

The GO-DACT 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

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ABSTRACT

The GO-DACT is an investigator-initiated, multicentric randomized placebo-controlled double-blinded trial, that assesses dactylitis as primary endpoint. Psoriatic arthritis patients naïve to methotrexate and biologic disease modifying anti-rheumatic drugs, with at least one active dactylitis, were assigned to golimumab in combination with methotrexate or placebo in combination with methotrexate, for 24 weeks. Both clinical (dactylitis severity score and the Leeds dactylitis index) and imaging (high resolution magnetic resonance imaging), among others, were assessed as outcomes. The main objective of GO-DACT is to provide evidence to improve the treatment algorithm and care of psoriatic arthritis patients with active dactylitis. In this manuscript we describe the GO-DACT protocol and general concepts of the methodology of this trial.

Keywords: Clinical trial; Dactylitis; Treatment algorithm; Psoriatic arthritis

BACKGROUND

Psoriatic arthritis (PsA) is a pleomorphic chronic inflammatory arthritis with a broad clinical spectrum, including peripheral arthritis, spondylitis, enthesitis and dactylitis, in association with skin and/or nail psoriasis. Dactylitis and enthesitis are core PsA manifestations occurring clinically in 30 to 50% of PsA patients, that can severely impact health-related quality of life causing pain and functional impairment¹. Active dactylitis is additionally an unfavorable prognostic factor associated with erosive disease and its relevance is further supported by its inclusion in the CLASSification for Psoriatic ARthritis (CASPAR) criteria².

The therapeutic strategies for dactylitis are, nevertheless, largely empirical and the interpretation of available data limited by the heterogeneity of the outcome measures applied. The Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) review on dactylitis treatment highlights the paucity of evidence in this field and the need for studies having

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dactylitis as the primary endpoint^{3,4}.

Most physicians will use non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroid injections as first-line therapy, although they have not been formally studied^{3,5}. Considering conventional synthetic disease modifying anti-rheumatic drugs (csDMARDs), methotrexate (MTX) is recommended as first-choice csDMARD for patients with active peripheral disease that do not respond to NSAIDs and local corticosteroids, as the standard of practice, in several countries⁵⁻⁸. MTX lacks, however, evidence of efficacy from randomized controlled trials in the treatment of both dactylitis and enthesitis⁹. The most recently updated European League Against Rheumatism (EULAR) recommendations consider the use of biologic DMARDs (bDMARDs), preferentially tumor necrosis factor inhibitors (TNFi), in patients with dactylitis (and enthesitis), even if no csDMARDs have been tried, but the final decision to introduce a bDMARD is based on the general clinical judgment of the treating physician⁷. Among TNFi, golimumab, a human TNFi monoclonal antibody, has documented efficacy in improving dactylitis and enthesitis, and adding MTX to golimumab was associated with a further improvement of 10% in dactylitis, enthesitis and nail psoriasis scores in randomized controlled trials¹⁰. However, as with other available TNFi, the effects on dactylitis and enthesitis have been reported only as secondary outcomes and no previous randomized controlled trial has been performed assessing dactylitis as primary endpoint.

The treatment algorithm for dactylitis and enthesitis is, therefore, still debatable, as evidenced by the low levels of agreement in national and European guidelines, highlighting the need to generate data from randomized controlled trials, aiming at the improvement of clinical care^{6,7}.

Taking these data altogether 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 in psoriatic arthritis patients.

STUDY AIMS

The aim of GO-DACT is to assess efficacy and safety of golimumab in combination with MTX in comparison with MTX monotherapy in the treatment of active dactylitis, in MTX- and bDMARD-naïve PsA patients.

PRIMARY OBJECTIVE AND ENDPOINT

The primary objective of GO-DACT is 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- and bDMARD-naïve PsA patients.

The primary endpoint was defined as changes from baseline in the Dactylitis Severity Score (DSS) at 24 weeks.

SECONDARY OBJECTIVES AND ENDPOINTS

The secondary objectives of GO-DACT are to assess the efficacy of golimumab in combination with MTX versus MTX monotherapy at 24 weeks, in MTX- and bDMARD-naïve PsA patients on:

- Dactylitis using secondary endpoints such as: changes from baseline in the DSS at 12 weeks, in the Leeds Dactylitis Index (LDI) at 12 and 24 weeks; the proportion of patients achieving DSS20, DSS50 and DSS70 at 12 and 24 weeks; the proportion of patients achieving LDI20, LDI50 and LDI70 at 12 and 24 weeks; the proportion of patient achieving dactylitis remission at 12 and 24 weeks, and the proportion of patients with tender and non-tender dactylitis at 12 and 24 weeks.
- Enthesitis based in changes from baseline in the Leeds Enthesitis Index (LEI) and the Spondyloarthritis Research Consortium of Canada (SPARCC) enthesitis score at 12 and 24 weeks; and the proportion of patients achieving enthesitis remission at 12 and 24 weeks.
- Peripheral joint involvement using as endpoint the changes from baseline in the 68 tender and the 66 swollen joint counts at 12 and 24 weeks.
- Patient's and physician's reported outcomes such as: changes from baseline of patient and physician disease activity assessment using visual analogue scales (VAS) at 12 and 24 weeks.
- Axial disease using changes from baseline of the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and the Ankylosing Spondylitis Disease Activity Score (ASDAS) at 12 and 24 weeks, in patients with axial involvement.
- Skin and nail psoriasis as assessed by the proportion of patients achieving the Psoriasis Area and Severity Index (PASI) 50, 75 and 90 responses at 12 and 24 weeks, and the changes from baseline in the target Nail Psoriasis Severity Index (target NAPSI) score, at week 12 and 24.
- Function defined by the changes from baseline in

the functional indexes: Health Assessment Questionnaire Disability Index (HAQ-DI) and Bath Ankylosing Spondylitis Functional Index (BASFI) at 12 and 24 weeks, as endpoints.

