Study Protocol and Statistical Analysis Plan

Efficacy of golimumab in early axial spondyloarthritis (axSpA) in relation to gut inflammation, an early remission induction study (GO GUT).

NCT03270501

version 5.0 - 19 January 2021

PART 1: TRIAL-RELATED PART OF THE PROTOCOL

1. Title of the trial

Efficacy of golimumab in early axial spondyloarthritis (axSpA) in relation to gut inflammation, an early remission induction study (GO GUT).

2. Trial number

Protocol: AGO/2017/004

EudraCT number: 2017-001728-23

3. Objectives and hypothesis

3.1 Primary objectives

1. To describe and confirm the relationship between subclinical gut inflammation and axSpA.

2. To evaluate whether there is a higher need of anti-tumor necrosis factor α (anti-TNFα) treatment in axSpA patients with (subclinical) gut inflammation compared to those without.

3.2 Secondary objectives

1. To describe the clinical response of a treat-to-target principle in early axSpA and explore the possibility of drug-free remission.

2. To evaluate the relation between the presence of (subclinical) gut inflammation and the therapeutic response to anti-TNFα in patients with axSpA.

3. To evaluate the relationship between (subclinical) gut inflammation on the one hand and remission induction and relapse on the other hand in patients with axSpA.

3.3 Hypothesis

The hypothesis of the study is that the presence of (subclinical) gut inflammation at baseline in patients with early active axSpA predisposes to a more severe disease defined as more need to use anti-TNFα therapy and a shorter time to relapse after stopping anti-TNFα therapy after obtaining sustained clinical remission. Overall, we hypothesize that subclinical gut inflammation is an important predictor in therapy response and outcome. These data could provide us better insights into the complex interactions between gut and joint inflammation and guide us in the therapeutic approach.

3.4 Primary endpoint and timepoint of the endpoint.

Clinical remission, evaluated on 2 consecutive follow-up visits (interval: 12 weeks).

3.5 Secondary endpoint and timepoint of the endpoint.

Mucosal healing, evaluated by ileocolonoscopy at time of clinical remission.

4. General information

4.1 Investigators

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4.2 Sponsor

Ghent University.

4.3 Funding

Research grant by Merck Sharp & Dohme (MSD).
Golimumab will be provided by MSD.

4.4 Departments

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Department of Radiology, Ghent University Hospital.
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Department of Radiology, Imelda hospital Bonheiden.

5. Introduction

Spondyloarthritis (SpA) is an immune-mediated, inflammatory rheumatic disease concept, consisting of a group different diseases, sharing common genetic, clinical and radiological characteristics. Patients develop inflammatory back pain and/or pauci-articular peripheral arthritis/enthesitis. In the long term, chronic inflammation of the axial skeleton can cause osteoproliferation and ankylosis of sacroiliac joint and spine.

An important feature of SpA is the frequent association with extra-articular symptoms such as anterior uveitis, psoriasis and inflammatory bowel disease (IBD), especially Crohn's disease (CD) and to a lesser extent ulcerative colitis [1]. About 50% of SpA patients have microscopic signs of bowel inflammation, without gastrointestinal symptoms. These microscopic lesions can be indistinguishable from lesions seen in early CD, suggesting that these might represent a subclinical form of the disease. Even more, IBD and SpA might be two ends of the same disease spectrum. This hypothesis is further strengthened by the identification of common genetic susceptibility factors linking SpA and IBD pathogenesis [2-4]. Hence, gut involvement seems to be important for SpA pathogenesis. A clear clinical relationship between gut and joint inflammation with remission of the latter being associated with disappearance of the first and vice versa is showed in the past [5-7]. Interestingly, patients with chronic gut inflammation showed a higher risk of evolving to ankylosing spondylitis (AS) and were more likely to start anti-TNFα therapy. Furthermore, they seem to respond better to the treatment with biologicals. This underlines the potential clinical implications of microscopic gut inflammation in SpA and suggests that gut inflammation predisposes to a more extensive, persistent disease [unpublished data; 7,8]. In addition, results from the Ghent Inflammatory Arthritis and spondylitis (GIANT) cohort showed that chronic gut inflammation is linked to more extensive bone marrow

edema of the sacroiliac joints on magnetic resonance imaging (MRI) [9]. It has also been suggested that inducing mucosal healing is an important factor for long-term remission [10].

In 2017 the Assessment of Spondyloarthritis international Society (ASAS) and the European League Against Rheumatism (EULAR) published an update of the axSpA treatment guidelines. In this update ASAS and EULAR stress on the importance of installing a treat-to-target principle. However, they do not suggest a preferred target, but leave the decision to the clinician and his patient. All patients should be treated with 2 different non-steroidal anti-inflammatory drugs (NSAIDs) during 4 weeks in total, before switching to an anti-TNFα agent. This period is significantly shorter than the previous recommendation of 3 months treatment with NSAIDs [11].

