegen betaling)?

Nee:☐
Ja: ☐
Indien NEEN, Zet een kruisje bij Nee en ga verder **naar vraag I**.

De volgende vragen hebben betrekking op de **afgelopen zeven dagen**, vandaag niet inbegrepen

h. Hoeveel uur was u tijdens de afgelopen zeven dagen afwezig van uw betaalde werk vanwege problemen i.v.m. uw gezondheid? Reken hierbij de uren die u gemist hebt op dagen waarop u ziek was, later op het werk kwam, vroeger wegging enz. i.v.m. uw gezondheid. Reken hier de tijd die u gemist hebt omdat u aan deze studie deelneemt niet bij.

_____ UUR

i. Hoeveel uur bent u tijdens de afgelopen zeven dagen afwezig geweest van uw betaalde werk vanwege een andere reden, zoals vakantie, feestdagen, tijd die u vrij hebt genomen, om aan deze studie deel te nemen?

……. UUR

j. Hoeveel tijd hebt u in de afgelopen zeven dagen daadwerkelijk (betaald) gewerkt?

(Indien “0” ga door naar vraag 6)

……. UUR

k. Hoezeer heeft uw gezondheid tijdens de afgelopen zeven dagen uw productiviteit beïnvloed terwijl u op het werk was? Denk aan de dagen waarop u beperkt werd in de hoeveelheid of het soort werk dat u kon doen, minder bereikte dan u gewild had of niet zo zorgvuldig kon werken als gewoonlijk. Indien uw gezondheid weinig invloed op uw werk had, kies dan een laag getal. Kies een hoog getal indien uw gezondheid veel invloed had op uw werk.

Mijn gezondheid had geen invloed op mijn werk	0	1	2	3	4	5	6	7	8	9	10	Mijn gezondheid heeft mij volledig belet mijn werk te doen

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l. Hoezeer heeft uw gezondheid tijdens de afgelopen zeven dagen uw vermogen beïnvloed uw normale dagelijkse bezigheden, buiten uw baan, uit te voeren? Met normale bezigheden bedoelen we de activiteiten die u gewoonlijk uitvoert zoals huishoudelijk werk, winkelen, voor de kinderen zorgen, lichaamsbeweging, studeren enz. Denk aan de momenten waarop u beperkt werd in de hoeveelheid of soort activiteiten die u kon doen of minder bereikte dan u gewild had. Indien de gezondheid weinig invloed had op uw activiteiten, kies dan een laag getal. Kies een hoog indien de gezondheid veel invloed had op uw activiteiten.

Mijn gezondheid had geen invloed op mijn dagelijkse activiteiten	0	1	2	3	4	5	6	7	8	9	10	Mijn gezondheid heeft mij volledig belet mijn dagelijkse activiteiten uit te voeren

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Addendum 7k:
Patient-Reported Outcomes

EDUCATION AND WORKING STATUS (Baseline)

Q1 Uw hoogst behaalde diploma is:
- ☐ Lager onderwijs
- ☐ Secundair onderwijs (ASO, TSO, KSO)
- ☐ Beroepsonderwijs (BSO)
- ☐ Buitengewoon onderwijs (BUSO)
- ☐ Hoger niet-universitair onderwijs
- ☐ Universitair onderwijs
- ☐ Post-universitair onderwijs

Q2 Verricht u **momenteel** betaalde arbeid *(studentenjob niet inbegrepen)*?
- ☐ Ja
- ☐ Nee

Q3 Indien u 'nee' antwoordde op Q2 (u werkt momenteel niet), heeft u **voorheen** betaald werk verricht?
- ☐ Ja
- ☐ Nee

Q4 Indien u ooit werkte (nu of in het verleden), wat is de datum dat u startte met uw eerste betaalde job *(studentenjob niet inbegrepen)*?
___/___/____

Q5 Indien u 'nee' antwoordde op Q2 (u verricht geen betaalde arbeid), wat is de reden hiervoor?
- ☐ Student
- ☐ Gepensioneerd *(= u ontvangt een pensioenuitkering)* sinds ___/___/_____
- ☐ Huisman/huisvrouw sinds ___/___/_____
- ☐ Werkloos sinds ___/___/_____
- ☐ Arbeidsongeschikt - gedeeltelijk of geheel *(= u ontvangt een ziekte- of invaliditeitsuitkering)* sinds ___/___/_____
  omwille van:
  - ☐ reuma
  - ☐ andere reden, specifieer: ..…….....

