PROTOCOL

A MULTICENTRE, RANDOMIZED, DOUBLE-BLIND, PARALLEL–GROUP STUDY TO COMPARE THE EFFICACY OF GOLIMUMAB IN COMBINATION WITH METHOTREXATE (MTX) *VERSUS* MTX MONOTHERAPY, IN IMPROVING DACTYLITIS AND ENTHESITIS, IN MTX NAÏVE PSORIATIC ARTHRITIS PATIENTS

PROTOCOL NUMBER: 50307

EUDRACT: 2013-000643-40

1.0 INVESTIGATOR SIGNATURE PAGE

Abbreviated Title	GO-DACT
Title	A multicentre, randomized, double-blind, parallel–group study to compare the efficacy of golimumab in combination with methotrexate (MTX) v*ersus* MTX monotherapy, in improving dactylitis and enthesitis, in MTX naïve psoriatic arthritis patients
Sponsor	Instituto de Medicina Molecular da Faculdade de Medicina da Universidade de Lisboa
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Date of Finalization of This Current Version of the Protocol	5th December 2013
Previous Versions of the Protocol	31st May 2013

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Date: 06 - DEC - 2013

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2.0 TITLE PAGE

Abbreviated Title	***GO-DACT***
Title	A multicentre, randomized, double-blind, parallel–group study to compare the efficacy of golimumab in combination with methotrexate (MTX) versus MTX monotherapy, in improving dactylitis and enthesitis, in MTX naïve psoriatic arthritis patients
Sponsor	Instituto de Medicina Molecular da Faculdade de Medicina da Universidade de Lisboa
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IND No.	Not Applicable
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Trial Physician	***Elsa Vieira-Sousa***
Phase	IIIB
Date of Finalization of This Current Version of the Protocol	5th December 2013
Previous Version(s) of the Protocol	31st May 2013

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3.0 SYNOPSIS

TITLE OF TRIAL: A multicentre, randomized, double-blind, parallel–group study to compare the efficacy of golimumab in combination with methotrexate (MTX) *versus* MTX monotherapy, in improving dactylitis and enthesitis, in MTX naïve psoriatic arthritis patients..

ABBREVIATED TITLE: *GO-DACT*

OBJECTIVES:

Primary Trial Objective: To demonstrate differences of efficacy of golimumab in combination MTX in comparison with MTX monotherapy, in improving dactylitis at 24 weeks *versus* baseline, in MTX naive PsA patients.

Secondary Trial Objective:

To assess the efficacy of golimumab in combination with MTX versus MTX monotherapy on:

- enthesitis
- feet and hands inflammation assessed by MRI
- peripheral and axial joint involvement
- skin and nail involvement
- function
- composite indexes of disease activity
- quality of life

To assess the safety of golimumab in combination with MTX versus MTX monotherapy on:

- serious and non-serious adverse events
- immunogenicity of golimumab in association with MTX

Trial Design

Overview:

This is a national multicentre, interventional, double-blinded, placebo-controlled, parallel design trial of golimumab in combination with MTX versus MTX monotherapy, in MTX naïve psoriatic arthritis patients with active dactylitis. We expect to include 136 patients, which will be centrally randomized to active and placebo treatment, carried out in a 1:1 manner.

This trial will include patients older than 18 years, with the diagnosis of psoriatic arthritis according to the CASPAR criteria, and ≥1 tender dactylitis, refractory to at least two systemic NSAIDs, at optimal dosage, for 3 months.

Duration of Participation: Each subject will participate in the trial for a maximum of approximately 32 weeks from the time the subject signs the Informed Consent Form (ICF) through the final contact. After a screening phase of approximately 28 days, each subject will receive assigned treatment for 6 months. After the end of treatment, each subject will be

followed for safety monitoring and sustained efficacy assessment for 60 days.

Duration of Trial: This trial will have the duration of approximately 2 years since the first subject signing informed consent to last contact with last subject, at end of the trial.

Key Inclusion/Exclusion Criteria:

Inclusion criteria: Patients older than18 years, with the diagnosis of PsA according to CASPAR criteria, established at least 3 months prior to screening, with ≥1 tender dactylitis refractory to at least two systemic NSAIDs, at optimal dosage, for 3 months, willing to give informed consent.

Exclusion criteria are those considered for any antiTNF agent and MTX or that might interfere with trial evaluations or patient's safety.

INVESTIGATIONAL PRODUCT, DOSE, MODE OF ADMINISTRATION

Investigational Product: Golimumab, a fully human monoclonal antibody, administered at a subcutaneous (SC) dose of 50 mg, once monthly, preferably on the same day of every month.

Reference Product: placebo

Both golimumab and placebo will be administrated in association with MTX at a dose between 10 mg and 25mg/weekly.

STATISTICAL METHODS:

Data Set(s) to be Analyzed: The evaluable population will consist of those subjects who received at least one dose of golimumab/placebo plus MTX and have dactylitis severity score (DSS) calculated at baseline and at least one post-baseline visit. All safety analyses will be performed on all subjects who received at least one dose of golimumab or placebo plus MTX.

Sample Size: Considering a dropout rate of 20%, it is expected that a total of 136 patients need to be randomized to achieve primary endpoint.

Efficacy Analysis: All efficacy data will be analyzed according to assigned treatment group.

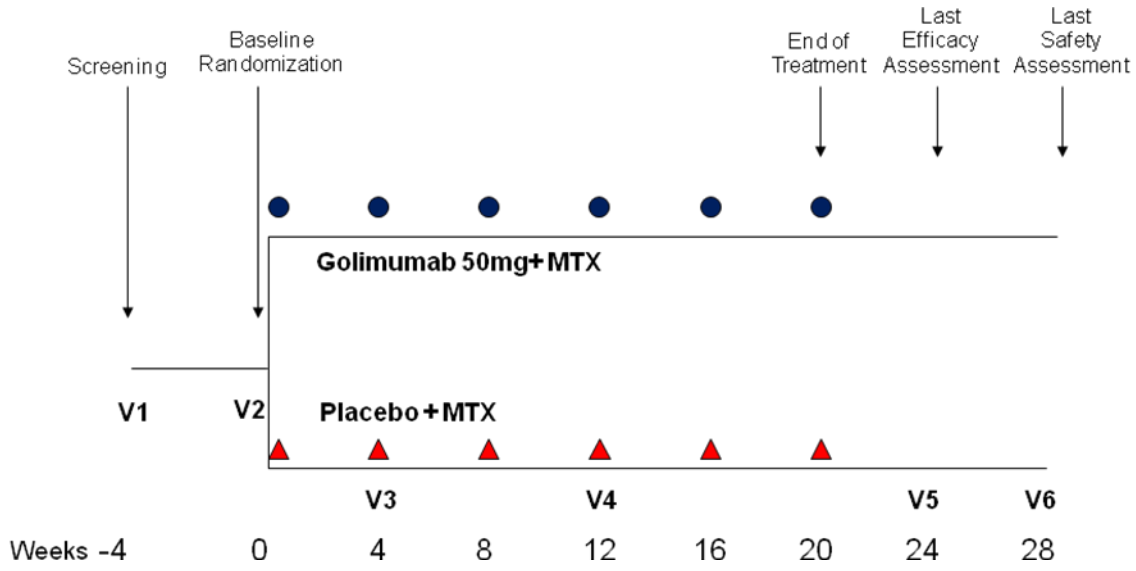
Descriptive statistics will be used to summarize all primary dactylitis severity score (DSS) and secondary endpoints such as LDI, LEI, SPARCC, PsAMRIS-H and PsAMRIS-F, tender 68 and swollen 66 joints, patients and physician global assessment VAS, target NAPSI, BASDAI,BASFI, HAQ-DI, composite indexes of disease activity, SF36 and DLQI. Comparison between treatment groups will be made by T-student test (or Mann-Whitney, if normality assumption is not verified).

The Qui-square test (or Fisher exact test) will be used to compare the proportion of patients achieving DSS, LDI, ACR, PSARC, PASJAI, PASI, ASAS and ASDAS responses and MDA.

Safety Analysis: Adverse events will be analyzed and the incidence summarized by the total number of patients in each treatment group experiencing a given event.

Interim Analysis: An interim analysis is planed when 50% of the patients have been included.

4.0 TRIAL DESIGN DIAGRAM



5.0 TRIAL FLOW CHART

	Screening	Baseline					EOT[8]	EOS	FU
Visit number [1]	V1	V2	V3		V4			V5	V6
Timing: weeks	-4	0	4	8	12	16	20	24	28
Golimumab/placebo plus MTX [2]		X	X	X	X	X	X		
Subject related info/assessments									
Informed consent	X								
Inclusion /exclusion criteria	X	X							
Withdrawal criteria		X	X		X			X	X
Randomization		X							
Demographics	X								
Medical history	X								
Physical examination	X	X						X	
Vital signs and weight	X	X	X		X			X	
Prior/concomitant medications	X	X	X		X			X	X
HLAB27, RF, Anti-CCP	X								
Hands and feet and/or axial X-ray	X								
Safety assessments									
Pregnancy screening[3]	X								
HIV1/2 and hep. B/ C	X								
TB screening[4]	X								
Chest X-ray	X								
ECG [5]	X								
Laboratory tests[6]	X		X		X			X	
Adverse events		X	X		X			X	X
Local tolerability at injection site		X	X		X			X	
Antibodies to golimumab	X		X					X	
Efficacy assessments									
Dactylitis Severity Score,Leeds Dactylitis	X	X	X		X			X	
LEI and SPARCC	X	X	X		X			X	
BSA/PASI/target NAPSI/DLQI	X	X	X		X			X	
68 TJ and 66 SJ	X	X	X		X			X	
Patient' global VAS	X	X	X		X			X	
Physician'global VAS	X	X	X		X			X	
BASDAI, BASFI, ASAS, ASDAS	X	X	X		X			X	
HAQ-DI	X	X	X		X			X	
PASDAS,CPDAI, DAPSA, DAS28, CDAI, SDAI	X	X	X		X			X	
ACR20/50/70, PSARC, PSAJAI	X	X	X		X			X	
SF36	X	X	X		X			X	
MDA									
CRP and ESR	X	X	X		X			X	
Hands and wrist or feet and ankle MRI[7]		X						X	
Trial material									
Dispense of medication		X	X		X			X	
Drug accountability		X	X		X			X	

Tables Notes

1 Visit name abbreviation: End of treatment (EOT), end of study (EOS) and follow-up visit (FU),

2 Golimumab/MTX and placebo/MTX injection can be administered up to seven days after study visit at which the protocol designated study assessments are conducted.

3 Pregnancy tests will be conducted for female patients of child bearing potential.

4 Tuberculosis screening (TB) will be performed according to local guidelines.

5 One ECG must be obtained during screening. This can be obtained any time during the screening period. Original tracings of ECG need to be available for monitoring.