Golimumab is a fully human monoclonal antibody that binds and inhibits TNFα [12,13]. In Europe it is used, among others, in AS and non-radiographic axSpA who do not respond to NSAIDs. The effectiveness of golimumab is also shown in IBD [14]. Two randomized clinical trials (RCTs) have examined the therapeutic effects of golimumab in patients with SpA: the GO-RAISE and GO-AHEAD trial. Both trials showed a better ASAS 20 response at week 14 and 16, respectively, in the golimumab group compared to placebo. Clinical improvement was already seen 4 weeks after first subcutaneous administration of the medication. The treatment response was higher in patients with overt signs of inflammation, i.e. sacroiliitis on MRI and/or higher C-reactive protein (CRP) levels, than in patients without detectable inflammation. Thus, objective signs of inflammation could be a good predictor of treatment response. In terms of effect on imaging it showed that both sacroiliac joint and spine inflammation is reduced when treated with golimumab [15,16]. The safety profile of golimumab is comparable with that of other TNFα-inhibitors and is generally well-tolerated by patients.

6. The present study

6.1 Participants

6.1.1 Number of participants

The total number of patients needed is estimated to be 147 (cfr. infra: 10.1 Calculation of the sample size). The subjects will be recruited through the department Rheumatology of the Ghent University Hospital, at the Reuma Institute in Hasselt, and at the Imelda hospital in Bonheiden.

6.1.2 Inclusion criteria

In this trial we will include 147 subjects for which all of the following criteria must be met:

- Subject must have a diagnosis of axSpA and classified according to ASAS criteria.
- Subject is between 18 and 46 years at the screening visit.
- Subject has at least 3 months and maximum 1 year (almost) daily chronic back pain.
- Subject has an active disease defined as a positive MRI (according to ASAS definition) or elevated CRP (in patients who are HLA-B27+) and an ASDAS score > 2.1 (at least high disease activity).

6.1.3 Exclusion criteria

- Full anti-inflammatory dose of NSAIDs for more than 4 weeks for the duration of the axSpA symptoms.
- Prior exposure to any biologic therapy with a potential therapeutic impact on SpA, including anti-TNF therapy.
- Exposure to disease-modifying drugs (DMARDSs; i.e. methotrexate and sulfasalazine) in the last 3 months before the ileocolonoscopy.
- Exposure to systemic corticosteroid treatment in the last 14 days before the ileocolonoscopy.
- Infection(s) requiring treatment with intravenous antibiotics/antivirals/antifungals within 30 days prior to the baseline visit or oral antibiotics/antivirals/antifungals within 14 days prior to the baseline visit.
- Have a known hypersensitivity to human immunoglobulin proteins or other components of golimumab.
- History of central nervous system (CNS) demyelinating disease or neurologic symptoms suggestive of CNS demyelinating disease.
- History of listeriosis, histoplasmosis, chronic of active hepatitis B infection, hepatitis C infection, human immunodeficiency virus (HIV) infection, immunodeficiency syndrome, chronic recurring infections or active tuberculosis.
- Have a history of, or concurrent, chronic heart failure, including medically controlled, asymptomatic congestive heart failure.
- Evidence of dysplasia or history of malignancy (including lymphoma and leukemia) other than a successfully treated non-metastatic cutaneous squamous cell or basal cell carcinoma or localized carcinoma in situ of the cervix.
- Have received, or are expected to receive, any live virus or bacterial vaccination within 3 months prior to the first administration of study agent, during the trial, or within 6 months after the last administration of study agent.
- Positive pregnancy test at screening
- Female subjects who are breast-feeding or considering becoming pregnant during the study.
- Female subjects who do not use contraceptives.
- History of clinically significant drug or alcohol abuse in the last 12 months.
- Clinically significant abnormal screening laboratory results as evaluated by the investigator.
- Positive rheumatoid factor (RF) or anti-cyclic citrullinated peptide (anti-CCP) antibody at screening if the titers are crossing 3 times the upper limit of the normal.
- Subject with diagnosis and current symptoms of fibromyalgia.
- Any medical or psychological condition that, in the opinion of the investigator, could jeopardize or compromise the subject's ability to participate in this study.

6.1.4 Replacement of participants

Screen failures will be replaced by individuals that meet the inclusion criteria in order to reach the proposed target population of 147 patients.
Drop-outs will not be replaced.

6.1.5 Limitations for the participants

There are no specific limitations for the participants other than the ones listed at section 6.1.3 Exclusion criteria, with the exception that there is an obligation for female subjects to use contraceptives.

6.1.6 Advantages and disadvantages for the participants

In Belgium anti-TNFα treatment for axSpA is only reimbursed for patients with sacroiliitis on MRI according to ASAS and an elevated CRP. In this trial the European guidelines are used, so participants qualify for treatment with anti-TNFα if they have sacroiliitis on MRI (according to ASAS definition) or an elevated CRP (they do not have to meet both criteria) [11]. Up until now Golimumab is not reimbursed in Belgium for the treatment of axSpA. Thus, this means an advantage for the participants.

As all the investigations and treatments in this trial are considered routine clinical care, there are no specific disadvantages for the participants.

General risks concerning the procedures included in the study protocol:

- Risk of blood sampling: hematoma at the puncture site, residual bleeding at the puncture site. Some patients may feel dizzy or faint during blood sampling. The qualified nurse who performs the blood sampling will act professionally in order to minimize these risks.
- Risk of ileocolonoscopy: this examination is generally safe. There is minimal risk of perforation of the intestinal mucosa.
- Risk of NMR: some patients may feel anxious because subjects are asked to lay flat in a small tunnel (claustrophobia). No risk for allergic reactions since no contrast agents are being used.