Q6 Indien u 'ja' antwoordde op Q2 (u verricht betaalde arbeid), hoeveel dagen per week werkt u?
_____ dagen per week

Q7 Indien u 'ja' antwoordde op Q2 (u verricht betaalde arbeid), hoeveel uren per week werkt u?
_____ uren per week

Q8 Indien U ooit werkte (nu of in het verleden), wat is/was uw huidige of laatst betaalde job?
……..

Q9 Indien U ooit werkte (nu of in het verleden), wat is/was het **statuut** van uw huidige of laatst betaalde job?
- ☐ Ambtenaar
- ☐ Arbeider
- ☐ Bediende
- ☐ Zelfstandige
- ☐ Vrij beroep (arts, advocaat, notaris, …)
- ☐ Andere, specifieer: ……

Q10 Wat is/was voor u van toepassing met betrekking tot uw huidige of laatst betaalde job?

- ☐ Full time
- ☐ Part time omwille van gezondheidsredenen:
  - ☐ Omwille van reuma
  - ☐ Omwille van andere gezondheidsreden, specifieer: ……..
- ☐ Part time omwille van andere redenen (bv. opvang van de kinderen, zorg voor een ouder), specifieer: ……

Q11 Wat is/was de **aard** van uw huidige of laatst betaalde job?

- ☐ Vnl. lichamelijk werk (meer dan 60% van de tijd)
- ☐ Vnl. geestelijk werk (meer dan 60% van de tijd)
- ☐ Zowel lichamelijk als geestelijk werk

Q12 In welke **sector** bent/was u werkzaam bij uw huidige of laatste betaalde job?

- ☐ Pedagogisch beroep (leerkracht, docent, instructeur, kleuterleidster, …)
- ☐ Creatief of taalkundig beroep (auteur, journalist, kunstenaar, productontwerper, interieurontwerp, grafisch vormgever, fotograaf, bibliothecaris, …)
- ☐ Commercieel beroep (vertegenwoordiger, sales, PR, marketing, winkelier, kassierster, verkoopmedewerker, …)
- ☐ Bedrijfseconomisch of administratief beroep (secretariaat, boekhouder, econoom, beleidsadviseur, HR, receptionist, transportplanner, logistiek medewerker, …)
- ☐ Managers (in administratieve of commerciële dienstverlening, in ICT, in een zorginstelling, in het onderwijs, in de logistiek, in de horeca of detail- of groothandel)
- ☐ Openbaar bestuur, veiligheid of juridisch beroep (jurist, overheidsambtenaar, politie, brandweer, militair, beveiligingspersoneel, …)
- ☐ Technisch beroep (bioloog, natuurwetenschapper, ingenieur, architect, technicus industrie en bouw, procesoperator, bouwarbeider, assemblagemedewerker, metaalbewerker, lasser, automecanicien, elektricien, slager, bakker, meubelmaker)
- ☐ ICT beroep (software- en applicatie ontwikkelaar, netwerkspecialist, radio of TV)
- ☐ Agrarisch beroep (land- en tuinbouw, hovenier, veeteler, …)
- ☐ Zorg en welzijn beroep (arts, verpleegkundige, zorgkundige, kinesitherapeut, psycholoog, maatschappelijk assistent, laborant, apotheker, …)
- ☐ Dienstverlenend beroep (kok, kelner, kapper, schoonheidsspecialist, schoonmaak)
- ☐ Transport en logistiek beroep (piloot, bus-, tram-, taxi- of vrachtwagenchauffeur, laden en lossen, vuilnisman, …)
- ☐ Overige, specifieer: ……

EDUCATION AND WORKING STATUS (Follow-up 3 of 6 maanden)

Q13 Sinds de **start van deze studie**: *(meerdere antwoorden mogelijk)*

- Doet u nog steeds dezelfde job
- Bent u nog steeds student
- Bent u veranderd van job sinds ___/___/_____
  Specifieer naam, statuut, aard, sector en full/part time van uw **voorgaande** job:
  ……
- Bent u op pensioen gegaan sinds ___/___/____
- Bent u afgestudeerd en beginnen werken sinds ___/___/_____
- Bent u werkloos geweest
  van ___/___/_____ tem ___/___/_____
  van ___/___/_____ tem ___/___/_____
  van ___/___/_____ tem ___/___/_____
  van ___/___/_____ tem ___/___/_____

Q14 Hoeveel keren was u **in de afgelopen 3/6 maanden**, gedurende korte of langere periode, afwezig op het werk **omwille van een gezondheidsprobleem** (indien u een betaalde job had)?
___ keer omwille van reuma
___ keer omwille van een ander gezondheidsprobleem

Q15 Hoeveel werkdagen per keer heeft u zich **in de afgelopen 3/6 maanden** ziek gemeld **omwille van een gezondheidsprobleem** (indien u een betaalde job had)?