- **Quality of life** using changes from baseline in the quality of life indexes: Medical Outcomes Study Short Form 36 (SF-36) and Dermatology Life Quality Index (DLQI) at 12 and 24 weeks, as endpoint.
- **Composite indexes of disease activity and response**, using the following endpoints: changes from baseline in the Psoriatic Arthritis Disease Activity Score (PASDAS), the Composite Psoriatic Disease Activity Index (CPDAI), the Disease Activity Index for Psoriatic Arthritis (DAPSA), the Disease Activity Score 28 (DAS28), the Simplified Disease Activity Index (SDAI), the Clinical Disease Activity Index (CDAI) at week 12 and 24; and the 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 (PsAJAI) response, the Assessment of Spondyloarthritis International Society (ASAS) 20 and 40 response and the ASDAS clinical important, major improvement and inactive disease criteria, and the minimal disease activity (MDA) at 12 and 24 weeks.
- **Feet and hands inflammation** assessed by magnetic

resonance imaging (MRI) defined by changes from baseline in psoriatic arthritis MRI scoring system for the hands (PSAMRIS-H) and for feet (PSAMRIS-F) at week 24, and changes from baseline of dactylitis MRI score at week 24.

The safety and tolerability of golimumab in combination with MTX versus MTX monotherapy were also evaluated and the number of participants who experience an adverse event and that develop anti-golimumab antibodies was determined.

METHODOLOGY

STUDY DESIGN

GO-DACT is an interventional investigator-initiated randomized, double-blind, placebo-controlled, multicentric, 24 weeks, phase 3b, parallel design trial of golimumab in combination with MTX versus MTX monotherapy, in MTX- and bDMARD-naïve psoriatic arthritis patients with active dactylitis.

After a screening phase of approximately 28 days, each subject received the assigned treatment for 24 weeks. At the end of treatment, each subject was followed for safety monitoring and sustained efficacy assessment for 60 days after the last dosing visit (Figure 1).

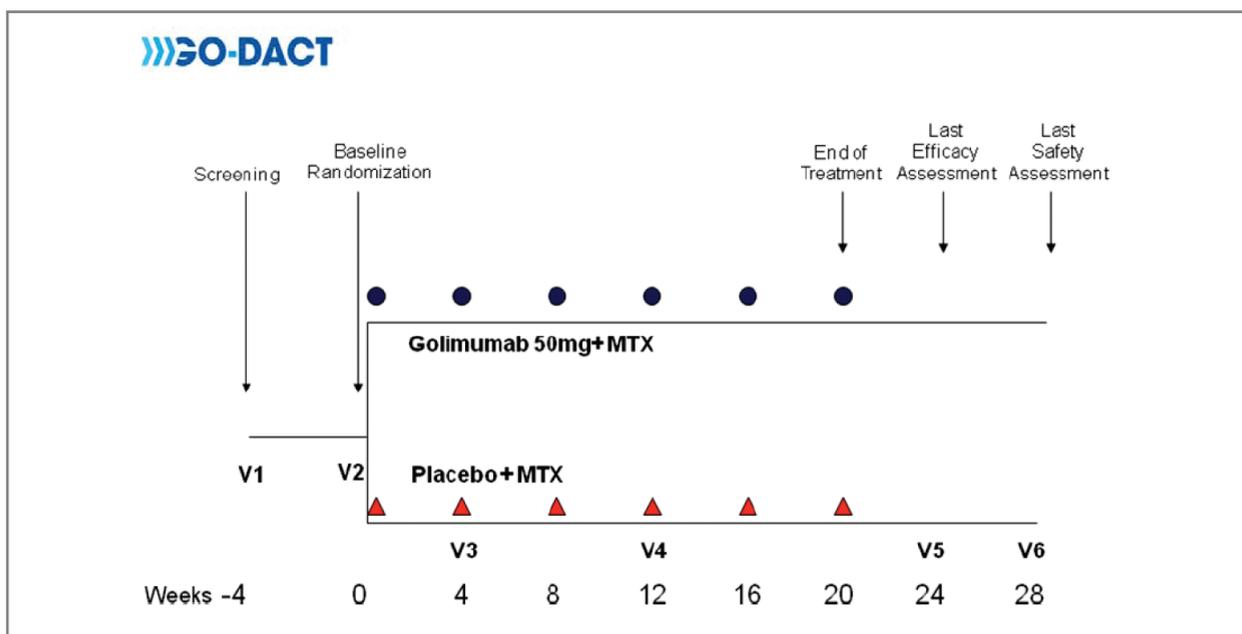


FIGURE 1. Clinical trial diagram methotrexate (MTX); visit (V)

PATIENT POPULATION

Female and male patients, older than 18 years, with the diagnosis of psoriatic arthritis according to the CASPAR criteria, and at least one tender dactylitis and another site of active inflammation (joints, entheses, spine, skin or nails), naïve to MTX and bDMARDs therapy, refractory to at least two systemic NSAIDs, at optimal dosage for 3 months, were eligible for inclusion.