6 Hematology, chemistry, urinalysis.

7 Feet and ankle MRI will be performed within up to 2 week before baseline visit and up to two weeks after V5.

8 For patients that experience early termination, the end of study visit will be anticipated.

6.0 BACKGROUND AND RATIONALE

Psoriatic arthritis (PsA) is a pleomorphic chronic inflammatory arthritis with a broad clinical spectrum, ranging from peripheral arthritis to axial spondylitis, enthesitis, dactylitis and uveitis, in association with psoriasis and nail dystrophy. Dactylitis and enthesitis are core manifestations that occur clinically in 30 to 50% of PsA patients, often in early disease.[1] Dactylitis is additionally an unfavorable prognostic factor associated with erosive disease and its relevance is further supported by its inclusion in the classification criteria for psoriatic arthritis (CASPAR) [2-3].
The clinical assessment of dactylitis and enthesitis has although limitations, as for dactylitis scarce correlation between clinical and imaging finding has been shown and the prevalence of enthesitis is underestimated in comparison with ultrasound and magnetic resonance imaging (MRI) findings. [2] The complementary use of imaging tools is therefore of fundamental importance to improve the characterization of these manifestations and to discriminate between responders and non responders to therapy. Because disease activity severity has been proven to be similar in the early phases of spondyloarthritis (nosologic group in which PSA is included) in comparison with established disease, both in observational cohorts and more recently in clinical trials, prompt treatment of dactylitis and enthesitis, which are often early and severe manifestations, is of fundamental importance to reduce the impact of the disease in patient's quality of life. [4-7]

When considering available therapies methotrexate (MTX) is recommended by the European League Against Rheumatism (EULAR) as the preferential treatment for patients with active peripheral disease that do not respond to non steroidal anti-inflammatory drugs and local corticosteroids injections, if indicated. [8] Due to a large experience with the use of MTX, generally good tolerability, low cost and its concomitant benefits on skin lesions, this is also the gold standard practice in our country. MTX as well as other commonly used first line synthetic disease modifying anti-rheumatic drugs (DMARDs), such as leflunomide and sulfassalazine, lack however evidence based proof of efficacy in the treatment of both dactylitis and enthesitis. [8-9]

All tumor necrosis factor inhibitors (TNFi) approved for PsA (infliximab, adalimumab, etanercept and golimumab) have demonstrated efficacy both for skin and joint involvement, as well as preventing joint damage. In particular infliximab, golimumab and etanercept have also shown efficacy in randomized controlled trials in improving clinically assessed dactylitis and enthesitis but only as secondary endpoints.[10]
Both EULAR and Portuguese guidelines consider the use of TNFi in the management of dactylitis and enthesitis but the final decision to introduce a TNFi is based on the general clinical judgment of the treating physician. [8, 11] When considering predictors of response both shorter disease duration and enthesitis, among others, are associated with better response to TNFi in prediction models [12] Furthermore in a clinical setting TNFi were more efficacious in inhibiting radiographic progression in PsA patients in comparison with MTX.[13]
The treatment algorithm for dactylitis and enthesitis is therefore still debatable, as it is evidenced by the lowest level of agreement in EULAR recommendations, highlighting a

need to increase available randomized controlled trials data to improve clinical care [8].

Golimumab, a human TNFi monoclonal antibody, has well documented efficacy in improving dactylitis and enthesitis.[14] Effects on dactylitis and enthesitis have although been reported only as secondary outcomes in the GO-REVEAL study, with the golimumab 100mg arm showing significantly greater improvement for dactylitis scores and both golimumab 50mg and 100mg arms showing also significantly larger improvement for enthesitis scores at 24 weeks. [14-15]
The concept that, in opposition to what is observed in rheumatoid arthritis trials, the association of MTX to TNFi in psoriatic arthritis would not bring additional benefits seems to be changing and applicable only to MTX non-responders patients. [8] In fact, recent results from the GO-REVEAL trial, at week 52, suggest that adding MTX to golimumab is associated with a further improvement of 10% in dactylitis, enthesitis and nail psoriasis scores.[16] Additionally the RESPOND trial supports that in MTX naive patients MTX might potentiate the effect of infliximab. [17] In addition it has been demonstrated that MTX treated patients have lower production of anti drug antibodies. [18-19]
Taking these data together we hypothesized that a better understanding of the therapeutic effect of golimumab in association with MTX, in comparison with MTX monotherapy, will contribute to improve the management of dactylitis and enthesitis. This evaluation will be empowered by the use of sensitive imaging tools such as MRI.
We therefore expect that the results from this trial will bring new insight into PsA pathogenesis and the positioning of golimumab in combination of MTX and MTX monoterapy, in dactylitis and enthesitis treatment algorithm.

7.0 TRIAL OBJECTIVES AND ENDPOINTS

7.1 Primary objective

- To demonstrate differences of efficacy of golimumab in combination with MTX in comparison with MTX monotherapy, in improving dactylitis at 24 weeks *versus* baseline, in MTX naïve PsA patients.

7.2 Secondary objectives

To assess the efficacy of golimumab in combination with MTX versus MTX monotherapy on:

- enthesitis
- feet and hands inflammation assessed by MRI
- peripheral and axial joint involvement
- skin and nail involvement
- function

- composite indexes
- quality of life

To assess the safety of golimumab in combination with MTX versus MTX monotherapy on:

- serious and non-serious adverse events
- immunogenicity of golimumab in association with MTX

7.3 Primary endpoint

- Changes from baseline of the Dactylitis Severity Score (DSS) at 24 weeks.
-

7.4 Secondary endpoints

Efficacy:

- Changes from baseline of the dactylits severity score (DSS) at 12 weeks.

- Changes from baseline of the Leeds Dactylitis Score (LDI) at 12 and 24 weeks.

- Proportion of patients achieving DSS20, DSS50 and DSS70 at 12 and 24 weeks.

- Proportion of patients achieving LDI20, LDI50 and LDI70 at 12 and 24 weeks.

- Proportion of patient achieving dactylitis remission at 12 and 24 weeks in comparison with baseline

- Proportion of patients with tender and non tender dactylitis at 12 and 24 weeks in comparison with baseline

- Changes from baseline of the LEI and SPARCC scores at 12 and 24 weeks.

- Proportion of patients achieving enthesitis remission, at 12 and 24 weeks comparing with baseline

- Changes from baseline in psoriatic arthritis MRI scoring system for the wrists and hands (PSAMRIS-H) and for feet and ankle (PSAMRIS-F) at week 24.

- Changes from baseline of dactylitis MRI score at week 24.

- Changes from baseline in 68 tender and 66 swollen joint counts at 12 and 24 weeks.

- Changes from baseline of patient and physician disease activity assessment using visual analogical scales at 12 and 24 weeks.

- Changes from baseline of Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and Ankylosing Spondylitis (AS) Disease Activity Score (ASDAS) at 12 and 24 weeks, in patients with axial involvement.

- Proportion of patients achieving Psoriasis Area and Severity Index (PASI) 50, 75 and 90 response at 12 and 24 weeks.

- Changes from baseline in target Nail Psoriasis Severity Index (target NAPSI) score, at week 12 and 24.

- Changes from baseline in functional indexes Health Assessment Questionnaire Disability Index (HAQ) and Bath Ankylosing Spondylitis Functional Index (BASFI) at 12 and 24 weeks.

- Changes from baseline in composite indexes Psoriatic Arthritis Disease Activity Score (PASDAS), Composite Psoriatic Disease Activity Index (CPDAI), Disease Activity Index for Psoriatic Arthritis (DAPSA), Disease Activity Score (DAS28), Simplified Disease Activity Index (SDAI), Clinical Disease Activity Index (CDAI) at week 12 and 24.

- Proportion of patients achieving the American College of Rheumatology (ACR) 20, 50 and 70 response, the Psoriatic Arthritis Response Criteria (PSARC) response, the Psoriatic Arthritis Joint Activity Index (PSAJA)I response, the Assessment of Spondyloarthritis International Society (ASAS) 20 and 40 response and the Ankylosing Spondylitis (AS) Disease Activity Score (ASDAS) clinical important, major ASDAS improvement and inactive disease at 12 and 24 weeks.

- Changes from baseline in quality of life indexes Medical Outcomes Study Short Form 36 (SF36) and Dermatology Life Quality Index (DLQI) at 12 and 24 weeks.

- Proportion of participants achieving minimal disease activity (MDA) at 12 and 24 weeks.

Safety:

- Number of participants who experience an adverse event

- Number of participants who develop anti-golimumab antibodies

8.0 TRIAL DESIGN

This is a national multicentre, interventional, double-blinded, placebo-controlled, parallel design trial of golimumab in combination with MTX *versus* MTX monotherapy, in MTX naïve psoriatic arthritis patients with tender dactylitis. We expect to include 136 patients, centrally randomized to golimumab 50mg or to placebo arms both in combination with MTX. The subgroup of patients with concomitant active enthesitis will also be separately analyzed.

8.1 Beginning and End of the Trial

Each subject is considered to be enrolled in the trial when the subject has provided written informed consent.

Each subject is considered to have ended participation in the trial when he/she has completed the last protocol-specified contact (eg, visits or telephone contacts) or prematurely discontinues from the trial.

A subject is considered to have discontinued after he/she has withdrawn consent or has been discontinued under the conditions specified in Section 9.4

A subject is considered to have been lost to follow-up if he/she is unable to be contacted by the investigator. The end of participation for a subject lost to follow-up is the last known contact (eg, visit or telephone contact).

The overall trial begins when the first subject is enrolled (ie, signs the informed consent form). The overall trial ends when the last remaining subject has ended participation in the trial, by completing the trial, being discontinued from the trial, or being lost to follow-up.

Each subject will be monitored for the occurrence of AEs immediately after the subject has signed informed consent through 60 days after the last dosing visit. Follow-up procedures related to pregnancy or serious adverse events (SAEs) may continue beyond the end of the clinical trial.

All the treatments provided during the trial are approved and available to patients after finishing the trial, according to the physician decision based on disease activity.

Each subject will participate in the trial for approximately 224 days (32 weeks) from the time the subject signs the Informed Consent Form (ICF) through the final protocol-specified contact. After a (screening) phase of up to 28 day (4 weeks) each subject will receive assigned treatment (Section 11) for approximately 168 day (24 weeks). After the end of treatment, each subject will be followed for safety monitoring for 28 days (4 weeks).

9.0 STUDY POPULATION: SELECTION AND WITHDRAWAL OF SUBJECTS

9.1 Overview

This trial will include patients older than 18 years, with the diagnosis of psoriatic arthritis according to the CASPAR criteria, and active disease defined by tender dactylitis and at least one other site of active inflammation (joints, enthesis, spine, skin or nails), naïve to MTX therapy. Exclusion criteria are those considered for any TNFi agent or that might interfere with trial evaluations or patients safety including, but not only, known or suspected allergy to trial product or related products; current chronic inflammatory autoimmune diseases other than PsA; active current infection or history of recurrent or chronic infections, past (< 5years) or current malignancy with the exception of skin basal cell carcinoma; moderate to severe heart failure (New York

Heart Association class III/IV); pre-existing central nervous system demyelinating disorders and any contra-indications to perform MRI.

It is expected that a total of 136 patients need to be randomized considering a dropout rate of 20%.

9.2 Inclusion criteria

To be eligible for this trial, patients must fulfill **all** of the following inclusion criteria.

Each subject must be/have…..

- Able and willing to give written informed consent and comply with the requirements of the study protocol.
- Age ≥ 18 years old, at baseline. A subject may be of both gender and any race/ethnicity.
- PsA diagnosis according to CASPAR criteria, established at least 3 months prior to screening. [2]
- Active psoriatic arthritis, at the time of entry into the study, defined by:
    - ≥1 tender dactylitis, refractory to at least two systemic NSAIDs, at optimal dosage, for 3 months.

      and

    - at least one other site of active inflammation (joints, enthesis, spine, skin or nails).
- Naïve to MTX therapy.
- Patients can have been previously treated with synthetic DMARDs (except MTX) or corticosteroids but must have withdrawn according to the following schedules:
    - All synthetic DMARDs and oral corticosteroids withdrawn at least <u>two weeks</u> prior to screening or 5 half lives according, to what is longer, except for leflunomide.
    - <u>leflunomide ≥ 12 weeks</u> or ≥ 2 weeks after standard cholestyramine or activated charcoal washout.
    - Up to a maximum of two local corticosteroids injection are allowed, administrated, at least four weeks prior to screening (indication for local corticoids injection is dependent on expert opinion decision).