- 1e keer: ___ werkdagen omwille van reuma ander gezondheidsprobleem
- 2e keer: ___ werkdagen omwille van reuma ander gezondheidsprobleem
- 3e keer: ___ werkdagen omwille van reuma ander gezondheidsprobleem
- 4e keer: ___ werkdagen omwille van reuma ander gezondheidsprobleem

Q16 Werd u ooit opgenomen in het ziekenhuis voor een korte of langere periode **omwille van uw reuma**?

- Nee
- Ja
  - Hoeveel dagen werd u opgenomen in het ziekenhuis? ____ dagen
  - In welke periode werd u opgenomen in het ziekenhuis? ___/___/_____

Q17 Geniet U van fiscale, financiële of sociale voordelen via een inschrijving bij de FOD Sociale Zekerheid (via het 18 punten systeem)?
Het gaat hier om een integratietegemoetkoming die wordt toegekend aan de gehandicapte persoon vanaf 21 jaar die ten gevolge van verminderde zelfredzaamheid, bijkomende kosten heeft om zich in het maatschappelijk leven in te passen. Cave: ***verschilt*** *van de inkomensvervangende tegemoetkoming die wordt uitgekeerd aan een persoon ouder dan 21 jaar die wegens zijn handicap niet in staat is om een derde te verdienen van wat een gezonde persoon op de algemene arbeidsmarkt kan verdienen.*

- Ja
- Nee

Q18 Hebt U nood aan een integratietegemoetkoming of zou U dergelijke tegemoetkoming willen aanvragen?

- Ja
- Nee

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 Biopsie vragenlijst

Mogen wij u vragen
om onderstaande vragen met betrekking tot de uitgevoerde biopsie te beantwoorden?

1. Hoeveel pijn of ongemak hebt u ondervonden tijdens de procedure?
   Omcirkel uw

   ☐ Geen ☐ Mild ongemak ☐ Matig ongemak ☐ Milde pijn ☐ Ernstige pijn

2. Duid aan hoe uw gewricht voelde in de voorbije 3-4 dagen wat betreft pijn, stramheid of zwelling:

   Pijn :
   Hoeveel pijn hebt u gehad in het gebiopseerde gewricht?

0	1	2	3	4	5	6	7	8	9	10
Geen pijn										Ernstige pijn

   Gewrichtsstramheid :
   Hoeveel stramheid hebt u gehad in het gebiopseerde gewricht?

0	1	2	3	4	5	6	7	8	9	10
Geen stramheid										Ernstige stramheid

   Gewrichtszwelling :
   Hoeveel zwelling hebt u gehad in het gebiopseerde gewricht?

0	1	2	3	4	5	6	7	8	9	10
Geen zwelling										Ernstige zwelling

3. Heeft u de eerstvolgende dagen na de biopsie pijnstillers moeten nemen omwille van pijn aan het gebiopseerde gewricht?

   ☐ ja ☐ neen

4. Indien u reeds pijnstillers nam voor de biopsie, was het nodig om de dosis aan te passen/verhogen omwille van de biopsie?

   ☐ ja ☐ neen

5. Indien u vraag 3 of 4 met ‘Ja’ beantwoord heeft:
   Specifieer hieronder welke pijnstiller(s) u heeft genomen en noteer de dagelijkse dosis

Naam Pijnstiller	**Dagelijkse dosis**	**Start datum**	**Stop datum**
…… ……	…… mg	……	…… …….
…… ……	…… mg	……	…… …….
…… ……	…… mg	……	…… …….
…… ……	…… mg	……	…… …….
…… ……	…… mg	……	…… …….

6. Zou u dit onderzoek opnieuw laten uitvoeren mocht dit in de evolutie van uw ziekte op een bepaald ogenblik belangrijk zijn?

   ☐ ja ☐ neen

Addendum 10

CIOMS FORM

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



GCD-SOP-601.4
Intake Form Instructio

Addendum 11

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)

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***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 :