Key exclusion criteria were those considered for any TNFi agent that could interfere with trial evaluations or patients safety including: known or suspected allergy to trial product or related products; current or chronic inflammatory autoimmune diseases other than PsA; active current infection or history of recurrent or chronic infections, past (< 5 years) 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. Previous use of any bDMARDs and MTX was prohibited. Previous local corticosteroids were allowed, up to a maximum of two injections, administered at least four weeks prior to screening. Other csDMARDs, except MTX, were also permitted if pre-

viously stopped according to their respective recommend washout periods.

TRIAL PROCEDURES

Recruitment and Informed consent

GO-DACT was approved by 13 Hospital Boards in Portugal (Figure 2) including:

- Hospital de Santa Maria, Centro Hospitalar Lisboa Norte, Lisboa
- Instituto Português de Reumatologia, Lisboa
- Hospital de Egas Moniz, Centro Hospitalar Lisboa Ocidental, Lisboa
- Hospital de São João, Centro Hospitalar de São João, Porto
- Hospital de Garcia de Orta, Almada
- Hospital Infante D. Pedro, Centro Hospitalar do Baixo Vouga, Aveiro
- Hospitais da Universidade de Coimbra, Centro Hospitalar Universitário de Coimbra, Coimbra
- Unidade Local de Saúde do Alto Minho, Ponte de Lima
- Centro Hospitalar de Vila Nova de Gaia, Vila Nova de Gaia
- Hospital de São Teotónio, Viseu

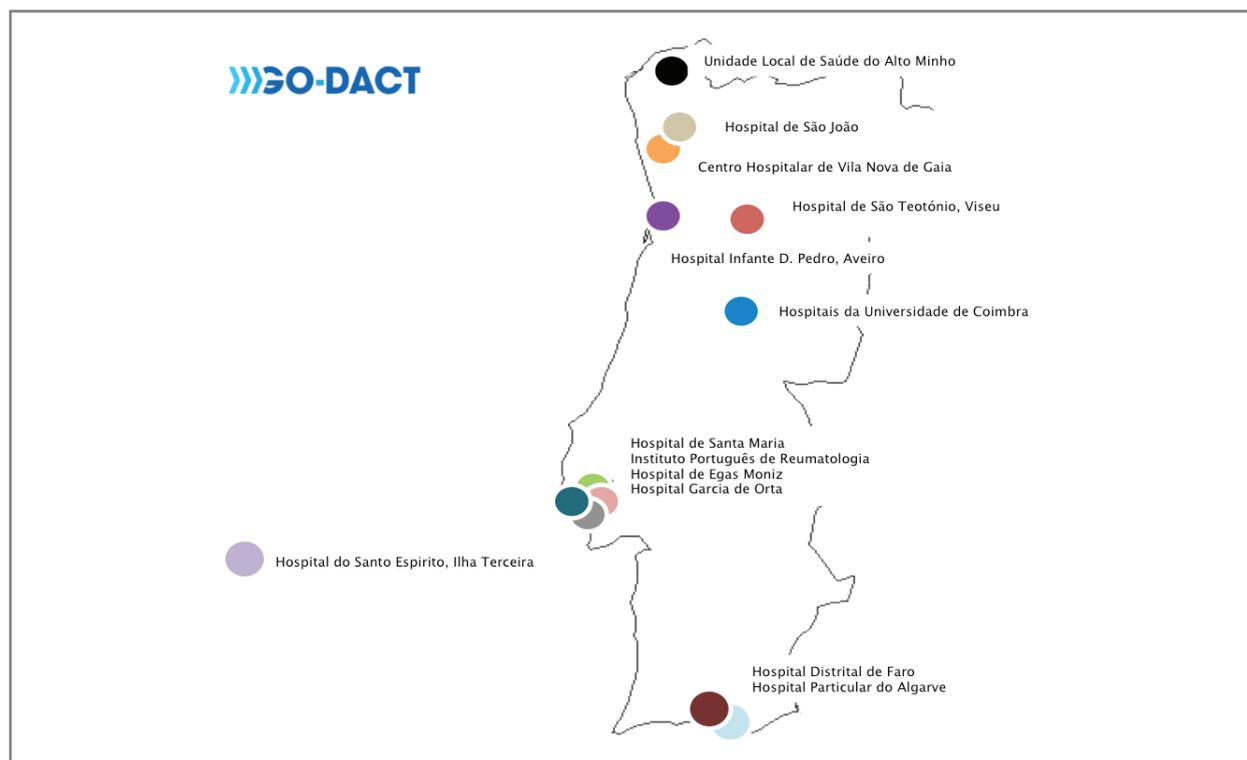


FIGURE 2. Trial centres distribution in Portugal

- Hospital Particular do Algarve, Faro
- Hospital Distrital de Faro, Centro Hospitalar do Algarve, Faro
- Hospital de Santo Espírito de Angra do Heroísmo, Ilha Terceira

Patients were recruited from rheumatology clinics and a detailed patient information form with verbal explanation of the trial was provided to all patients. Patients were given at least 24 hours to carefully read the information, as well the opportunity to raise questions before consenting their participation. Written informed consent was obtained from all subjects before any trial activity.