- NSAIDs (up to the maximum recommend dose) if the dose has been stable for at least 4 weeks prior to baseline and the patient is expected to remain on the baseline dose for the 6 months of the study.
- Female subjects or male subjects and his female sexual partner of childbearing potential must agree to use a medically accepted method of contraception prior to enrollment, while receiving protocol-specified medication and for 6 months after stopping the medication.
    - Medically accepted methods of contraception include condoms (male or female) with a spermicidal agent, diaphragm or cervical cap with spermicide, medically prescribed intrauterine device (IUD), inert or copper containing IUD, hormone-releasing IUD, systemic hormonal contraceptive, and surgical sterilization (eg, hysterectomy or tubal ligation). Other methods may be used as required by local legislation.
    - Postmenopausal women are not required to use contraception (postmenopausal is defined as at least 12 consecutive months without a spontaneous menses).

9.3 Exclusion criteria

A subject meeting any of the exclusion criteria listed below must be excluded from participating in the trial.

The subject has ….

- Known or suspected allergy to trial product or related products.

- Body weight > 100 Kg.

- Current chronic inflammatory autoimmune disease other than PsA that might confound the evaluations of safety and toxicity such as, but not limited to, ankylosing spondylitis, rheumatoid arthritis, tophaceous gout, reactive arthritis, pseudogout, arthropathy of inflammatory bowel disease, systemic erythematosus lupus, mixed connective tissue disease, scleroderma or variants, and polymyositis

- Active current infection or history of recurrent or chronic bacterial, viral, fungal, mycobacterial or other infections, including but not limited to tuberculosis and atypical mycobacterial disease, hepatitis B and C, HIV and herpes zoster.

- History of severe systemic bacterial, viral or fungal infections within the past 12 months prior to screening.

- Past or current malignancy with the exception of:

a. Adequately treated and cured basal cell carcinoma of the skin occurring more than 12 months prior to screening.
b. Other cancer with a complete response duration of > 5 years or any period of time longer than that, respectively for those malignancies which are considered as resolved after passing this duration of response.

- Any clinically significant medical condition or situation, other than the condition being studied that, in the opinion of the investigator, would interfere with the trial evaluations or patients safety and optimal participation in the trial such as, but not limited to:
    - Moderate to severe heart failure (NYHA class III/IV)
    - Pre-existing central nervous system demyelinating disorders
    - Increased liver enzymes: alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 2 times the upper limit of normal (ULN).
- Female subject must not be breast-feeding.
- Female subject must not be pregnant or intending to become pregnant.
- Any contra-indications to perform MRI:
    - Patients who have a metal device affected by MRI
    - Allergy or other contraindications to an i.v. injection of gadolinium-diethylenetriamine pentaacetic acid
    - Claustrophobia sufficient to interfere with the patient undergoing the MRI scan.
- Previous treatment with TNFi agent or other biologic agents.
- Previous MTX therapy.
- Latent tuberculosis, in the absence of at least one month of isoniazid therapy, according to local guidelines. [20]

9.4 Criteria for premature withdrawal

Patients have the right to withdraw from the study at any time for any reason. There should be an attempt to have all patients complete the end of trial visit as detailed in the flowchart.

When applicable, patients should be informed of circumstances under which their participation may be terminated by the investigator without the patient's consent. The investigator may withdraw patients from the study in the event of intercurrent illness, adverse events, treatment failure, lack of compliance with the study and/or study procedures (e.g., dosing instructions, study visits), or any reason where it is felt by the investigator that it is in the best interest of the patient to be terminated from the study. The reason(s) for withdrawal must be documented and explained to the patient. If the reason for removal of a patient from the study is an adverse event, the specific event will be recorded on the CRF. There should be an attempt to follow the patient until the event has resolved or stabilized.

Withdrawal is permanent: once a subject is discontinued, he/she shall not be allowed to enroll again. An end of study visit must be performed according to described in Section 10, preferable 4 weeks after the last treatment administration.

<u>At a minimum collect the following information when a subject discontinues:</u>

1. The reason the subject discontinued;

2. The date of the last dose of test products from the trial;

3. The date of the last assessment and/or contact. A follow-up contact (telephone or visit) will be arranged as appropriate;

4. (Serious) Adverse Events ([S]AEs);

5. Compliance with the test product administration as specified in this protocol;

6. Final Assessments:

Every effort should be made to ensure that all procedures and evaluations scheduled for the final trial visit are performed.

7. Retrieve all investigative product and test articles from the subject.

9.5 Replacement of subjects and centers

A patient that discontinues from the trial will not be replaced.

A center may be replaced for the following administrative reasons:

– Excessively slow recruitment
– Poor protocol adherence
– GCP/ICH related censure

10.0 TRIAL PROCEDURES AND ASSESSMENTS

10.1 VISIT PROCEDURES

The subjects will be asked to attend a screening visit (Visit 1), 3 visits (visit 2 to 4), one end-of-study visit (visit 5) and one follow-up visit (visit 6) for a total of 6 visits during a period of 32 weeks (including screening period).

10.1.1 Screening (visit 1)

Before any screening procedures take place, potential subjects will be provided with written and oral information about the trial and the procedures involved. Subjects will be fully informed about their responsibilities and of all the procedures involved in the trial, the possible risks and disadvantages of being dosed with the trial product and their rights while participating in the trial.

They will have the opportunity to ask questions and time to consider participation. If the subjects wish to participate in the trial, they will be asked to sign and date, including time point, the most current Institution Review Board (IRB) / Independent Ethics Committee (IEC) -approved Informed Consent Form. The form must be signed and personally dated, including time, by the subjects as well as by the person who conducted the informed consent procedure before any trial-related activities are performed. A copy of the signed informed consent will be given to the subject.

Patients must fulfill all the entry and none of the exclusion criteria for participation in the study.

A medical history including personal and family history, previous and actual medication, will be registered.

Laboratory samples should be collected from the patient early in the screening period to allow time for the laboratory results to be available for review by the site for eligibility. However, the ECG, chest, hand and feet and axial X-rays can be obtained any time before randomization to study medication (see Section 10.2.4 for additional details on the ECG and chest X-ray).

The subject will be allocated an ascending four digit subject number through a web based system. The assessments and blood samplings will be performed according to Section 10.3 the flowchart and recorded in the Case Report Form (CRF).

The Investigator will review all information obtained from the screening procedures.

Screening failures i.e. screened subjects not being in compliance with all criteria, are to be excluded and the reason to be recorded in a Screening Failure Log and on a Screening Failure Form.

For screening failures, all recorded data will be entered in the CRF, but only data on the Screening Failure Form will be entered into the clinical database. At a minimum the reason for exclusion must be recorded in the Screening Failure Form.

If the initial screening period of 28 days is exceeded, all screening procedures must be repeated, except Hepatitis B and C, and TB testing which only need to be repeated if a period of more than 60 days has passed.

10.1.2 Visits 2 to 4

Visit 2 (baseline) only: Before any further trial activities are initiated, the inclusion and exclusion criteria will be checked. Subjects considered eligible to participate in the trial by fulfilling the inclusion criteria and none of the exclusion criteria will be randomized to golimumab plus MTX or placebo plus MTX. Subjects not passing the exclusion criteria will be excluded from this visit. Subjects may be rescreened at the discretion of the investigator. Hands and wrists or feet and ankle MRI will be performed to all included patient at baseline.

Visit 3 and 4: Assessments and blood samplings will be performed according to the flowchart and sections 5.3.11, and recorded in the CRF. MRI will be repeated up to two weeks after week 24 (end of study visit).

Dose administration: Dosing of subjects will be performed as described in Section 11. Trial product will be dispensed by Merck Sharp & Dohme (MSD) already labeled with randomization numbers. MTX will be given orally in weekly administrations. MTX should be started at 15mg/weekly at baseline (week 0), increased to 20mg/weekly at week 4 and to 25mg/weekly at week 8 maintaining the dose of 25mg/weekly throughout the trial period, except in case of intolerance or toxicity (section 11.1)

Drug accountability will be performed locally and registered at the trial-specific Subject IMP Accountability Log.

10.1.3 End of study visit (visit 5)

The EOS visit (Visit 5) will be the last efficacy assessment visit before leaving the trial.
The assessments and blood samplings listed will be performed according to and recorded in the CRF.
If a subject is withdrawn from the trial, the Investigator will ensure that the procedures for the End of Study visit are followed to the extent possible.

Even if the subject is not able to attend, the End of Study Form, Drug Accountability Form and Screening Failure Form must be completed.

After the end of study visit, the patient will be followed according to clinical practice.
Both golimumab and MTX are available for the treatment of active psoriatic arthritis.

The sponsor will notify the investigator when the study is closed to further patient enrollment.

10.1.4 Follow-up visit (FU)

The last visit will occur 4 weeks after the end of study visit to perform the last safety assessment. This might be performed in presence or through phone contact.

The end of the study will occur when the last patient, last visit occurs (LPLV). The
LPLV is either the date of the last patient visit of the last patient to complete the study, or the date at which the last data point from the last patient, which is required for statistical analysis (i.e., key safety and efficacy results for decision making), is received, whichever is the later date.
In addition, the sponsor will notify the investigator if the study is placed on administrative hold, or if the sponsor decides to discontinue the study or development program.

10.2 TRIAL PROCEDURES

All clinical assessments including both primary (DSS) and secondary (LDI, LEI, SPARCC, tender and swollen joint counts, VAS, target NAPSI, PASI, ACR,ASAS and ASDAS responses, etc) outcomes measures will be determined at baseline and at every visit for 24 weeks, according to flowchart. MRI will be performed at baseline and week.

10.2.1 Demographic

Information about date of birth (age), gender and race/ethnicity will be recorded.

10.2.2 Physical examination

Body measurements:

- height (without shoes) in meters
- body weight (without shoes and overcoat) in kg
- Body Mass Index (BMI) (kg/m2)

A physical examination of the following body systems will be performed:

- Head, ears, eyes, nose, throat, neck
- Respiratory system
- Cardiovascular system
- Gastrointestinal system, including mouth
- Musculoskeletal system
- Lymph nodes
- Central and peripheral nervous system
- Skin

These system assessments should be recorded as “normal” or “abnormal” with abnormalities specified. Any abnormalities that develop during the study are to be recorded on an Adverse Event page.

10.2.3 Relevant medical history, disease characterization and current medical conditions

Subject history should include information on family history and personal history. Relevant medical history and current medical conditions including medication will be recorded in the CRF at the screening visit.

Obtain smoking history. A comprehensive smoking history will be obtained by the investigator at the time of subject’s inclusion into the trial. The following definitions will be used:

- Nonsmoker: a person who never smoked.
- Current smoker: a smoker who has been smoking for at least 1 year at an average of at least one cigarette (or equivalent) per day during that year.
- Ex-smoker: a person who has stopped smoking for at least 3 months and was previously smoking for at least 1 year at an average of at least one cigarette (or equivalent) per day during that year.

Subjects who do not fall into these categories will be disregarded from the analysis.

Cigarette consumption will be quantified as the average number of cigarettes per day. For current and prior smokers, the number of years the subject was or has been a smoker will be obtained, and smoking history will be quantified as pack-years. One pack-year is equivalent to 20 cigarettes smoked per day for 1 year.

Register alcohol intake. The following definitions will be used:

- Never drinker
- Current drinker
- Ex-drinker

For alcohol consumers the average number of drinks will be quantified.

The subtype of psoriatic arthritis according to Moll and Wright classification criteria will be recorded.[21]

- DIP joint only
- Asymmetrical oligoarthritis
- Polyarthritis
- Spondylitis
- Arthritis mutilans.

Furthermore date of beginning of symptoms, date of diagnosis as well of any extra-articular manifestations including uveitis, psoriasis, ungueal dystrophy, dactylitis, enthesitis, Crohn disease, ulcerative colitis, non specific colitis and aortitis will be recorded.

Any joint or periarticular intervention including corticosteroids injections performed previously or during the trial, will be registered in the CRF.