6.2 Study design and procedures

Cfr. infra: 6.3 Flowchart.

6.2.1 Screening visit

At the screening visit the informed consent form (ICF) will be signed and inclusion/exclusion criteria will be checked. Subsequently routine blood tests (complete blood count, electrolytes, liver function, kidney function, CRP and Erythrocyte Sedimentation Rate - ESR) and additional study samples for inflammatory and genetic markers will be taken (4x5mL serum and 3x4mL EDTA). These additional samples will be stocked pseudonymized in a prospective research biobank (“Biobank van menselijk lichaamsmateriaal van patiënten met reumatische en/of musculoskeletale aandoeningen en gezonde controles”, EC 2019/0314, medical administrator: prof. dr. Dirk Elewaut). Also, HIV and hepatitis serology will be checked as part of the routine blood analyses and a Mantoux tuberculin skin test and a chest X-ray will be executed to exclude latent tuberculosis.

6.2.2 Baseline and follow-up

All subjects will undergo a baseline (pre-treatment) ileocolonoscopy to detect whether there is (subclinical) gut inflammation; this procedure is part of standard of care. Subjects must prepare for the ileocolonoscopy by avoiding consumption of high-fiber food or food rich in kernels from 3 days in advance.
Further preparation procedure for UZ Gent and the Reuma Institute Hasselt:

The day before the ileocolonoscopy, only liquid food is allowed. The evening before the examination, the subject needs to drink 1 portion of Plenvu in 500cc water and an extra 500cc of clear water. This needs to be repeated on the morning of the examination.
Further preparation procedure for Imelda hospital Bonheiden:
The day before the ileocolonoscopy at 12h a light meal is allowed, no fruit, no vegetables and no brown bread is allowed. Afterwards no food is allowed anymore, only drinking is allowed. And at 18h the subject needs to drink 2 portions of colofort in 2 liters water over 2 hours. On the morning at 7h the subject again needs to drink 2 portions of colofort in 2 liters water over 2 hours.

These preparations ensure an adequate cleaning of the intestines in order to optimize the endoscopists' view.
During the ileocolonoscopy, for all sites routine biopsies for pathological examination (4 biopsies in ileum, 8 biopsies in colon) and extra biopsies for RNA sequencing (2 biopsies in ileum, 2 biopsies in colon) will be taken. Additional for functional analyses, site specific (only in Ghent University Hospital), also 6 biopsies in ileum and 6 biopsies in colon will be taken. The investigators and the patient will be blinded for the results of this ileocolonoscopy until the subject is switched to golimumab. Only in case of major abnormalities necessitating medical intervention, the investigator will be made aware of the results of the ileocolonoscopy earlier. The central reader will make sure that 50% of the included patients will have subclinical gut inflammation and 50% of the patients will not have any subclinical gut inflammation. Additional blood samples will be drawn for functional analyses (site specific: only sampling of 4x10mL heparin blood in Ghent University Hospital) and 1 stool sample will be collected and stored pseudonymized in the prospective research biobank. After the trial has ended, all stool samples will be subject to biochemical and microbiome analyses (in one batch), performed by the laboratory attached to the department of Rheumatology of Ghent University Hospital.

At baseline, a treat-to-target principle will be installed. All subjects will receive a full anti-inflammatory dose NSAID for 2 weeks according to the routine clinical practice.

Visits are scheduled on week 0, 2, 4, 16, 28, 40 and 52 (± 2 weeks). If subjects have a clinically important improvement, defined as an ASDAS score < 1.3 or a decrease of at least 1.1 in ASDAS score resulting in a maximum of 2.1, subjects will continue with the same treatment. If subjects do not meet this disease activity state after a treatment with the first NSAID, a different NSAID will be installed at full anti-inflammatory dose during 2 weeks. Again, if subjects have a clinically important improvement (compared to the baseline situation before initiating the first NSAID therapy) after 2 weeks treatment with the second NSAID, subjects continue with this treatment. If this disease activity state is not reached at week 4, the NSAID treatment will be stopped and subjects will start treatment with golimumab (anti-TNFα therapy, 50mg every 4 weeks, subcutaneous injection) in monotherapy. At every trial visit routine blood tests (inflammatory markers at week 0, 2, 4 and a complete blood count, electrolytes, liver function, kidney function, inflammatory markers at screening, week 16, 28, 40 and 52) will be performed. Additional study samples for inflammatory markers (2x5mL serum) will be taken at every trial visit (except for the baseline visit at week 0, no additional serum samples) and stored in the prospective research biobank. After 4 weeks NSAID treatment, after 6 months golimumab treatment and at time of relapse stool samples (1 sample at each time point) and additional blood samples (site specific: only sampling of 3x10mL heparin blood in Ghent University Hospital) will be collected. The additional heparin blood samples are used immediately for functional analysis; the stool samples are stored pseudonymized in the prospective research biobank. After the trial has ended, all stool samples will be subject to biochemical and microbiome analyses (in one batch), performed by the laboratory attached to the department of Rheumatology of Ghent University Hospital.