Randomization

PsA patients were centrally randomized to blinded, every four weeks subcutaneous injections of golimumab 50 mg or to placebo, both in combination with MTX, using a web-based randomization system of Reuma.pt, the Rheumatic Diseases Portuguese Register (Figure 3). Patients were randomly assigned in blocks of 4 (2:2) to treatment arms. No stratification based on

age, gender, or other demographic or diseases characteristics was performed. Both patients and clinicians were blinded for treatment assignments.

Visits schedule

The trial visits schema was defined aiming at mimicking the visit schedule used in clinical practice for patients starting a bDMARD therapy. Subjects were asked to attend a screening visit (visit 1), a baseline visit (visit 2), two follow-up visits (visit 3 after 4 weeks and visit 4 after 12 weeks of baseline) and one end-of-study visit (visit 5) at 24 weeks after baseline. It also included a safety follow-up visit in person or by phone call (visit 6), for a total of 6 visits during a period of 32 weeks (including the screening period) (Figure 1 and Figure 4).

Pre-treatment assessment

Demographic information, previous relevant personal and family medical history, previous and actual medication, physical examination including body mass index (BMI) (kg/m^2) and organs and systems changes, as well as smoking and alcohol intake, were registered.

The screenshot shows a web browser window titled "reuma.pt" with a "Block randomization" interface. At the top, there are two input fields: "First subject ID:" and "Number of subjects per block:" (with a note: "Leave this field blank for randomization without blocks"). Below this is a "Treatments" section containing a table for "Registered treatments" with columns "Treatment label" and "Num. Subjects". There are "Add", "Modify", and "Remove" buttons for the table. A "Generate randomization" button is located below the table. At the bottom, there is a "Settings" tab with an "Algorithm" sub-tab, containing text explaining the requirements for block randomization: "To create a block randomization list it is necessary to provide the number of subjects per block and the number of subjects for each treatment. It is important to note that the total number of subjects (all treatments) must be divisible by the block size, and that the number of subjects for each treatment group must be divisible by the number of blocks. However, the number of subjects per block is not mandatory, and its absence results in a simple randomization process."

FIGURE 3. Representation of the web-based randomization system of the Rheumatic Diseases Portuguese Register (Reuma.pt), available at <http://reuma.pt/random/randomization.html> Identification (ID)

For disease characterization, the subtype of PsA according to Moll and Wright classification criteria¹¹, the date of beginning of symptoms and of diagnosis, extra-articular manifestations including uveitis, psoriasis, nail dystrophy, dactylitis, enthesitis, Crohn's disease, ulcerative colitis, non-specific colitis and aortitis, the presence of rheumatoid factor, anti-cyclic citrullinated peptides antibodies and the surface antigen human leukocyte antigen (HLA) B27 were recorded in the electronic case report form (eCRF). Hand and feet and/or axial radiographies were equally captured.

All patients were screened for hepatitis B and C, human immunodeficiency virus, active and latent tuberculosis, as according to local clinical practice, before starting the trial medication. When indicated, treatment for latent tuberculosis was implemented according to local guidelines^{12,13}. All women with child-bearing potential were screened for pregnancy and all patients performed an electrocardiogram (ECG).

Prior, Concomitant and Rescue Medications

Patients could not have been previously treated with MTX or any bDMARDs. If under treatment with csDMARDs (other than MTX) or corticosteroids, patients had to be withdrawn from these therapies, according to their respective recommended washout periods. No other csDMARDs (with the exception of MTX) or oral corticosteroids were allowed during the trial. Up to a maximum of two local corticosteroids injections were permitted, administered at least four weeks prior to screening. Subjects could not have received any investigational drugs within the 30 days prior to baseline and could not receive them during the trial.

During the conduct of the trial, the physician was allowed to use intra-articular injections of corticosteroids as rescue medication, with exception of hands and feet joints. The injection, if deemed necessary, was required to occur at least 4 weeks prior to the next scheduled examination. Joints injected with corticosteroids were counted as tender and swollen at each visit taking place within 4 months after the intra articular injection. Subjects were also allowed to take analgesics as rescue medication. The dose and frequency of all rescue medications needed to be registered in the eCRF and subjects were advised not to take any analgesic medication within 6 hours prior to the visits for dactylitis, joint and entheses evaluation.

Any concomitant medications (including over-the-counter medications, herbal medications, preventative vaccines, vitamins and food supplements) and pro-

cedures were recorded in the eCRF. A description of the type of drug or procedure, the amount, duration, reason for administration and outcome had to be documented. Any adverse event (AE) related to the administration of a concomitant medication or procedure had to be documented on the appropriate AE page of the eCRF.