Hand, feet and axial radiographs

An antero-posterior radiograph of the hands and feet will be performed to patients with peripheral involvement. For those with axial involvement pelvis (antero-posterior), lumbar and cervical (lateral) radiographs will be performed.

10.2.4 Safety and tolerability

Electrocardiogram (ECG)

A standard 12 lead ECGs must be obtained during screening and reviewed by the investigator or designee. This can be obtained any time during the screening period, preferably after the laboratory and history criteria have been met.

The Investigator must evaluate the ECG recordings and classify them as either: “normal”, “abnormal but not clinically significant”, or “abnormal, clinically significant” and will note the specific findings that lead to that interpretation.
Original ECG tracings, appropriately signed, will be archived at study site and must be available for monitoring.

Chest Radiograph (CXR)
The posterior-anterior (PA) CXR can be obtained any time during the screening period, preferably after the laboratory and history criteria have been met, and reviewed by the investigator or designee. At screening, if a CXR has been taken within the past 90 days that shows no clinically significant abnormality and there are no signs or symptoms suggestive of pulmonary disease that would exclude the patient, then a further CXR is not required.

Vital Signs
Vital signs will be measured at each visit. Body temperature (°C), pulse (beats/min) and systolic/diastolic blood pressure (mmHg) will be measured. The blood pressure should be measured in a supine position. Any clinically significant abnormalities noted in vital signs will be recorded as AEs in the CRF.

Tuberculosis Screening and Treatment
The screening and treatment for tuberculosis will comply with Portuguese guidelines. All patients will be referred to the Pneumology Diagnostic Centers (Centros de Diagnóstico Pneumológico-CDP) and exclusion of active tuberculosis and requirements for latent tuberculosis treatment will be determined by the pneumologist. After assessment a referral letter from the CDP will return to the investigator, registered in the CRF and kept in the patient records.

10.3 EFFICACY ASSESSMENT

10.3.1 Dactylitis assessment

Dactylitis severity score (DSS)

For each finger and toe dactylitis will be assessed in a scale of 0 to 3 ((0 = no dactylitis; 1 = mild dactylitis, 2 = moderate dactylitis, 3 = severe dactylitis) according to physician decision.
The dactylitis score is calculated as the sum of scores for all 20 digits and thus can range from 0 to 60. Scores > 0 indicate the presence of dactylitis.[22]
To achieve a DSS 20, 50, or 70 responses, at least 20%, 50%, or 70% of improvement need to be observed in the DSS score. The percentage of patients achieving DSS20,50 and 70 will be determined.

Leeds Dactylitis Index (LDI)

The LDI is a quantitative measure for dactylitis that uses a specific instrument to determine the diameter of a swollen finger or toe associated with evaluation of local tenderness. The clinician marks which fingers are affected on a diagram displaying fingers and toes. Circumferences of the affected and contralateral fingers are then measured around the proximal phalanx, as close as possible to the web space, using either a measuring tape or a precalibrated loop (the tool developed for measuring digital circumference is available online at www.mie-uk.com). The clinician then squeezes the affected fingers with moderate pressure and documents the patient's response: 0 - no tenderness, 1-tender, 2- tender and winces, and 3 -tender and withdraws. The ratio of circumference between an affected finger and the contralateral unaffected finger is recorded. If both sides are affected, the circumference of the affected finger is compared to normative data supplied in a table. The tenderness score (0–3) for a finger with dactylitis is recorded, and a total score is generated for each finger. If multiple fingers are affected, each score is added together to produce a total for the patient. A difference in digital circumference of 10% is used to define a finger with dactylitis.[23] A more recent modification of the LDI (LDI basic) replaced the original tenderness grading (0–3) by a binary score reflecting the presence or absence of tenderness (1 or 0, respectively) [24]
The LDI requires a tool to measure digital circumference (available from http://rehaboutlet.com, Miami, FL, USA). This tool will be provided to the centers.
To achieve a LDI 20, 50, or 70 responses, at least 20%, 50%, or 70% of improvement need to be observed in the LDI score.

Number of patients with dactylitis

The number of patients with tender and non tender dactylitis will be registered.

Dactylitis remission

Dactylitis remission is defined as a dactylitis severity score equal to zero.

10.3.2 Enthesis assessment

Leeds Enthesitis Index (LEI)

Tenderness on examination is recorded as either present (1) or absent (0) for each of the 6 sites, for an overall score range of 0–6. The 6 evaluated sites are the lateral epicondyle, the medial femoral condyle and the Achilles tendon insertion, all both on left and right sides. [25]

SPARCC (SpA Research Consortium of Canada) enthesitis score

The SPARCC (SpA Research Consortium of Canada) enthesitis score evaluates 16 enthesis sites: humerus medial and lateral epicondyle, supraspinatus insertion into greater tuberosity of humerus, greater trochanter, insertion of plantar fascia and

Aquilles tendon into the calcaneum, quadriceps insertion into superior border of patella and patellar ligament insertion into inferior pole of patella or tibial tubercle.[26] The modified version includes the greater trochanter, the Achilles tendon and the plantar fascia insertions.

Enthesitis remission
Enthesitis remission is defined by the absence of tender enthesis according to the LEI score.

10.3.3 Joint assessment

Tender and swollen joints

Tender and swollen joints

The 68 tender and 66 swollen joints counts will be evaluated. The joints assessed for tenderness included the distal interphalangeal of the hands, proximal interphalangeal and metacarpophalangeal joints of the hands, and metatarsophalangeal joints of the feet, the wrist joints, the elbows, shoulders, acromioclavicular, sternoclavicular, hip, knee, talo-tibial, and mid-tarsal joints. All of these except for the hips are assessed for swelling. Joint tenderness and swelling are graded as present (1) or absent (0). The assessment of tender and swollen joints are performed according to the EULAR hand book[27]

10.3.4 Patient and physician global assessment for disease activity

Patient' global assessment for arthritis and psoriasis activity
Patient' global assessment for arthritis activity
Patient' global assessment for psoriasis activity
Patient's global assessment for axial activity (only patients with axial involvement)

Physician' global assessment for arthritis and psoriasis activity
Physician' global assessment for arthritis activity
Physician' global assessment for psoriasis activity
Physician' global assessment for axial activity (only patients with axial involvement)

Assessments performed using visual analogical scales from 0 to 100cm.

10.3.5 Physical function

Health Assessment Questionnaire Disability Index (HAQ-DI)

This measure contains 20 items divided into 8 domains: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and common daily activities. Subjects rate the degree of difficulty they have had in the past week on a 4-point scale, ranging from 0 (no difficulty) to 3 (unable to do). The highest scores in each category are summed (0–24) and divided by the number of categories scored to yield a score from 0–3.

10.3.6 Axial disease assessment

The assessment of axial disease will be applied only to patients with axial involvement as determined by the investigator.

Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)
The BASDAI consists of a one through 10 scale (one being none and 10 being very severe), which is used to answer 6 questions pertaining symptoms of AS:
1. Fatigue
2. Spinal pain
3. Joint pain / swelling
4. Areas of localized tenderness (called enthesitis, or inflammation of tendons and ligaments)
5. Morning stiffness duration
6. Morning stiffness severity
To give each symptom equal weighting, the mean (average) of the two scores relating to morning stiffness is taken. The resulting 0 to 50 score is divided by 5 to give a final 0 – 10 BASDAI score.

Ankylosing Spondylitis (AS) Disease Activity Score (ASDAS)
The AS Disease Activity Score (ASDAS) is a composite disease activity instrument that measures disease activity state using an algorithm comprising assessment of back pain, morning stiffness duration, joint pain/swelling, patient global disease activity assessment, and CRP as follows: ASDAS = 0.1216*Back pain + 0.0586*Duration morning stiffness + 0.1106*Patient global + 0.0736*Peripheral pain/swelling + 0.5796*Ln(CRP+1). Clinically important and major ASDAS improvements are defined as a decrease of ≥1.1 and ≥2.0 units, respectively. ASDAS <1.3 is the threshold for an inactive disease state.

Bath Ankylosing Spondylitis Functional Index (BASFI)
The BASFI is a set of 10 questions designed to determine the degree of functional limitation in those patients with AS. The ten questions were chosen with a major input from patients with AS. The first 8 questions consider activities related to functional anatomy. The final 2 questions assess the patients' ability to cope with everyday life. A 10cm visual analog scale is used to answer the questions. The mean of the ten scales gives the BASFI score – a value between 0 and 10.

ASAS (Assessment in SpondyloArthritis) 20 and 40
The ASAS (Assessment in SpondyloArthritis) core set (1-6) consists of the following assessment domains (Zochling et al, 2006):

(1) Patient global assessment of disease activity, assessed on a 100 mm visual analogue scale (VAS)
(2) Inflammatory back pain, assessed on a 100 mm VAS
(3) Physical function, assessed by the Bath Ankylosing Spondylitis Functional Index (BASFI)
(4) Morning stiffness (spinal mobility), assessed using the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)

Improvement of >20% or >40% respectively and >1 unit in at least 3 domains on a scale of 10.
No worsening of >20% or >40% and >1 unit in remaining domain on a scale of 10.

10.3.7 Psoriasis assessment

Body Surface Area (BSA) score

BSA score will be calculated for all patients. The BSA score indicates the percentage of body surface that is affected considering that the patient's handprint (palm and fingers) correspond to 1% of the body.

Psoriasis Area Severity Index (PASI)

The PASI will be used for patients with psoriasis affecting ≥3% of body surface.
The PASI assesses the extent of psoriasis on four body surface areas (head, trunk and upper and lower limbs) and the degree of plaque erythema, scaling and thickness. [28]
The PASI score accounts for the extent of body surface area affected by the erythema, scaling and thickness and the severity of these measures. The score ranges from 0 (no disease) to 72 (maximal disease). The response PASI 50, 75 and 90 will be assessed.

10.3.8 Nail assessment

Target Nail Psoriasis Severity Index (target NAPSI)

In this system the most severely affected nail at baseline is divided into 4 quadrants and 1 point is awarded for each nail matrix and 1 point for each nail bed changes, per quadrant, ranging from 0 to 8 points per quadrant and a maximum total score of 32. Nail bed changes include: onycholisis (separation of nail bed), splinter hemorrhages (small dark brown linear marks under the nail), hyperkeratosis (thickened nail keratin), and oil-drop dyschromia (reddish-brown discoloration under the nail plate). Nail matrix psoriasis includes pitting (sharply defined depressions in the nail surface), leukonychia (white spots in the nail plate), crumbling, and red spots in the lunula. [29]

10.3.9 Health Related Quality of life

Dermatology Life Quality Index (DLQI)
The DLQI is a 10-item questionnaire with answers based on a 4-point Likert scale. Responses of “not at all,” “a little,” “a lot,” and “very much” are available for each question, and correspond to scores of 0, 1, 2, and 3, respectively. A response of “not relevant” is also offered for select questions.

Medical Outcomes Study Short Form 36 (SF-36)
The SF-36 is a patient questionnaire assessing 8 domains of health status: physical functioning (PF), pain, vitality, social functioning, psychological functioning, general health perceptions, and role limitations due to physical and emotional problems (70). It also can be subdivided into 2 summary scores, the physical and mental component scores.