Maximal study duration for a subject is 12 months.

6.2.3 Start of anti-TNFα

If a subject starts on anti-TNFα treatment, the timing of the study visits will be recalculated: part B +12 weeks, +24, +36, etc.

6.2.4 Remission

If subjects are in remission (ASDAS < 1.3) during the follow-up period on 2 consecutive study visits (with an interval of 12 weeks), subjects are considered to be in sustained clinical remission and golimumab or NSAID therapy will be stopped and a second ileocolonoscopy will be performed in those patients from whom the first colonoscopy showed (subclinical) gut inflammation. During the ileocolonoscopy, for all sites routine biopsies for pathological examination (4 biopsies in ileum, 8 biopsies in colon) and extra biopsies for RNA sequencing (2 biopsies in ileum, 2 biopsies in colon) will be taken. Additional for functional analyses, site specific (only in Ghent University Hospital), also 6 biopsies in ileum and 6 biopsies in colon will be taken. Additional blood samples (3x10mL heparin) will be taken prior to the ileocolonoscopy for simultaneous functional analysis (site specific: only sampling of heparin blood in Ghent University Hospital). A new MRI of the sacroiliac joints will be performed in all patients in which treatment was withdrawn because of sustained clinical remission on 2 consecutive clinical visits. For all those patients the study ends and follow-up and treatment will be foreseen every 6 months in our local Be-Giant register according to the routine clinical practice.

6.2.5 Relapse

- Relapse is defined as:

- Δ ASDAS ≥ 0,6 (compared to ASDAS at time of sustained clinical remission) and ASDAS ≥ 1,3 (17)

AND

- PASS (= patient acceptable symptom state) for the upcoming 6 months is NO (meaning: would the patient be satisfied if current clinical situation would continue for the next 6 months)

AND

- Expert opinion: the assessing physician believes that Δ ASDAS reported by the patient is most probably related to a relapse of spondyloarthritis. If not, an alternative hypothesis/probable diagnosis must be provided.

- In case of relapse, the time point will be registered in the study, extra blood samples will be drawn (2x5mL serum; site specific: 3x10mL heparin blood only in Ghent University Hospital) and the

subjects will be treated according to the routine clinical practice. In reality, this will most likely match the last remission-inducing treatment of the subject.

6.2.6 No remission achieved

When the subject is still not in sustained remission after 48 weeks of golimumab treatment, defined as ASDAS < 1.3 on 2 consecutive study visits, the patient will stop participating in this study and will be followed in the routine clinical practice.

6.2.7 Procedures

6.2.7.1 Screening visit

- ICF
- Check fulfillment of the inclusion and exclusion criteria
- Anamnesis
- Medical and family history
- Demographic data
- Symptom duration
- Current and past medication (NSAID): dosage and duration
- Clinical examination:
    - weight, length, vital symptoms (blood pressure, heart frequency)
    - BASMI
    - Total tender and swollen joint count (TJC/SJC) (78)
    - Dactylitis assessment
    - MASES + plantar fascia + quadriceps and patellar tendon
- Assessment of work participation (site-specific: only in Ghent University Hospital).
- Questionnaires: Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Spondylitis Functional Index (BASFI), Patient global assessment of disease activity, patient global pain assessment. Site-specific (only in Ghent University Hospital): Work Productivity and Activity Impairment (WPAI), health care consumption, EQ5D.
- Laboratory investigation (incl. 4x5mL serum + 3x4mL EDTA for additional research)
- Imaging: MRI SI joints (if not already done), chest X-ray
- Mantoux tuberculin test
- Pregnancy test for female subjects (on blood sample)