If concomitant medication was changed because of abnormal laboratory values of clinical significance, side effects, concurrent illness, or performance of a surgical procedure, the reason for the change had to be clearly documented in the subject's medical record.

Study intervention

Patients were randomized to one of the treatment arms: golimumab in combination with MTX versus placebo in combination with MTX.

Both golimumab 50 mg and placebo sterile solutions were presented as a 0.5 ml pre-filled syringe, indistinguishable from each other: no difference in the appearance of the two solutions was detectable. Golimumab or placebo were administered subcutaneously, every four weeks, for 24 consecutive weeks. Pre-filled syringes were labeled according to randomization numbers and sent to trial sites.

MTX was recommended to be started at a dose of 15mg/week, increased to 20mg/week at week 4 and aiming at 25mg/week at week 8, according to patient tolerability.

MTX was taken orally, once a week, for 6 successive months. Folic acid was given at least 24 hours after MTX intake, at a dose between 5 and 25mg once a week, according to the investigator's judgment. For patients that showed gastrointestinal intolerance to oral MTX, switching to the subcutaneous formulation was allowed.

Laboratory evaluations

Laboratory evaluations were performed as required in clinical practice for monitoring golimumab and MTX (Figure 4). These included:

- Hemoglobin, hematocrit, red blood cells and indices (mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration), white blood cells and absolute differential, platelet counts, creatinine, aspartate aminotransferase, alanine aminotransferase, C reactive Protein, erythrocyte sedimentation rate (using Westergren method) and type II urine including microscopic examination, at every determination

GO-DACT									
Visit name ¹	Screening	Baseline					EOT ⁸	EOS	FU
Visit number	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 information/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 & 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
Tolerability at injection site		X	X		X			X	
Antibodies to golimumab	X							X	
Efficacy assessments									
DSS and LDI	X	X	X		X			X	
LEI and SPARCC	X	X	X		X			X	
BSA/PASI/target NAPSI and 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 and 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 and PSAJAI	X	X	X		X			X	
SF36	X	X	X		X			X	
MDA									
CRP and ESR	X	X	X		X			X	
Hands/wrist or feet/ankle MRI ⁷		X						X	
Trial medication									
Dispense of medication		X	X		X			X	
Drug accountability		X	X		X			X	

FIGURE 4. Trial flow-chart

1 Visit name abbreviations: End of Treatment (EOT), End of Study (EOS) and Follow-up visit (FU).

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

3 Pregnancy tests conducted for female patients with child bearing potential.

4 Tuberculosis screening performed according to local guidelines.

5 One electrocardiogram (ECG) obtained during screening.

6 Hematology, chemistry, urinalysis.

7 Feet and ankle or hand and wrist magnetic resonance imaging (MRI) performed within up to 2 weeks before baseline visit and up to two weeks after V5.

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

Human leukocyte antigen B27 (HLAB27), rheumatoid factor (RF); anti-cyclic citrullinated peptides (anti-CCP); human immunodeficiency virus (HIV); Hepatitis B and C virus (Hep B/C), dactylitis severity score (DSS), Leeds Dactylitis Index (LDI), Leeds Enthesitis Index (LEI), Spondyloarthritis Research Consortium of Canada enthesitis score (SPARCC), Body Surface Area (BSA), Psoriasis Area Severity Index (PASI), Target Nail Psoriasis Severity Index (target NAPSI), Dermatology Life Quality Index (DLQI), tender joint count (TJ), swollen joint count (SJ), visual analogue scale (VAS), Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Spondylitis Functional Index (BASFI), Assessment of Spondyloarthritis International Society (ASAS), Ankylosing Spondylitis Disease Activity Score (ASDAS), Health Assessment Questionnaire Disability Index (HAQ-DI), Psoriatic Arthritis Disease Activity Score (PASDAS), Composite Psoriatic Disease Activity Index (CPDAI), Disease Activity Index for Psoriatic Arthritis (DAPSA), Disease Activity Score 28 (DAS28), Clinical Disease Activity Index (CDAI), Simplified Disease Activity Index (SDAI), American College Rheumatology response (ACR) 20, 50 and 70, Psoriatic Arthritis Response Criteria (PsARC), Psoriatic Arthritis Joint Activity Index (PsAJAI), Medical Outcomes Study Short Form 36 (SF-36), Minimal Disease Activity (MDA), reactive Protein (CRP), erythrocyte sedimentation rate (ESR), and (&x).

according to flow-chart.

- Urea, uric acid, glucose, potassium, sodium, chloride, calcium, phosphorous, total protein and albumin, alkaline phosphatase and total bilirubin (direct and indirect, if total bilirubin > upper limit of normal), fasting total cholesterol, high density lipoproteins, low density lipoproteins and triglycerides, were collected at screening.

Immunogenicity

One blood sample for determination of anti-golimumab antibodies was collected, at the same moment as for standard clinical laboratorial parameters, at screening and after 6 months of treatment.

Magnetic resonance imaging

A dedicated MRI protocol for identification of inflammation and bone damage in the hand and feet with high-resolution images for dactylitis assessment was developed.