10.3.10 Composite indexes

Psoriatic Arthritis Disease Activity Score (PASDAS)

This score uses an algorithm comprising assessment of the physician global VAS, patient global VAS, physical component of SF-36, swollen and tender joint counts, Leeds enthesitis count, tender dactylitis score and CRP. [30]

Composite Psoriatic Disease Activity Index (CPDAI)

Disease is assessed in up to 5 domains: peripheral joints, skin, enthesial, dactylitis, and spinal involvement. For each domain, individual instruments are used to assess the extent of disease activity as well as the impact on patient function and health-related quality of life. Domains are scored from 0–3, with empirical cutoffs for disease severity/activity proposed in each largely based on the literature (Table 3). Individual domain scores are summed to give an overall composite score (range 0–15).[31]

Disease Activity Index for Psoriatic Arthritis (DAPSA)

This index measures disease activity using the 68 tender and 66 swollen peripheral joint counts, patient global VAS, patient pain VAS, and C-reactive protein (CRP). The composite score is a simple sum of the scores.[32]

Disease Activity Score (DAS28)

DAS28 will be calculated based on assessments of the following 28 joints for tenderness and swelling: metacarpophalangeal I-V (10), thumb interphalangeal (2), hand proximal interphalangeal II-V (8), wrist (2), elbow (2), shoulders (2), and knees (2).[33]

Simplified Disease Activity Index (SDAI)

The SDAI is the numerical sum of five outcome parameters: tender joint count (28 joints assessment), swollen joint count (28 joints assessment), CRP in mg/dl, patient's global disease activity on a 0-10 cm VAS, and physician's global assessment on a 0-10 cm VAS.[34]

Clinical Disease Activity Index (CDAI)

The CDAI includes the same components as SDAI except CRP. [35]

American College Rheumatology response 20, 50 and 70

To achieve an ACR 20, 50, or 70 response, at least 20%, 50%, or 70%, respectively, improvement in tender and swollen joint counts and three of five scores of individual elements (VAS scores of patient pain, physician and patient global assessment, a disability measure (HAQ) and an acute phase reactant (ESR or CRP)) must be obtained without worsening of the other two.

Psoriatic Arthritis Response Criteria (PSARC)

To achieve a PSARC response, a patient has to achieve 2 of the following, one of which has to be a tender (68) and swollen (66) joint count, and no worsening of any measure: tender or swollen joint count improvement of 30% and/or patient global or physician global improvement of at least 1 point on a 5-point Likert scale.[36]

Psoriatic Arthritis Joint Activity Index (PSAJAI)

The PsAJAI is the weighted sum of 30% improvement in 6 measures with weights of 2 given to tender joint count, C-reactive protein (CRP) level, and physician global assessment of disease activity. Weights of 1 are given to the remaining 30% improvement measures, including pain, patient global assessment of disease activity, and Health Assessment Questionnaire [37]

10.3.11 Minimal disease activity

Patients were classified as achieving MDA if they fulfilled 5 of 7 outcome measures: tender joint count ≤1; swollen joint count ≤1; psoriasis activity and severity index ≤1 or body surface area ≤3; patient pain visual analog scale (VAS) score of ≤15; patient global disease activity VAS score of ≤20; Health Assessment Questionnaire (HAQ) score ≤0.5; and tender entheseal points ≤1. [38-39]

10.3.12 MRI assessment

MRI of the wrists and hands or the feet and ankle will be performed at baseline and week 24 depending on dactylitis location. If both hand and feet fingers are involved the most severely affected area will be selected.

Protocol
MRI examination will be performed on a 1.5-T device.

The following sequences will be acquired before intravenous injection: T1-weighted fast spin-echo sequences on the sagittal and coronal plane, proton density weighted fast spin-echo sequence with fat saturation on the sagittal and coronal plane and T1-weighted 3D Fast Field Echo.
Intravenous injection of gadolinium will be performed using an automatic injector at a standard dose of 0.1 mmol/kg (0.2 mL/kg) with a flow rate of 2.5 mL/s through a 20-G Abbocath® needle into a cubital vein. After injection, e-THRIVE dynamic sequence acquired with repeated acquisitions starting post-contrast will be reconstructed in the axial plane. T1-weighted fast spin-echo sequences with fat saturation on the axial and sagittal planes after contrast injection were also be acquired. [11]

Definitions
The MRI sets will be scored in respect to synovitis, erosions, tenosynovitis, soft tissue oedema, bone marrow oedema, according to the definitions of the OMERACT / PSAMRIS-H method that was developed for assessing hands of psoriatic arthritis patients, with the necessary adaptations to the territories of the feet and ankle under analysis for development of PSAMRIS-F.[40] Additionally enthesitis, enthesophytes and dactylitis will be recorded. Bone erosion will be defined as a bone defect with sharp margins, visible in 2 planes. Bone erosion lesion will be scored from 0 to 10 by the volume of the erosion as a proportion of the “assessed bone volume” by 10% increments judged on all available images. For the tarsal bones, the “assessed bone volume” will be the whole bone. For long bones, the “assessed bone volume” will be from the cortex of the articular surface to a depth of 1 cm. Bone edema will be defined as a lesion with ill-defined margins that have high signal intensity on T2-weighted sequences. Each bone will be scored separately (as for erosions). The scale will be 0–3 based on the proportion of bone with edema, as follows: 0, no edema; 1, 1%–33% of bone edematous; 2, 34%–66% of bone edematous; and 3, 67%–100%. Synovitis will be defined as the area in the synovial compartment that shows enhancement of a thickness greater than the width of the joint capsule after gadolinium. The scale will be 0–3. Score 0 is normal, and 1–3 (mild, moderate, severe) are by thirds of the presumed maximum volume of enhancing tissue in the synovial compartment. Enthesitis will be defined as intrasubstance and peri-enthesis contrast enhancement and the scale will be 0-3 by thirds of the presumed maximum volume of enhancing tissue. Enthesis bone erosion and edema will be defined as already described. Tenosynovitis will be scored on a 0-3 scale on the basis of thirds of the presumed volume of maximal synovial tissue enhancement. Soft tissue oedema will be registered as present or absent. Dactylitis will be scored separately according to previous described and published system by

Healy et al, 2008. Each feature will be scored as present/absent at each of three levels of the digit: metacarpophalangeal joint, proximal inter-phalangeal joint and distal inter-phalangeal joint: synovitis (capsular enhancement and intracapsular fluid), bone oedema, subcutaneous oedema, flexor tenosynovitis (peritendinous fluid and enhancement), extensor tenosynovitis (peritendinous fluid and enhancement), plantar/volar plate enhancement, collateral ligament enhancement and erosions. In addition, the presence of sesamoiditis at the thumb and great toe will be assessed. An MRI score will be developed for each digit with one point allocated for the presence of each feature at each joint level and a total score obtained by the simple summation of these features (maximum score for each of the second through fifth digits, 24; for the first digit, 17). [41]

The region of interest (ROI) for the dynamic study will be selected on the basis of the unequivocal synovial tissue that shows a progressive enhancement on the reconstruction of the axial and coronal planes of the different dynamic acquisitions and the tissue that exhibits maximum visual enhancement. We will use a small area (20–30 mm2) while avoiding intra-articular fluid as identified by pre-contrast and dynamic sequences.

MRI reading will be performed by two trained musculoskeletal radiologists with experience on the PSAMRIS score. The enhancement ratio of the synovial tissue will be calculated in 2 ways: (1) as the rate of early enhancement during the first 57 s according to the formula REE57 = S57/S200, where S57 and S200 are the signal intensity 57 and 200 s after gadolinium injection, respectively; and (2) as the relative enhancement (RE) according to the formula RE = S200 – S0. [8]

10.3.13 Laboratory evaluations

10.3.13.1 Screening

Hepatitis and HIV
All subjects will be screened for Hepatitis B surface antigen (HBsAg), antiHBs and antiHBc antibodies.
Screening for Hepatitis C will be based on HCV antibodies.
Evaluation for HIV seropositivity will be performed, and, if positive, confirmation by a second technique available at the laboratory site, e.g., Western blot.
Results will be available as source data and will not be recorded within the CRF.

Pregnancy test
Any female aged 18 years and above is considered a woman of child bearing potential (WoCBP), and must be included among female subjects undergoing obligatory pregnancy testing. Pregnancy tests are required for all female subjects regardless of reported sterilization. Serum pregnancy test (bHCG) will be performed at screening.
The result of the pregnancy tests at screening must be received before the subject receives the first administration of study treatment.

HLAB27, rheumatoid factor and anti-cyclic citrullinated peptides (anti-CCP) antibodies

All subjects will be tested at screening for the presence of surface antigen Human Leukocyte Antigen (HLA) B27, encoded by the B locus in the major histocompatibility complex class I, rheumatoid factor and for anti-cyclic citrullinated peptides antibodies.

10.3.13.2 Standard clinical laboratorial parameters

Venous blood will be drawn for routine blood tests and as part of the safety panel at the investigational sites.
Any clinically significant abnormalities noted in laboratory test values will be recorded as AEs in the CRF.
Unscheduled laboratory assessments for safety issues are permitted at any time.
The total volume of blood loss for laboratory assessments will be approximately (40 mL).
All laboratory tests for standard clinical assessment will be performed locally at each center lab.

The following laboratory analyses will be performed as outlined in the flowchart.
On dosing day all labs are to be obtained prior to administration
of study medication.

Hematology/CBC: Hemoglobin, hematocrit, RBC and indices (MCV, MCH, MCHC), WBC & absolute differential, platelet counts.
Blood Chemistry: Creatinine. *Urea, uric acid, random glucose, potassium, sodium, chloride, calcium, phosphorous, total protein and albumin will just be collected at screening*.
Lipid Panel: *Fasting total cholesterol, triglycerides, HDL, LDL, just at screening.*
Liver Profile: AST/SGOT, ALT/SGPT. *Alkaline phosphatase and total bilirubin (direct and indirect will be performed if total bilirubin >ULN), just at screening.*
Acute Phase Reactants: CRP and ESR (using Westergren method).
Urinalysis: Type II urine including microscopic examination.

10.3.13.3 Immunogenicity

Anti-golimumab antibodies will be assessed in serum by venopuncture at the same moment as for standard clinical laboratorial parameters.

Collection of blood samples: For each scheduled immunogenicity sample, 2 mL blood will be drawn into a plain barrier tube to obtain 1 mL serum. Enzyme-linked immunosorbent assay (ELISA) will be used for determinations.

11.0 TREATMENTS

11.1 Trial Treatments

The investigator shall take responsibility for and take all steps to maintain appropriate records and ensure appropriate supply, handling, storage, distribution, and usage of these materials in accordance with the protocol and any applicable laws and regulations.

MSD will provide adequate clinical supplies to dose approximately 136 subjects throughout the 6 months length of the trial. The clinical supplies will be labeled in accordance to local regulations.
Storage of the clinical supplies will be in accordance with the clinical supply label.

The following trial products will be supplied by MSD:

- Golimumab 50mg/ 0.5 ml in a pre-filled syringe.
- Placebo 0mg/ 0.5 ml sterile solution in a pre-filled syringe.

The golimumab 50 mg and placebo pre-filled syringes are indistinguishable from each other: no difference in the appearance of the two solutions is detectable.

Golimumab or placebo will be administrated subcutaneously, once a month, for 6 successive months.

MTX will be started at dose of 15mg/week, increased to 20mg/week at week 4 and aiming at 25mg/week at week 8, according to patient tolerability. A minimum dose of MTX 10mg/week is required in order to keep the patient in the trial.

MTX will be taken orally, once a week, for 6 successive months. Folic acid will be given at least 24 hours after MTX intake, at a dose between 5 and 25mg according to the investigator.

The following actions should be considered in case of suspicion of myelotoxicity:

Haemoglobin	**Action** *#&§
>10g/dl	Maintain dose
8-10g/dl	Reduce dose and reassess haemoglobin levels after 4 weeks
<8g/dl	Suspend methotrexate and reassess after 4 weeks. Methotrexate can be reintroduced at a lower dose if haemoglobin >10g/dl.

Neutrophils	**Action** *#&§
>1000 cells/mm^3	Maintain dose
500-1000 cells/mm^3	Suspend methotrexate and reassess after 4 weeks. Methotrexate can be reintroduced at a lower dose if neutrophils >1.000 cells/mm3
500 cells/mm^3	Discontinue methotrexate and withdraw subject.