6.2.7.2 Baseline

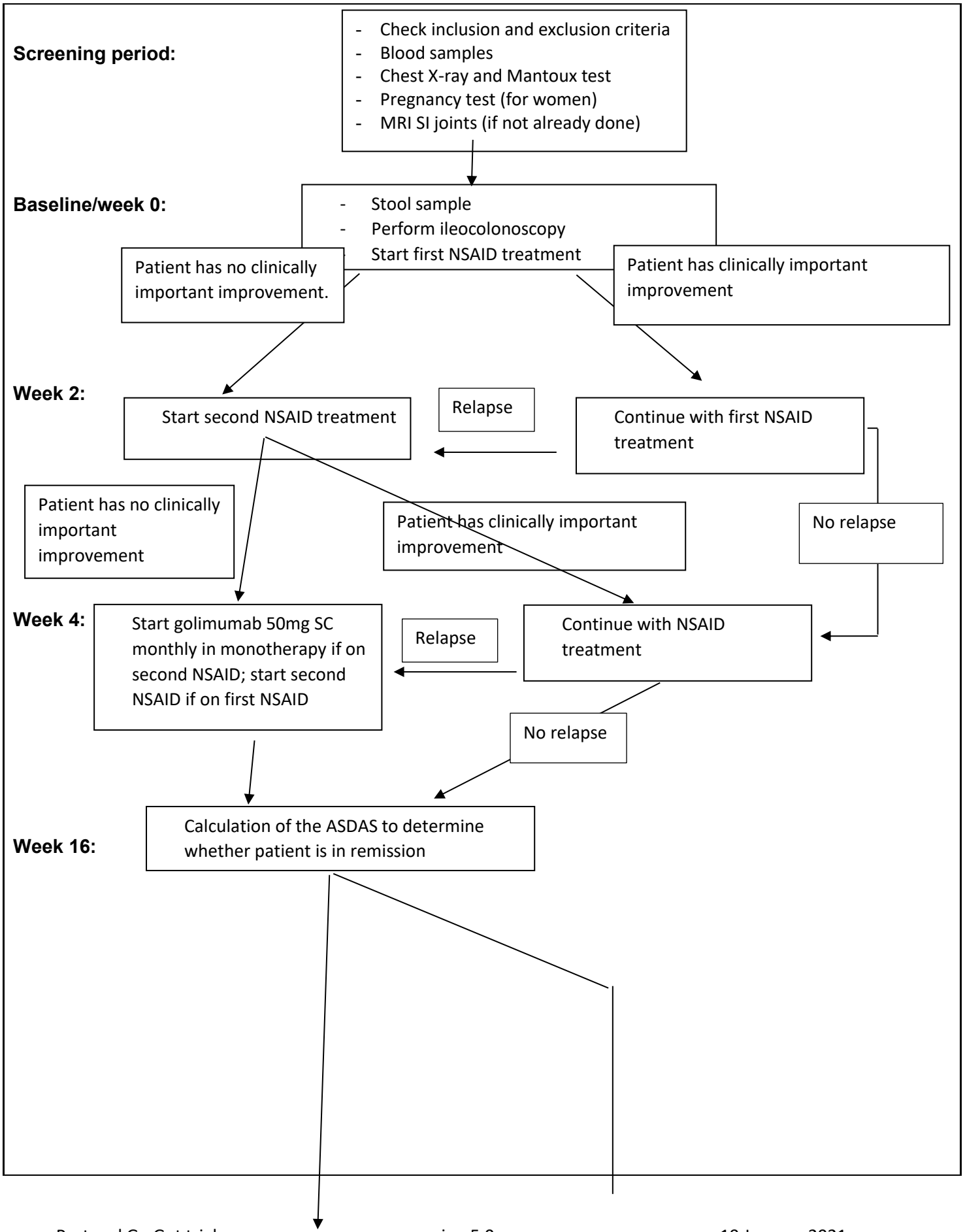
- Laboratory investigation (site-specific: only in Ghent University Hospital 4x10mL heparin blood for additional research)
- Stool sample
- Ileocolonoscopy including for all sites routine biopsies for pathological examination (4 biopsies in ileum, 8 biopsies in colon) and extra biopsies for RNA sequencing (2 biopsies in ileum, 2 biopsies in colon) will be taken. Additional for functional analyses, site specific (only in Ghent University Hospital), also 6 biopsies in ileum and 6 biopsies in colon will be taken.
- Start treat-to-target approach

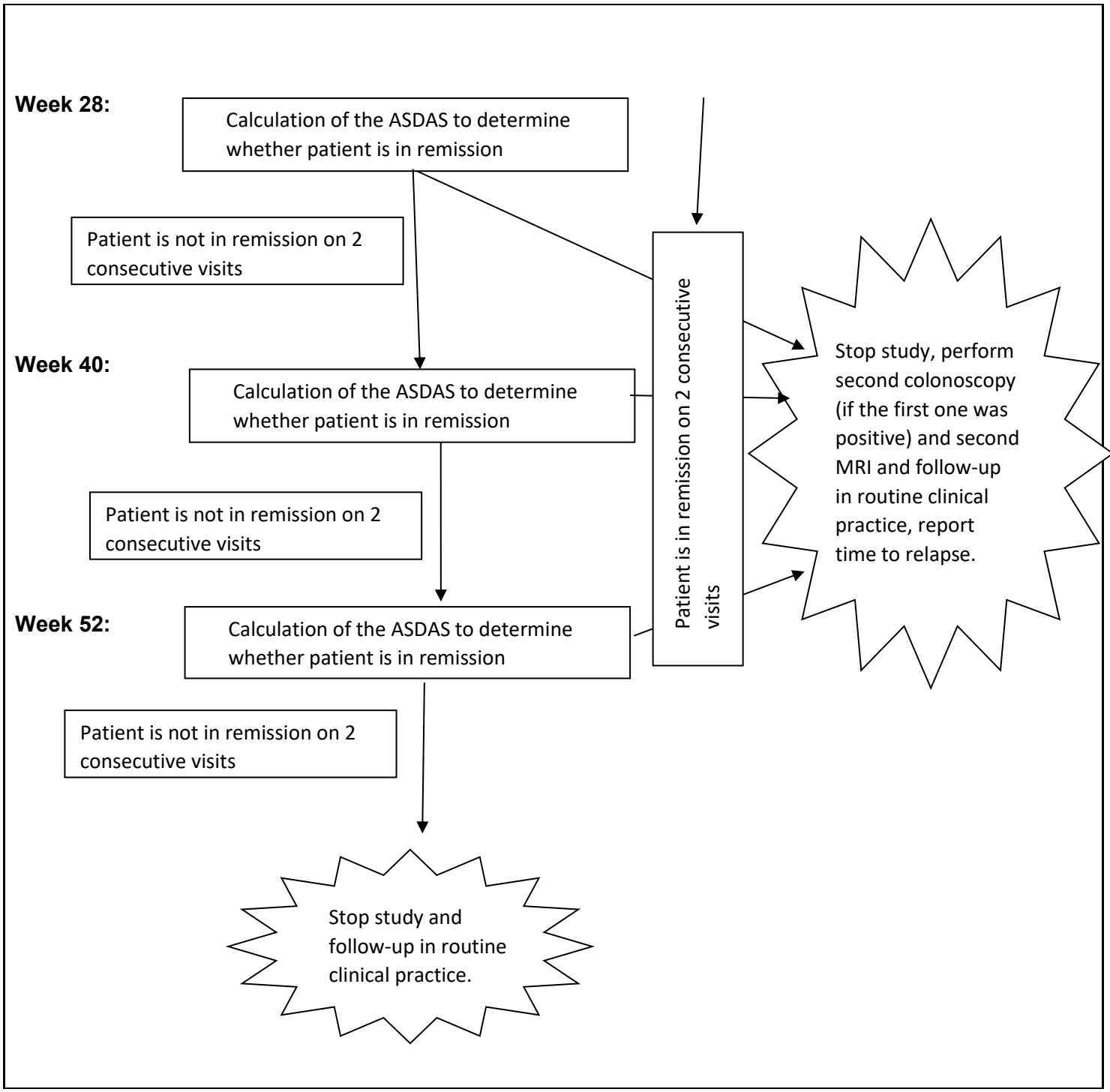
- AND if baseline visit is performed more than 4 weeks after the screening visit:
    - Anamnesis
    - Current and past medication (NSAID): dosage and duration
    - Clinical examination:
        - weight, length, vital symptoms (blood pressure, heart frequency)
        - BASMI
        - Total tender and swollen joint count (TJC/SJC) (78)
        - Dactylitis assessment
        - MASES + plantar fascia + quadriceps and patellar tendon
    - Questionnaires: cfr. 6.2.7.1 (excl. WPAI, health care consumption and EQ5D