Images were acquired before and after intravenous contrast to map and assess the degree of active inflammation with a high temporal resolution protocol. Morphological sequences (T1W) and fluid sensitive sequences (STIR) were used to assess structural changes in bone, tendons and capsular structures and to correlate morphology with edema and inflammation.

Unilateral MRI of the hand and wrist or the feet and ankle (depending on dactylitis location) was performed, at baseline and week 24. If both hand and feet were involved the most severely affected area was selected.

MRI examination was performed on a 1.5 Tesla whole-body scanner in 5 national imaging centres (Fundação Champalimaud; Dr. Campos Costa Imagiologia Clínica in Santa Maria da Feira, Hospital Particular do Algarve, Santo Tirso and Hospital do Santo Espírito, Angra do Heroísmo). For each Imaging Centre the MRI protocol was centrally validated before trial acquisitions.

Efficacy assessments

The assessment of dactylitis included: 1) The **DSS** determined by evaluating each dactylitis digit in a scale of 0 to 3 ((0 = no dactylitis; 1 = mild dactylitis, 2 = moderate dactylitis, 3 = severe dactylitis) and the total score calculated as the sum of scores for all 20 digits and thus ranging from 0 to 60 (primary efficacy endpoint). Scores > 0 indicate the presence of dactylitis(14); 2) the **DSS 20, 50, or 70 responses**, defined as the percentage of patients achieving at least 20%,

50%, or 70% of improvement in the DSS score; 3) the **LDI** based on the ratio of circumference between an affected finger and the contralateral unaffected finger (measured using the Leeds dactylometer commercialized by MIE medical research ltd®) and the tenderness score (0–3) of each finger with dactylitis¹⁵; 4) the **LDI 20, 50, or 70 responses**, defined as at least 20%, 50%, or 70% of improvement in the LDI score; 5) **number of patients with tender and non-tender dactylitis** and 6) **dactylitis remission** defined as a dactylitis severity score equal to zero.

Enthesitis was assessed through the: 1) **LEI** tenderness on examination was recorded as either present (1) or absent (0) at the lateral epicondyle, the medial femoral condyle and the Achilles tendon insertion, all both on left and right sides¹⁶; 2) the **SPARCC enthesitis score** consisted in the evaluation of tenderness at 16 entheses 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 tubercle¹⁷; and 3) the **enthesitis remission** defined by the absence of tender entheses, according to the LEI score.

For joint assessment, the **tender joint count** of 68 joints and the **swollen joint count** of 66 joints were considered, according to the EULAR handbook¹⁸.

Patient' and physician' global assessments for disease activity (arthritis and psoriasis), for arthritis activity, for psoriasis activity and for axial activity (only patients with axial involvement), were determined using VAS from 0 to 100mm.

For those patients with axial involvement, as determined by the investigator, the **BASDAI and ASDAS** were additionally applied.

The **BSA score** corresponding to the percentage of body surface affected by psoriasis, considering the patient's handprint (palm and fingers) as 1% of the body surface, and the **PASI** considering the four body surface areas (head, trunk and upper and lower limbs) and the degree of plaque erythema, scaling and thickness, were used to determine psoriasis plaque extension and severity. The PASI score ranges from 0 (no disease) to 72 (maximal disease) and the response PASI 50, 75 and 90 was determined¹⁹. The **target NAPSI** was used for nail psoriasis assessment. In the target NAPSI the most severely affected nail at baseline is divided into 4 quadrants and 1 point is awarded for each nail matrix (pitting, leukonychia, crumbling, and red spots in the

lunula) and 1 point for each nail bed changes (onycholysis, splinter hemorrhages, hyperkeratosis, and oil-drop dyschromia) per quadrant, ranging from 0 to 8 points per quadrant and a maximum total score of 32²⁰.

Physical function was evaluated using the **HAQ-DI** and the **BASFI** (only for patients with axial involvement).

To assess the health-related quality of life for psoriasis we used the **DLQI** and for global health the **SF-36**.

We considered different composite indexes of disease activity to capture disease activity in several domains, including the **DAS28**, the **DAPSA**, the **SDAI** and the **CDAI**, the **PASDA5** and the **CPDAI**. For those with axial disease we used the **ASDAS**.

Response criteria included the **ACR 20, 50 and 70**, the **PsARC**, the **ASAS 20 and 40 responses**, **clinical important, major improvement ΔASDAS and ASDAS inactive disease criteria**, the **PsAJAI** and the **PASI 50, 75 and 90**.

The **MDA** criteria defined as fulfilling 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 enthesal points ≤ 1 , was applied as a measure of remission.

The MRI characteristics of the most severely affected dactylitic finger or toe were assessed by changes from baseline on the **dactylitis MRI score** at week 24²¹.

The MRI characteristics of the selected foot and ankle or hand and wrist were determined by changes from baseline in psoriatic arthritis MRI scoring system for the hands (**PSAMRIS-H**) and for feet (**PSAMRIS-F**) at week 24^{22,23}.

Specific training was given for investigators and trial team concerning efficacy assessment tools.

SAFETY AND TOLERABILITY

Subjects enrolled in the study were monitored for both AEs and serious adverse events (SAEs) immediately after the subject signed the informed consent.