Platelets	**Action** *#&§
>100.000 cells/mm^3	Maintain dose
50.000-100.000 cells/mm^3	Reduce dose and reassess platelets levels after 4 weeks
<50.000 cells/mm^3	Suspend methotrexate and reassess after 4 weeks. Methotrexate can be reintroduced at a lower dose if platelets >100.000 cells/mm^3

* Other causes of cytopenias must be excluded.
# Reduce or interrupt any concomitant potentially myelotoxic drugs.
& Dose adjustments should also be based in the physician assessment of the risk of each individual patient.
§ An increase of folic acid supplementation must be considered.

The following actions should be considered in case of suspicion of hepatotoxicity:

ALT and/or AST values	**Action** *#&§
< 3x ULN	Reduce dose and reassess after 4 weeks.
3 up to 5x ULN	Suspend methotrexate and reassess after 4 weeks. Methotrexate can be reintroduced at a lower dose if ALT and/or AST < 3x ULN.
>5x ULN	Suspend methotrexate and reassess after 4 weeks. Methotrexate can be reintroduced at the lowest dose (10mg/week) if ALT and/or AST <3x ULN, with monthly monitoring. If any clinical signs of hepatitis or liver insufficiency, such as fever, jaundice, nausea, low albumin, raised bilirubin or alkaline phosphatise or prolonged prothrombin time, discontinue methotrexate and withdraw subject.

* Other causes of increased ALT and/or AST must be excluded.
# Reduce or interrupt any concomitant potentially hepatotoxic drugs.
& Dose adjustments should also be based in the physician assessment of the risk of each individual patient.
§ An increase of folic acid supplementation must be considered.

The first dose of the investigational product will be administered at the trial site at Visit 2 by a trial nurse. Patient education for self administration will be performed as in current clinical practice. Subsequent dosing will be done once a month by self administration by the patient . The patients will receive both golimumab and placebo subcutaneously in association with methotrexate. Patients will be further contacted by phone to ensure compliance to trial medication.

Packaging and labeling of trial products

Labeling and packing the trial products will be performed by MSD in accordance with local law and trial requirements.

Pre-filled syringes will be labeled according to randomization numbers and sent to trial sites. Trial product will be packed in non subject specific boxes and sent to the site according to requirements.

Dispensing

The investigator or qualified designee(s) will dispense trial treatments at the designated site(s) to subjects who have provided written informed consent and have met the entry criteria. Clinical supplies may not be used for any purpose other than that which is stated in this protocol.

Storage and drug accountability of trial product

Trial treatment supplies must be stored in a secure, limited-access location under the storage conditions specified on the supply label. Site storage conditions should be monitored by the site personnel for adherence to label specifications and reviewed during site visits.

Accurate and current accounting of the dispensing and return of investigational product(s) will be maintained on an ongoing basis by a member of the trial site staff:

Investigational medicinal product(s) dispensed to each site will be recorded in the trial-specific Site Investigational Medicinal Product (IMP) Accountability Log.

Investigational medicinal product(s) dispensed to each subject will be recorded in the trial-specific Subject IMP Accountability Log (or equivalent document approved by the sponsor).

The Site IMP Accountability Log and Subject IMP Accountability Log will be verified by the trial monitor. The original Site IMP Accountability Log and Subject IMP Accountability Log will be approved by the investigator and retained at the trial site and a copy supplied to MSD when the trial is complete.

The syringes will be discarded by the trial nurse immediately after return by the patient at every visit.

The trial monitor will instruct the site on the return of all investigational product(s) supplies. A final inventory of the total amount of investigational product(s) received at each trial site against the amount used and destroyed must be recorded in the Site IMP Accountability Log. Inventory records must be readily available for inspection by the trial monitor and/or auditor, and open to government inspection at any time.

11.2 Selection and Timing of Dose for Each Subject

Golimumab selected dose and frequency of administration is the one approved for psoriatic arthritis treatment.

11.3 Determining the Timing of Dose Administration for Each Subject

There are no special requirements for the timing of the golimumab doses in relation to time of day, meals, or concomitant medications.

Golimumab will be administered according to the dosing schedule explained in flowchart allowing a window of ±7 days. In case a golimumab dose is administered outside this window and if the investigator agrees that the subject can remain in the trial, then the day of that month when golimumab was administered will become the new target day for subsequent administration, again with a ±7-day window.

The same criterion shall be used if a golimumab dose must be delayed for safety reasons.

11.4 Non-Trial Treatments

Prior, Concomitant and Rescue Medications

Medications, Supplements, and Other Substances Prohibited Prior to Baseline and During the Trial

A subject must not have received any investigational drugs within the
30 days prior to Baseline, and must not receive them during the current trial.
Patients cannot have been previously treated with MTX.

Concomitant Medications, Supplements, and Other Substances Allowed During the Trial

No other DMARDs (with the exception of MTX) or oral corticosteroids are allowed during the trial.
During the conduct of the trial, the physician is allowed to use intra-articular injections of corticosteroids as rescue medication, with exception of hand and feet joints. The injection, if deemed necessary, should occur at least 4 weeks prior to the next

scheduled examination. Joints that are injected with corticosteroids must be counted as tender and swollen at each visit falling within 4 months after the injection. The use of this rescue medication should be documented as such in the CRF and will be subject to secondary endpoint analysis.
For patients that show gastrointestinal intolerance to oral MTX switching to subcutaneous formulation can be considered.
Subjects are allowed to take analgesics as rescue medication.
The dose and frequency of all rescue medications needs to be registered in the CRF.

Subjects should be advised not to take an analgesic medication within 6 hours prior to the visits for dactylitis, joint and enthesis, evaluation.

Any concomitant medications (including over-the-counter medications, herbal medications, preventative vaccines, vitamins and food supplements) and procedures must be recorded in the eCRF. A description of the type of drug or procedure, the amount, duration, reason for administration of drug or procedure, and the outcome of any procedures must be documented. Adverse events related to the administration of a concomitant medication or the performance of a procedure must also be documented on the appropriate AE page of the eCRF.
If concomitant medication it's changed because of abnormal laboratory values of clinical significance, side effects, concurrent illness, or performance of a surgical procedure. The reason for change must be clearly documented in the subject's medical record. Note that the use of any concomitant medication must relate to the documented medical history, prophylaxis, or an adverse event (AE) of the subject.

11.5 Procedures for monitoring subject compliance with administration of trial treatments

At all protocol-specified visits, the investigator or qualified designee is to record whether treatment had been taken per protocol in the preceding interval. If not, the date(s) and reason for each dosing noncompliance must be recorded.

12.0 TRIAL SCHEDULE

This trial is planned to be started in December 2013 and its first subject first visit (FSFV) planned for January 2014. The recruitment period is estimated in 18 months. The planned data for completion of the last subject last visit (LSLV) is December 2015 and the end of the trial in January 2016.

13.0 RANDOMIZATION, BREAKING OF BLINDED CODES

This trial will be conducted as a randomized double-blinded trial, with centralized allocation and randomization to active and placebo treatment, carried out in a 1:1 manner. During randomization patients must always be assigned to the lowest randomization number, which will be used through the trial.
No stratification based on age, sex, or other characteristics will be performed.

Randomization will be performed using a web based system and randomization numbers will be sent to MSD. Golimumab and placebo syringes will be labeled according to randomization numbers.

Both golimumab and its matching placebo will be identical in appearance and will be packaged identically. Neither the subject nor the investigational staff (investigator, pharmacist, nurse and evaluators) will know which treatment the subject is receiving.

The blinding should be kept for all staff involved in the trial related activities, until the trial is completed and the database is released for statistical analysis.

Subjects who drop out will not be replaced.

13.1 Breaking of blinded codes

The subject's code may be broken in a medical emergency, if knowing the identity of the treatment allocation would influence the treatment of the subject.

If the trial site needs to break the code, the principal investigator should, if possible, be contacted prior to breaking the code.

Whenever a code is broken, the person breaking the code must record the time, date and reason as well as his/her initials in the source documents. In all cases, the monitor must be notified within 24 hours after the code has been broken.

All other individuals directly involved in this study will remain blinded until the final analysis of the primary parameter.

14.0 STATISTICAL AND ANALYTICAL PLAN

The blinding of the randomized subjects will be maintained until the database has been released for statistical analysis. The official clinical database will not be unblinded until clinical/scientific review has been completed, protocol violators have been identified (if appropriate) and data is declared complete.

The principal investigator and co-investigators will be responsible for the analysis of trial data with exception of those for interim analysis.

14.1 Sample size calculation

We expect that approximately 40% of the psoriatic arthritis patients followed/referred to rheumatology centres will have tender dactylitis.

For sample size calculation we used ps: power and sample size calculation program.

Assessment of dactylitis severity score: this will be a study of controls and experimental subjects in a proportion of 1 control(s) per experimental subject. From the GO-REVEAL trial data the response within each subject group was normally distributed with a standard deviation of 4.8.[14] If the true difference in the experimental and control means is 2.6, we will need to study 108 patients (54 experimental subjects and 54 control subjects) to be able to reject the null hypothesis that the population means of the experimental and control groups are equal with probability (power) 0.8. The Type I error probability associated with this test of this null hypothesis is 0.05.
Considering a dropout rate of 20% before week 24, 108/(1-0.2)= 135, it is expected that approximately 136 patients are required to be included to achieve primary endpoint.

14.2 Statistical methods

Categorical variables will be summarized by frequency and percentage.
Continuous variables will be summarized by mean, median, standard deviation, and interquartile range.

An intention to treat analysis will be performed including all randomly assigned patients who received at least one dose of study medication and have at least one efficacy and safety post-treatment assessment.

14.2.1 Baseline characteristics

All demographic, disease characterization, previous medical history, previous and current therapies, current medical history among other variables will be listed by treatment group and subject. For these parameters summary statistics will be provided by treatment group.

14.2.2 Efficacy endpoints

All efficacy data will be analyzed according to assigned treatment group.

<u>Primary efficacy endpoints</u>

T-student test (or Mann-Whitney, if normality assumption will not be verified) will be used to compare means for dactylitis severity score between treatment groups. The mean change of score and respective standard deviations will be calculated and comparison between treatment groups will be made by T-student test (or Mann-Whitney, if normality assumption is not verified).

Effect estimation will be made by differences between treatment mean scores and will be adjusted for eventual non-homogenous baseline characteristics.

Secondary efficacy endpoints

Descriptive statistics will be used to summarize all secondary endpoints such as LDI, LEI, SPARCC, PsAMRIS-H and PsAMRIS-F, tender 68 and swollen 66 joints, patients and physician´ VAS, BASDAI, ASDAS, BASFI, target NAPSI, HAQ-DI, SF36, DLQI and composite indexes among others by treatment group. The mean change of score and respective standard deviations will be calculated and comparison between treatment groups will be made by T-student test (or Mann-Whitney, if normality assumption is not verified).

The Qui-square test (or Fisher exact test) will be used to compare the proportion of patients achieving DSS20,50,70, ACR20,50,70, PASI75,90, ASDAS clinical important and major improvements, ASAS20,40, MDI responses among others.

MRI

MRI reading will be performed by two blinded trained musculoskeletal radiologists with experience on the PSAMRIS score. Inter-reader and intra-reader agreements will be calculated.
Descriptive statistics of each lesion for individual joints, dactylitis and enthesis, and aggregated scores by region will be calculated. The data will be analyzed individually by joint and lesion and as aggregated scores. Pairwise comparisons between two time points for each individual joints, dactylitis and enthesis and for aggregated scores by region will be calculated.

14.2.3 Interim analysis

One interim analysis is planned when 50% of the estimated sample size (68 patients) is achieved and data will be reviewed by an independent data monitoring committee (IDMC). The levels of significance will be calculated according to O'Brien-Fleming stopping boundaries using EAST software.