6.2.7.3 Follow-up visits

- Anamnesis
- Current and past medication: dosage and duration
- Clinical examination:
    - weight, length, vital symptoms (blood pressure, heart frequency)
    - BASMI
    - Total tender and swollen joint count (TJC/SJC) (78)
    - Dactylitis assessment
    - MASES + plantar fascia + quadriceps and patellar tendon
- Questionnaires: cfr. 6.2.7.1 (WPAI, health care consumption and EQ5D are site-specific (only in Ghent University Hospital) and only at time of switch from NSAID to anti-TNF and at time of sustained remission).
- Assessment of work participation (site-specific: only in Ghent University Hospital) only at time of switch from NSAID to anti-TNF and at time of sustained remission.
- Laboratory investigation (incl. 2x5mL serum at every follow-up visit for additional research; site-specific: only at Ghent University Hospital 3x10mL heparin after 4 weeks of NSAIDs, 6 months of golimumab, at time of sustained clinical remission (if and on the same day as the second ileocolonoscopy incl. biopsies cfr. 6.2.7.2) and at time of relapse))
- Stool sample (after 4 weeks NSAID, 6 months golimumab and at time of relapse)

6.3 Flowchart




Week 28:
Calculation of the ASDAS to determine whether patient is in remission
Patient is not in remission on 2 consecutive visits
Week 40:
Calculation of the ASDAS to determine whether patient is in remission
Patient is not in remission on 2 consecutive visits
Week 52:
Calculation of the ASDAS to determine whether patient is in remission
Patient is not in remission on 2 consecutive visits
Stop study and follow-up in routine clinical practice.
Patient is in remission on 2 consecutive visits
Stop study, perform second colonoscopy (if the first one was positive) and second MRI and follow-up in routine clinical practice, report time to relapse.

6.4 Study table

	Clinical examination (incl. BASMI)	Patient questionnaires	Blood: 4x5mL serum + 3x4mL EDTA	Blood: 2x5mL serum	Blood: 4x10mL heparin †	Pregnancy test (for female subjects)	Screening tuberculosis: chest X-ray and Mantoux	Stool sample	Ileocolon oscopy°	ASDAS	MRI SIG	Medication (golimumab) (starts after treatment failure on NSAIDs)
Screening	X	X	X			X	X			X	X *	
Baseline	X	X			X			X	X	X		
Follow-up visits	X	X		X						X		X (every 4 weeks)
Extra after 4 weeks NSAIDs					X (only 3 tubes)			X				
Extra after 6 months anti-TNF					X (only 3 tubes)			X				
Extra at remission					X (only 3 tubes, if and on same day as colono-scopy)				If first ileocolono scopy was positive		X	
Extra at relapse	X	X		X	X (only 3 tubes)			X		X		

† Site-specific: only in Ghent University Hospital (Center 01); * MRI SIG at screening if not already done in the context of diagnosis; ° Ileocolonoscopy including for all sites biopsies for pathological examination (4 in ileum, 8 in colon) and RNA sequencing (2 in ileum, 2 in colon). Additional for functional analyses (site specific: only in Ghent University Hospital: 6 in ileum, 6 in colon).