Subjects having AEs or SAE were monitored with relevant clinical assessments and laboratory tests, as determined by the investigator. Actions taken as a result of AEs and SAEs, and follow-up results were recorded in the eCRF, as well as, in the subject's source documentation.

Specific orientations for the management of laboratorial changes under MTX were developed to guide clinicians during patients monitoring (Figure 5).

ELECTRONIC CASE REPORT FORM

A dedicated case record form was developed for GO-DACT at Reuma.pt. Reuma.pt is a web-based register used by rheumatologists for patient's information register, with restricted access by personal credentials assigned to the researchers, approved by Comissão Nacional de Proteção de Dados (CNPd). Specific fields for this trial were developed and could only be accessed by trial investigators at each centre (Figure 6). Each subject was identified by a unique subject identification number.

ETHICAL CONSIDERATIONS

GO-DACT was conducted in accordance to the ethical principles of the Declaration of Helsinki, Good Clinical Practice and approved by the National Ethics Committee (CEIC), National Authority of Medicines and Health Products (INFARMED) and CNPD. The study is registered at ClinicalTrials.gov with the number NCT02065713.

GO-DACT	
Haemoglobin	Action*#&§
>10g/dl	Maintain dose
8-10g/dl	Reduce dose and reassess haemoglobin levels after 4 weeks
<8g/dl	Suspend MTX and reassess after 4 weeks. MTX can be reintroduced at a lower dose if haemoglobin >10g/dl.
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 MTX and reassess after 4 weeks. MTX can be reintroduced at a lower dose if platelets >100.000 cells/mm ³
Neutrophils	Action*#&§
>1000 cells/mm ³	Maintain dose
500-1000 cells/mm ³	Suspend MTX and reassess after 4 weeks. MTX can be reintroduced at a lower dose if neutrophils >1.000 cells/mm ³
500 cells/mm ³	Discontinue MTX and withdraw subject.
* 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.	
ALT and/or AST values	Action*#&§
< 3x ULN	Reduce dose and reassess after 4 weeks.
3 up to 5x ULN	Suspend MTX and reassess after 4 weeks. MTX can be reintroduced at a lower dose if ALT and/or AST <3x ULN.
>5x ULN	Suspend MTX and reassess after 4 weeks. MTX 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 phosphatase or prolonged prothrombin time, discontinue MTX 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.	

FIGURE 5. Guidance on how to proceed in case of myelotoxicity and hepatotoxicity to methotrexate (MTX), upper limit of normal (ULN); alanine aminotransferase (ALT); aspartate aminotransferase (AST)