14.2.4 Safety and tolerability

The safety analysis population will include all patients who receive at least one golimumab/placebo dose and had at least one post-dose safety assessment. All safety parameters will be summarized and presented in tables based on this safety population. Adverse events will be analyzed and the incidence summarized by the total number of patients in each treatment group experiencing a given event. Patients will be assigned to treatment groups as treated.

15.0 ADVERSE EVENTS

15.1 Definitions and reporting

A. For purpose of this Protocol the below terms shall be defined as follows:

"**Adverse Event" or "AE"** shall mean any untoward medical occurrence in a Study subject who is administered the Study Drug regardless of whether or not a causal relationship with the Study Drug exists. By way of example and without limitation, an AE can be any unfavorable and unintended sign (for example, an abnormal laboratory finding), symptom, or disease temporally associated with the use of the Study Drug,

"Serious Adverse Event" or "SAE" shall mean any untoward medical occurrence in a Study subject who is administered the Study Drug that results in death, a life-threatening drug experience, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect, cancer, or is a new cancer if the cancer is the condition of the study, or overdose. Other important medical events that may jeopardize the patient or may require intervention to prevent one of the outcomes listed previously should also be considered "serious".

"Suspected Unexpected Serious Adverse Reaction" or "SUSAR" shall mean any Serious Adverse Event, the nature, severity or frequency of which is not consistent with information in the most current investigator's brochure, or with respect to a marketed product the most current Summary of Product Characteristics (SPC) or Package Insert.

B. Serious Adverse Event and Suspected Unexpected Serious Adverse Reaction Reporting: Principal Investigator forwards to MSD's Global Safety ("MSD") group, any SAE and SUSAR information, including, but not limited to, all initial and follow-up information involving any Study subject in the Study. Notification is made in the form of a completed CIOMS I within one (1) business days of learning of the SAE or SUSAR. This SAE and SUSAR information is transmitted to MSD using the contact information provided below or such other modified contact information as provided by MSD in writing. All SAE and SUSAR information is transmitted in the English language and contains the reporter's name and the Study subject identifier code. SUSAR

information will be reported unblinded if the Study Drug has been blinded in the Study. Randomization codes for all other SAEs will be provided to MSD at end of Study. The reporting investigator provides a causality assessment for all reported SAEs.

C. Non-serious Events of Interest are handled in the same manner as SAEs. In the case of this protocol, the following events are considered Events of Interest:

- 5q minus syndrome
- Blast cell count increased
- Blast cell proliferation
- Blast cells present
- Essential thrombocythaemia
- Hypergammaglobulinaemia benign monoclonal
- Megaloblasts increased
- Myelodysplastic syndrome
- Myelodysplastic syndrome transformation
- Myelodysplastic syndrome unclassifiable
- Myelofibrosis
- Myeloid metaplasia
- Myeloproliferative disorder
- Polycythaemia vera
- Refractory anaemia
- Refractory anaemia with an excess of blasts
- Refractory anaemia with ringed sideroblasts
- Refractory cytopenia with multilineage dysplasia
- Refractory cytopenia with multilineage dysplasia and ringed sideroblasts
- Adenomatous polyposis coli
- Anal leukoplakia
- Anal polyp
- Anal polypectomy
- Anogenital dysplasia
- Barrett's oesophagus
- Colon adenoma
- Colon dysplasia
- Colon polypectomy
- Colonic polyp
- Crohn's disease
- Cronkhite-Canada syndrome
- Duodenal polyp
- Erythroplasia of lip
- Gastric dysplasia
- Gastric polypectomy
- Gastric polyps
- Gastrointestinal dysplasia
- Intestinal polyp
- Intestinal polypectomy
- Intraductal papillary mucinous neoplasm
- Leukoplakia oesophageal
- Leukoplakia oral
- Melanoplakia oral
- Oesophageal dysplasia
- Oesophageal polyp
- Oral polypectomy
- Pharyngeal leukoplakia
- Polyp colorectal
- Rectal polyp

- Rectal polypectomy
- Small intestinal polypectomy
- Tongue dysplasia
- Bladder dysplasia
- Bladder leukoplakia
- Bladder polypectomy
- Corneoconjunctival intraepithelial neoplasia
- Dysplasia
- Laryngeal dysplasia
- Laryngeal leukoplakia
- Laryngeal polypectomy
- Precancerous mucosal lesion
- Thyroid C-cell hyperplasia
- Vocal cord leukoplakia
- Benign hydatidiform mole
- Bowenoid papulosis
- Breast dysplasia
- Cervical dysplasia
- Endometrial dysplasia
- Endometrial hyperplasia
- Endometrial metaplasia
- Erythroplasia of penis
- Erythroplasia of vulva
- Leukoplakia of penis
- Penile dysplasia
- Penile wart
- Penile warts excision
- Prostatic dysplasia
- Queyrat erythroplasia
- Vaginal dysplasia
- Vulval warts removal
- Vulvar dysplasia
- Vulvovaginal adenosis
- Vulvovaginal human papilloma virus infection
- Actinic keratosis
- Arsenical keratosis
- Dysplastic naevus
- Dysplastic naevus syndrome
- Epidermodysplasia verruciformis
- Erythroplasia
- Leukoplakia
- Parapsoriasis
- Precancerous skin lesion
- Sebaceous naevus

D. All reports of Study Drug exposure during pregnancy or lactation (including a female partner of a male Study subject using the Study Drug), whether associated with an AE or not, are reported to MSD in accordance with the timelines and contact information for an SAE. Principal Investigator follows pregnancies to term to obtain the outcome of the pregnancy. The outcome of the pregnancy is forwarded to MSD.

E. Institution and Principal Investigator report to the Ethics Committee any SAE or SUSAR that arises from the Study. MSD ensures timely reporting of SUSAR to the relevant competent authorities. By timely it is meant that SUSAR concerning death of a subject or life-threatening situations are submitted within 7 calendar days after such a

case is known by an investigator of this study, and within 15 calendar days for all other SUSAR.

F. SAE reports and any other relevant safety information are forwarded to MSD preferably by e-mail: pharmacovigilance.portugal@merck.com. Fax may also be used: +351 214 465 799.

G. Principal Investigator remains responsible for redacting and submitting to all relevant parties the Development Safety Update Reports (DSUR) according to the applicable legislation. The Principal Investigator also forwards the final DSUR to MSD.

H. In the event Principal Investigator or Institution becomes aware of a defect or possible defect in the Study Drug, Institution and Principal Investigator notify MSD within one business day of first becoming aware of the possible defect.

I. Principal Investigator notifies MSD within twenty-four (24) hours in the event that any regulatory authority notifies the Study site of a pending inspection/audit that concerns the Study or Institution's ability to perform clinical research. In addition, Principal Investigator forwards to MSD any written communication received as a result of the inspection/audit within twenty-four (24) hours of receipt of such communication and allows MSD to assist in responding to any citations involving the Study Drug. Such responses shall be made as soon as possible under the circumstances or within any earlier deadline set by the issuing regulatory authority. Principal Investigator also provides to MSD copies of any documents provided to any inspector or auditor. In the event the regulatory authority requests or requires any action to be taken to address any citations, Principal Investigator and Institution agree, after consultation with MSD, to take such action as necessary to address such citations.

J. MSD may provide the Sponsor and Principal Investigators, at Study initiation and on an ongoing basis, with information regarding the Study Drug, including but not limited to safety information. The Sponsor and Principal Investigators agree to hold this information in confidence.

Overdose

An overdose is a significant variation from the recommended/scheduled dosage for a product. In this current trial an overdose of the investigational product golimumab is any dose higher than the doses specified in Section 6 of this protocol for subcutaneous administration. Single doses of golimumab up to 10 mg/kg body weight IV have been administered in a clinical trial without dose-limiting toxicity. In case of an overdose of golimumab that exceeds the normal monthly dosing regimen, it is recommended that the patient be monitored for any signs or symptoms of adverse effects and appropriate symptomatic treatment be instituted immediately.

Product Quality Complaint

A product quality complaint (PQC) is any written, electronic or oral communication that alleges a product defect. A PQC includes suspected product counterfeit, diversion or tampering. A PQC does not include Product Complaints alleging an AE.

Planned Hospitalization
A hospitalization planned by the subject prior to signing the ICF is considered a therapeutic intervention and not the result of a new SAE and should be recorded as medical history. If the planned hospitalization or procedure is executed as planned, the record in the subject's medical history is considered complete.
However, if the event/condition worsens during the trial, it must be reported as an AE.

Medication Error
A medication error is any preventable event that may cause or lead to inappropriate medication use, including unintended accidental exposure or subject or patient harm while the medication is in the control of a health care professional, subject or patient, or consumer. Such events may be related to professional practice, clinical trials, health care products, procedures, and systems, including prescribing, order communication, product labeling, packaging, and nomenclature; compounding, dispensing, distribution, administration, education, monitoring, and use.

Potential Medication Error
A potential medication error is an individual case safety report of information or complaint about product name, labeling, or packaging similarities that does not involve a subject or patient (eg, if a subject reports that one of the investigational products looks like a different product, the report would be considered a potential medication error).

Trial Procedure Related Events
A clinical trial procedure related event is an AE that could be associated with the trial procedures, rather than the investigational product or its administration.
Trial procedures include all treatment procedures and medical procedures for physical examinations, medical investigations, and laboratory assessments or other activities specified in the protocol for the purpose of the clinical trial.

15.2 Monitoring

Monitoring Adverse Events
Subjects will be monitored for the occurrence of SAEs immediately after the subject has signed informed consent. Subjects enrolled in the study will be monitored for both AEs and SAEs.
Subjects will be questioned and/or examined by the investigator or a qualified designee for evidence of AEs. The questioning of subjects with regard to the possible occurrence of AEs will be generalized such as, "How have you been feeling since your last visit?" The presence or absence of specific AEs should not be elicited from subjects.

Subjects having AEs will be monitored with relevant clinical assessments and laboratory tests, as determined by the investigator.

AEs, actions taken as a result of AEs, and follow-up results must be recorded in the CRF, as well as in the subject's source documentation. Follow-up laboratory results should be filed with the subject's source documentation.
For all AEs that require the subject to be discontinued from the trial and SAEs, relevant clinical assessments and laboratory tests will be repeated as clinically appropriate until final resolution or stabilization of the event(s).

Monitoring Laboratory Assessments
Assessments of laboratory parameters including CRP, RF, and anti-CCP, HLAB27, ESR will be performed locally. These laboratory values will be reported to the investigator by the laboratory and he/she will review them for significance and consideration as an AE.

15.3 Assessment of Adverse Event

Assessment of Severity
Where the determination of AE severity rests on medical judgment, the determination of severity must be made with the appropriate involvement of a medically-qualified investigator.
The severity of AEs will be graded according to the following definitions:
Mild: awareness of sign, symptom, or event, but easily tolerated;
Moderate: discomfort enough to cause interference with usual activity and may warrant intervention;
Severe: incapacitating with inability to do normal daily living activities or significantly affects clinical status, and warrants intervention;

Assessment of Causality
A medically qualified investigator must assess the relationship of any AE (including SAEs) to the use of the investigational product, as unlikely related, possibly related, or probably related, based on available information, using the guidelines listed below:

Unlikely related: no temporal association, or the cause of the event has been identified and attributed to other disease or drug; or the drug, biologic, or device cannot be implicated based on available information;
Possibly related: temporal association, but other etiologies are likely to be the cause; however, involvement of the drug, biologic, or device cannot be excluded based on available information;
Probably related: temporal association, other etiologies are possible, but unlikely based on available information.

16.0 ADHERENCE TO ETHICAL, REGULATORY AND ADMINISTRATIVE CONSIDERATIONS

The trial must be conducted in accordance with Good Clinical Practice (GCP) as outlined in the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Guidelines, E6 Good Clinical Practice: Consolidated Guidance and other applicable laws and regulations. In addition, the trial must be conducted in accordance with the European Union (EU) Clinical Trial Directive (CTD) and local regulations.