6.5 Medication

- NSAID therapy will be given orally in full anti-inflammatory dose according to the routine clinical practice.
- Golimumab, provided by MSD, will be given subcutaneous at the dose of 50 mg every 4 weeks.

6.5.1 Composition and dosing

Golimumab is a human monoclonal antibody (mab) with an IgG1 heavy chain isotype and a kappa light chain isotype that binds TNFα with high affinity and specificity. The molecule is produced by a stable, recombinant murine cell line transfected with DNA coding for the heavy and light chains of the mab. Golimumab is supplied as a liquid in a prefilled syringe (PFS) for subcutaneous administration. Each prefilled syringe contains 50mg (0.5mL fill of liquid) golimumab, histidine, sorbitol and polysorbate 80 at pH 5.5. No preservatives are present. The prefilled syringe with golimumab will be administrated subcutaneously every 4 weeks. This is the same dose/regimen used as in the previously performed Phase III golimumab studies.

6.5.2 Producer
Golimumab (Simponi): Janssen Biologics B.V.

6.5.3 Distributor
Golimumab: Janssen Biologics B.V.

6.5.4 Packaging
Golimumab will be supplied as a sterile liquid in a 0.5mL single-use prefilled syringe for subcutaneous administration.

6.5.5 Administration way
Golimumab will be administrated subcutaneously every 4 weeks.

6.5.6 Labelling
The following particulars will be added to the original packaging, but will not obscure the original labelling:

I) Studie/Etude Go-Gut EUDRACT nr: 2017-001728-23
II) Naam/nom SPONSOR: Prof. dr. Dirk Elewaut – UGent
III) Naam/nom Dr.:
IV) Centrum/centre:
V) Patient Nr./N° patient:
VI) Bezoek Nr./N° de visite:
Alleen voor klinisch onderzoek/Uniquement récherche biomédicale

6.5.7 Storage conditions
Golimumab will be stored in a locked refrigerator, which will be temperature-controlled by using a continuous temperature logger (2 °C to 8 °C) in original carton until time of use. It will be protected from light. It will be not frozen or shaken.

6.5.8 Known side effects of the medication
For the known side effects of golimumab we refer to those described in the latest update of the SmPC available on the EMA website.

Upper respiratory tract infection was the most common adverse drug reaction (ADR) reported in the controlled Phase III rheumatoid arthritis (RA), psoriatic arthritis (PsA), and AS studies through week 16, occurring in 7.2% of golimumab treated patients as compared with 5.8% of control patients. The most serious ADRs that have been reported for Simponi include serious infections (including sepsis, pneumonia, TB, invasive fungal and opportunistic infections), demyelinating disorders, lymphoma, HBV reactivation, CHF, autoimmune processes (lupus-like syndrome) and haematologic reactions. ADRs observed in clinical studies and reported from world-wide post-marketing use of golimumab are listed in Table 1. Within the designated system organ classes, the adverse drug reactions are listed under headings of frequency and using the following convention: Very common (≥ 1/10); Common (≥ 1/100 to < 1/10); Uncommon (≥ 1/1,000 to < 1/100); Rare (≥ 1/10,000 to < 1/1,000); Very rare (< 1/10,000); Not known (cannot be estimated from the available data).

Table 1

Tabulated list of ADRs

Infections and infestations *Very common*: Upper respiratory tract infection (nasopharyngitis, pharyngitis, laryngitis and rhinitis) *Common*: Bacterial infections (such as cellulitis), viral infections (such as influenza and herpes), bronchitis, sinusitis, superficial fungal infections *Uncommon*: Septic shock, sepsis, tuberculosis, lower respiratory tract infection (such as pneumonia), opportunistic infections (such as invasive fungal infections [histoplasmosis, coccidioidomycosis, pneumocytosis], bacterial, atypical mycobacterial infection and protozoal), pyelonephritis, abscess, bacterial arthritis, infective bursitis *Rare*: Hepatitis B reactivation
Neoplasms, benign, malignant and unspecified *Uncommon*: Neoplasms (such as skin cancer, squamous cell carcinoma and melanocytic naevus) *Rare*: Lymphoma, leukaemia, melanoma *Not known*: Merckel cell carcinoma *
Blood and lymphatic system disorders *Common*: Anaemia *Uncommon*: Leucopaenia, thrombocytopenia *Rare*: Pancytopaenia *Not known*: Aplastic anaemia *

Immune system disorders

Common: Allergic reactions (bronchospasm, hypersensitivity, urticaria), autoantibody positive

Rare: Serious systemic hypersensitivity reactions (including anaphylactic reaction) , vasculitis (systemic), sarcoidosis

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Endocrine disorders

Uncommon: Thyroid disorder (such as hypothyroidism, hyperthyroidism and goitre)

Metabolism and nutrition disorders

Uncommon: Blood glucose increased, lipids increased

Psychiatric disorders

Common: Depression, insomnia

Nervous system disorders

Common: Dizziness, paraesthesia, headache

Uncommon: Demyelinating disorders (central and peripheral), balance disorders, dysguesia

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Eye disorders

Uncommon: Visual disorders (such as blurred vision and decreased visual acuity), conjunctivitis, eye allergy (such as pruritis and irritation)