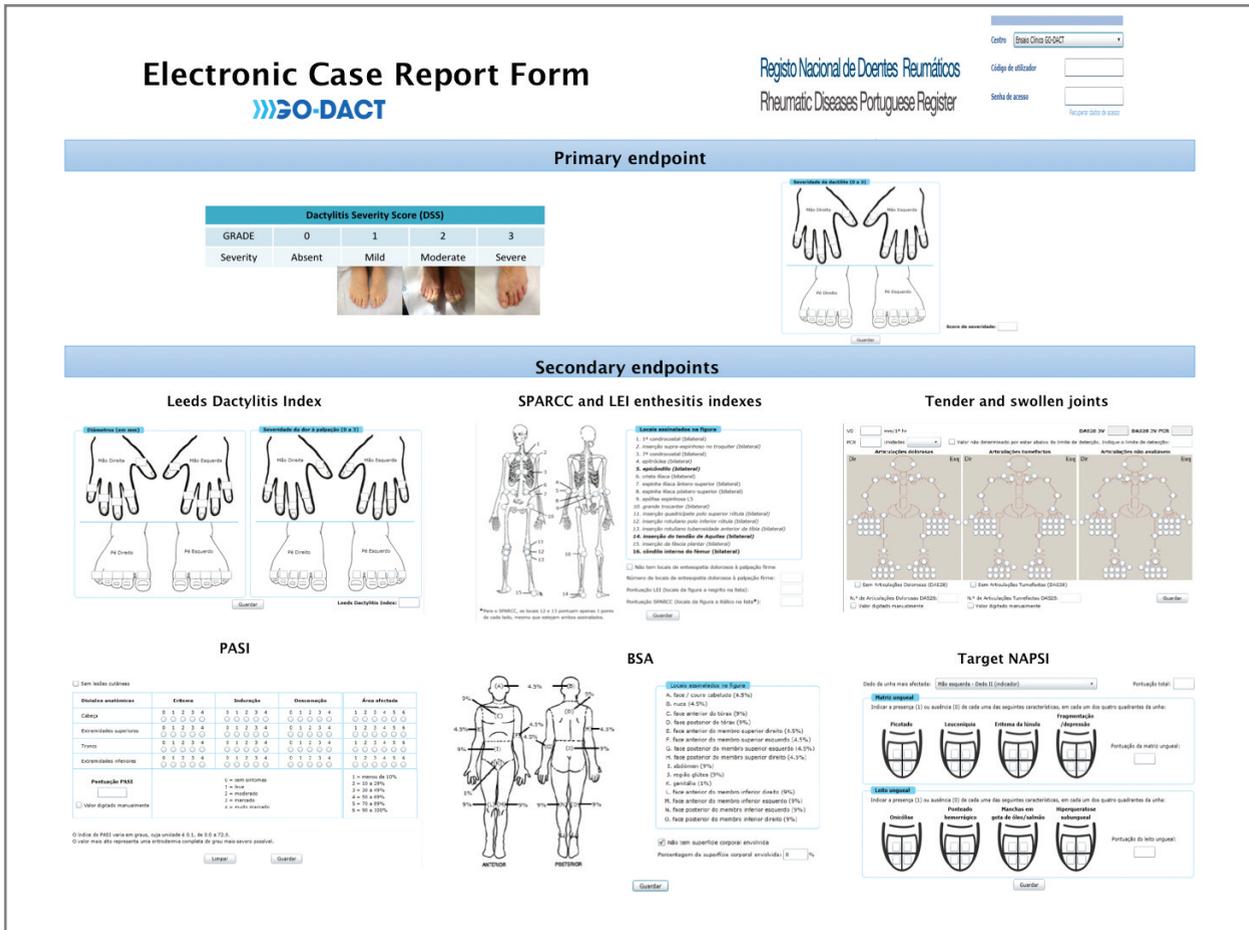


FIGURE 6. Illustrative screens of GO-DACT¹ electronic case report form developed in the Rheumatic Diseases Portuguese Register (Reuma.pt) Leeds Enthesitis Index (LEI); Spondyloarthritis Research Consortium of Canada enthesitis score (SPARCC); Psoriasis Area Severity Index (PASI); Body Surface Area (BSA); Target Nail Psoriasis Severity Index (tNAPSI)

STATISTICAL AND ANALYTICAL PLAN

SAMPLE SIZE CALCULATION

GO-DACT is a study of controls and experimental subjects randomized in blocks of 4 (2:2). A total sample size of 90 patients was estimate based on assuming the absolute change in dactylitis severity score from the GO-REVEAL trial data considering a difference of 2,52 and a standard deviation of 4,01, to achieve a 0.05 significance between groups and a drop out of 10%²⁴. For sample size calculation, the ps: power and sample size calculation software was used. An interim analysis was planned when 50% of the patients have been included.

BASELINE CHARACTERISTICS

All demographic, medical history, previous and cur-

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

Differences in baseline characteristics will be assessed using Fisher's exact test (including a generalized version for variables with more than two categories) for categorical variables and the non-parametric Wilcoxon rank-sum test for continuous variables.

PRIMARY EFFICACY ENDPOINT

For each participant, the change in score will be calcu-

lated as the final score at 24 weeks minus the baseline score. We will use the Mann-Whitney test to compare these changes of the dactylitis severity score between treatment groups.

The effect of the intervention will be estimated by the differences between the two treatment arms in the changes in scores and significance will be assessed at $\alpha=0.05$.

SECONDARY EFFICACY ENDPOINTS

Descriptive statistics will be used to summarize all secondary endpoints such as LDI, LEI, SPARCC, tender 68 and swollen 66 joints, patients and physician VAS, BASDAI, ASDAS, BASFI, target NAPS, HAQ-DI, SF36, DLQI and composite indexes, among others, by treatment group. The changes in scores will be calculated and comparisons between treatment groups will be made by the Mann-Whitney test. Fisher's exact test will be used to compare in the two groups the proportion of patients achieving DSS20,50,70, ACR20,50,70, PASI50,75,90, ASDAS clinical important and major improvements, ASAS20,40 and MDI responses, among others.

For MRI findings, a descriptive statistic of each lesion, for individual joints, dactylitis and enthesitis, and aggregated scores by region will be calculated. The data will be analyzed individually by joint and lesion and as aggregated scores such as the PsAMRIS-H and the PsAMRIS-F^{22,23}. Pairwise comparisons between two time-points for each individual joints, dactylitis and enthesitis and for aggregated scores by region will be calculated.

SAFETY

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.

TRIAL MEDICATION MANAGEMENT

The investigational medical product was managed by Reuma.pt farmácias, a software developed for the GO-DACT trial, associated to Reuma.pt (Figure 7). This platform managed the reception, dispensing and accountability of the trial medication, at the 13 local pharmacies at research sites, throughout the trial. At each visit, kits were assigned to each patient according to his previously randomized study arm and the number of kits for that visit described by the study protocol in a double blinded designed.

Prior to trial activities, specific training for the use of Reuma.pt farmácias was given to pharmacists and trial coordinators.

FINAL REMARKS

GO-DACT is the first randomized controlled trial developed to study dactylitis as primary endpoint in pso-



FIGURE 7. Illustrative screens of Reuma.pt Farmácias, a dedicated software developed in Rheumatic Diseases Portuguese Register (Reuma.pt) for trial medication management, available at <http://reuma.pt/farmacias.html>

riatic arthritis patients. Both clinical and imaging outcomes were used to assess the effect of golimumab or placebo both in combination with methotrexate, in the improvement of dactylitis at week 24. The main objective of GO-DACT is therefore to provide evidence to improve the treatment algorithm and care of psoriatic arthritis patients with active dactylitis.

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