16.1 Ethical Conduct of the Trial

16.1.1 Independent Ethics Committee or Institutional Review Board

Prior to initiation of the trial at any site, the trial, including the protocol, informed consent, and other trial documents must be approved by an appropriate IRB/IEC. The IRB/IEC must be constituted according to applicable regulatory requirements. As appropriate, amendments to the protocol must also be approved by the IRBs/IECs before implementation at the sites, unless warranted to eliminate an immediate hazard. The IRB/IEC approval should be obtained in writing, clearly identifying the trial, the documents reviewed (including informed consent), and the date of the review. The trial as described in the protocol (or amendment), informed consent, and other trial documentation may be implemented only after all the necessary approvals have been obtained.

In the event that the IRB/IEC requires changes in the protocol, the sponsor shall be advised and must approve the changes prior to implementation. The investigator shall not modify the trial described in the protocol once finalized and after approval by the IRB/IEC without the prior written approval of sponsor.

16.1.2 Subject Information and Consent

The details of the protocol must be provided in written format and discussed with each potential subject, and written informed consent must be obtained for all subjects before any trial-related procedure is performed. In obtaining informed consent, the information must be provided in language and terms understandable to the subject. The subject, or the subject's legal representative, must give their written consent to participate in the trial. The signed and dated consent form itself must be retained by the investigator as part of the trial records. A copy of the signed and dated consent form must be given to the subject. The consent form must include all of the required elements of informed consent in accordance with ICH Guidelines E6 and local laws.

The consent form must be approved by the appropriate IRB/IEC and sponsor before trial initiation at a trial site. Any subsequent changes to the approved informed

consent form must be reviewed and approved by the appropriate IRB/IEC and sponsor before implementation.

16.1.3 Subject Identification Card

A Subject Identification Card is provided to each subject to carry on his or her person (eg, in a wallet) at all times while the subject is participating in the trial. The Subject Identification Card must be provided to the subject no later than when IMP is dispensed. The card is to be shown to caregivers in the event of an emergency.

At a minimum, the card must contain the following information:

1. Protocol number;
2. The subject's protocol identification number;
3. A statement identifying the card-carrier as a participant in a clinical trial (eg, "This person is participating in a clinical research trial.");
4. A statement indicating the investigational drug that the patient is receiving (eg, "This person is taking an experimental drug or placebo"); and
5. Contact information in the event of an emergency or hospitalization. The contact information on the card is to be the investigator or a designated site contact.

Monitors will request that Investigators provide Subject Identification Cards to each subject. Investigators will be asked to request that subjects carry the cards with them while they are participating in the trial.

The Investigator/site should collect the cards at the end of the trial and retain them with other clinical trial documents.

16.1.4 Registration of the Trial

The trial will be registered on a publicly accessible database – clinicaltrials.gov

The results will be disclosed on a publicly accessible database- clinicaltrials.gov

16.2 Reporting Trial Data

16.2.1 Data Collection Forms

The Rheumatic Disease Portuguese Register (reuma.pt), developed for the registry of all patients undertaking biologics in Portugal will be used as electronic case report form. The reuma.pt is approved by Comissão Nacional de Proteção de Dados (CNPD). This is a web based register with restricted access by password attributed to investigators. Specific fields for this trial were developed and only accessed by trial investigators. The trial monitor will equally have access to required clinical data.

The investigator must maintain records and data during the trial in compliance with all applicable legal and regulatory requirements. Each data point must be supported by a source document at the trial site. Any records or documents used as the source of information (called the "subject source data") are to be retained for review by authorized representatives of the sponsor or a regulatory agency.

The investigator will ensure that there are sufficient time, staff, and facilities available for the duration of the trial to conduct and record the trial as described in the protocol and according to all applicable guidances, laws, and regulations.

All data collection forms (eg, CRFs, diaries; EDC screens), electronic database entries, etc, should be completed *as soon as possible* after the evaluation has occurred. All dates appearing on subject data collection forms for laboratory tests, cultures, and other data collected, must be the dates on which the specimens were obtained, or the procedures performed.

16.2.2 Preparing Case Report Forms for All Subjects

A CRF must be completed for all subjects who have given informed consent. The subject names, initials, or other personal information that is beyond the scope of the trial must not be collect from any subject. Subjects are not to be identified by name or initials on the CRF or any trial documents. The only acceptable identification for a subject who may appear on a CRF or trial document is the unique subject identification number. The investigator must maintain contact information for each participant so that all can be quickly contacted by the investigator, if necessary.

All entries into CRFs are the responsibility of the investigator and must be completed by the investigator or a qualified designee. Ensure that all questions are answered and that no empty data blocks exist. Ensure that no information is recorded outside the data blocks. The investigator will attest in writing at the beginning of the trial that his/her electronic signature is the legally binding equivalent of a written signature and will acknowledge by entering his/her electronic signature that he/she has verified the accuracy of the recorded data.

16.2.3 Preparing Case Report Forms for Subjects Who Fail Screening

Data are to be collected from the time the informed consent form is signed until the subject is determined to have failed screening. A CRF with a minimum of the following information must be completed for subjects who fail screening: (1) demographics, (2) subject status, (3) reason for screen failure, and (4) serious adverse events.

16.2.4 Publications and Other Rights

16.2.4.1 Rights to Publish by the Investigator

The investigator has the right to publish or publicly present the results of the trial in accordance with this Section 16.2.4 of the protocol. In the event that the protocol is a part of a multi-site trial, it is understood that it is the intent of the sponsor and the

investigator to initially only publish or present the trial results together with the other sites, unless specific written permission is obtained in advance from the sponsor to publish separate results. The sponsor shall advise as to the implications of timing of any publication in the event clinical trials are still in progress at sites other than the investigator's site.

The investigator agrees not to publish or publicly present any interim results of the trial without the prior written consent of the sponsor. The investigator further agrees to provide to the sponsor 45 days prior to submission for publication or presentation, review copies of abstracts or manuscripts for publication (including, without limitation, slides and texts of oral or other public presentations and texts of any transmission through any electronic media, eg, any computer access system such as the Internet, World Wide Web, etc) that report any results of the trial. The sponsor shall have the right to review and comment with respect to publications, abstracts, slides, and manuscripts and the right to review and comment on the data analysis and presentation.

If the parties disagree concerning the appropriateness of the data analysis and presentation, and/or confidentiality of the sponsor's confidential information, investigator agrees to meet with the sponsor's representatives at the clinical trial site or as otherwise agreed, prior to submission for publication, for the purpose of making good faith efforts to discuss and resolve any such issues or disagreement.

16.2.4.2 Use of Proprietary or Confidential Information in a Publication

No publication or manuscript shall contain any trade secret information of the sponsor or any proprietary or confidential information of the sponsor and shall be confined to new discoveries and interpretations of scientific fact. If the sponsor believes there is patentable subject matter contained in any publication or manuscript submitted for review, the sponsor shall promptly identify such subject matter to investigator. If sponsor requests and at sponsor’s expense, investigator shall use its best efforts to assist sponsor to file a patent application covering such subject matter with the USA Patent and Trademark Office or through the Patent Cooperation Treaty prior to any publication.

16.2.4.3 Use of Trial Information in a Publication

Investigator is granted the right subject to the provisions of this protocol to use the results of all work provided by investigator under this protocol, including but not limited to, the results of tests and any raw data and statistical data generated for investigator's own teaching, research, and publication purposes only. Investigator/Institution agrees, on behalf of itself and its employees, officers, trustees, and agents, not to cause said results to be knowingly used for any commercial purpose whatsoever except as authorized by the sponsor in writing.

16.2.4.4 Authorship of Publications

Authors of publications must meet the International Committee of Medical Journal Editors (ICMJE) guidelines for authorship and must satisfy the 3 criteria that follow:

a). Authors must make substantial contributions to the conception and design of the trial, acquisition of data, or analysis of data and interpretation of results;

b). Authors must draft the publication or, during draft review, provide contributions (data analysis, interpretation, or other important intellectual content) leading to significant revision of the manuscript with agreement by the other authors;

c). Authors must provide written approval of the final draft version of the publication prior to submission.

All contributors who do not meet the 3 criteria for authorship should be listed in an acknowledgments section within the publication, if allowed by the journal, per the ICMJE guidelines for acknowledgment.

16.3 Trial Documents and Records Retention

During the trial and after termination of the trial – including after early termination of the trial – the investigator must maintain copies of all documents and records relating to the conduct of the trial. This documentation includes, but is not limited to, protocols, CRFs and other data collection forms, adverse event reports, subject source data, correspondence with health authorities and IRBs/IECs, consent forms, investigator's curricula vitae, monitor visit logs, laboratory reference ranges, and laboratory certification or quality control procedures and laboratory director curriculum vitae. Subject files and other source data must be kept for the maximum period of time permitted by the hospital, institution or private practice, or as specified below.

The investigator must retain trial records for the amount of time specified by applicable laws and regulations. At a minimum, trial records must be retained for the amount of time specified by ICH Guidelines, the EU Good Clinical Practices Directive, or applicable local laws, whichever is longer:

1. The ICH Guidelines specify that records must be retained for a minimum of 2 years after a marketing application for the indication is approved (or not approved) or 2 years after notifying the appropriate regulatory agency that an investigation is discontinued.
2. The European Union (EU) Commission Directive 2003/63/EC which requires that Essential Documents (including Case Report Forms) other than subjects' medical files, are retained for at least fifteen (15) years after completion or discontinuation of the trial, as defined in the protocol.

All trial documents shall be made available if required by relevant health authorities.

Archived data may be held on microfiche or electronic record, provided that a back-up exists and that a paper copy can be obtained from it, if required.

17.0 INVESTIGATORS AND TRIAL ADMINISTRATIVE STRUCTURE

17.1 Sponsor

The sponsor of this trial is indicated in Section 1, Investigator Signature Page and Section 2, Title Page.

The sponsor is Instituto de Medicina Molecular of Faculdade de Medicina de Lisboa as Institution and Elsa Vieira-Sousa as principal investigator

17.2 Investigators

17.2.1 Selecting Investigators

Only investigators qualified by training and experience to perform a clinical investigation with Golimumab are selected. The sponsor will contact and select all investigators (ie, the legally responsible party[ies] at each trial site), who, in turn, will select their staff.

17.2.2 Financial Disclosure Requirement

In connection with the clinical trial described in the protocol, the investigator certifies that, if asked, the investigator will read and answer the Certification/Disclosure Form or equivalent document truthfully and to the best of investigator's ability. Investigator also certifies that, if asked, the investigator will have any other applicable party(ies) (eg, subinvestigators) read and answer the Certification/Disclosure Form as a condition of their participation in the trial.

If the financial interests reported on the Certification/Disclosure Form change during the course of the trial or within 1 year after the last subject has completed the trial as specified in the protocol, the investigator and the other applicable party(ies) are obligated to inform the sponsor of such financial change.

17.2.3 Clinical Study Report Coordinator Investigator

A Clinical Study Report (CSR) will be prepared by the sponsor or its qualified designee to describe the results of the trial. One of the investigators shall be selected by the sponsor to review the CSR and provide approval of the final CSR in writing. The investigator chosen to review and approve the CSR is to be called the CSR Coordinating Investigator. A second investigator shall be selected as the Alternate CSR Coordinating Investigator. The Alternate CSR Coordinating Investigator is to review and approve the CSR should the first CSR Coordinating Investigator be unable to do so. The sponsor is to select the CSR Coordinating Investigator and Alternate CSR Coordinating Investigator from the investigators using the following criteria:

-Must be the Principal Investigator at a trial site actively enrolling subjects and participating in the trial.

-Must be willing and capable of completing the necessary reviews and providing approval of the CSR in writing.

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