Cardiac disorders

Uncommon: Congestive heart failure (new onset or worsening), arrhythmia, ischemic coronary artery disorders

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Vascular disorders

Common: Hypertension

Uncommon: Thrombosis (such as deep venous and aortic), Raynaud's phenomenon, flushing

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Respiratory, thoracic and mediastinal disorders

Uncommon: Asthma and related symptoms (such as wheezing and bronchial hyperactivity)

Rare: Interstitial lung disease

Gastrointestinal disorders

Common: Constipation, dyspepsia, gastrointestinal and abdominal pain, nausea

Uncommon: Gastrointestinal inflammatory disorders (such as gastritis and colitis), gastro-oesophageal reflux disease, stomatitis

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Hepatobiliary disorders

Common: Alanine aminotransferase increased, aspartate aminotransferase increased

Uncommon: Cholelithiasis, hepatic disorders

Skin and subcutaneous tissue disorders

Common: Alopecia, dermatitis, pruritus, rash

Uncommon: Psoriasis (new onset or worsening of pre-existing psoriasis, palmar/plantar and pustular), urticaria, vasculitis (cutaneous)

Rare: skin exfoliation

Musculoskeletal and connective tissue disorders

Rare: Lupus-like syndrome

Renal and urinary disorders

Uncommon: Bladder disorders

Rare: Renal disorders

Reproductive system and breast disorders

Uncommon: Breast disorders, menstrual disorders

General disorders and administration site conditions

Common: Pyrexia, asthenia, injection site reaction (such as injection site erythema, urticaria, induration, pain, bruising, pruritus, irritation and paraesthesia), impaired healing, chest discomfort

Injury, poisoning and procedural complications
Uncommon: Bone fractures

*: Observed with other TNF-blocking agents, but not observed in clinical studies with golimumab.

6.5.9 Fertility, pregnancy and lactation

Data on fertility, pregnancy and lactation is described in the latest update of the SmPC available on the EMA website.

Pregnancy

There are no adequate data on the use of golimumab in pregnant women. Due to its inhibition of TNF, golimumab administered during pregnancy could affect normal immune responses in the newborn. Studies in animals do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development (see section 5.3 of SmPC).

Golimumab crosses the placenta. The use of golimumab in pregnant women is not recommended; golimumab should be given to a pregnant woman only if clearly needed. Following treatment with a TNF-blocking monoclonal antibody during pregnancy, the antibody has been detected for up to 6 months in the serum of the infant born by the treated woman. Consequently, these infants may be at increased risk of infection. Administration of live vaccines to infants exposed to golimumab in utero is not recommended for 6 months following the mother's last golimumab injection during pregnancy (see sections 4.4 and 4.5 of SmPC).

Breastfeeding

It is not known whether golimumab is excreted in human milk or absorbed systemically after ingestion. Golimumab was shown to pass over to breast milk in monkeys, and because human immunoglobulins are excreted in milk, women must not breast feed during and for at least 6 months after golimumab treatment.

Fertility

No animal fertility studies have been conducted with golimumab. A fertility study in mice, using an analogous antibody that selectively inhibits the functional activity of mouse TNFα, showed no relevant effects on fertility (see section 5.3 of SmPC).

Female participants are obliged to use contraception (oral, condom, IUD, …) during the trial and until 6 months after the end of the trial. It's recommended to use double contraception by both the study participants and his/her partner.

Male participants: no risks concerning their partners' pregnancy.

6.5.10 Drug accountability

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

Drug accountability will be documented with the description of the batch number, date of administration to the patient, expiration date, the amount that is administered and the route of administration on a separate drug accountability log in order to maintain transparency.

6.6 Additional research

We will also examine non-invasive surrogate markers for gut inflammation and therefore we will collect blood samples at every study visit and stool samples at baseline, after 4 weeks of NSAID treatment, after 6 months of golimumab treatment and at time of relapse. These are to investigate e.g. the serum and fecal calprotectin levels and to perform in depth immunophenotyping (flow cytometry) and microbiome analysis. At the screening visit we will also collect additional blood samples for genetic analyses (relevant single nucleotide polymorphisms for overlap SpA and IBD). All analyses will be performed within a context relevant to the SpA concept.

All biological samples (blood, stool, gut biopsies and its derivatives) will be collected and stored pseudonymized during 20 years in the prospective research biobank of the department of rheumatology of the Ghent University Hospital ("Biobank van menselijk lichaamsmateriaal van patiënten met reumatische en/of musculoskeletale aandoeningen en gezonde controles", EC 2019/0314, medical administrator: prof. dr. Dirk Elewaut). For the Imelda Hospital in Bonheiden (Center 03) these biological samples will first be stored on site as part of the prospective research biobank of the department of rheumatology of the Ghent University Hospital and shipped regularly (cooled transport at -80°C) in batch to the Gent University Hospital. The only exception concerns the gut biopsies from patients recruited at the Reuma Institute Hasselt (Center 02): these samples will be collected in Jessa Hospital, will be locally registered and stored (temporarily) in the Jessa Biobank (medical administrator: dr. Jean-Luc Rummens – no processing required except for immediate freezing) and will be transferred at once (cooled transport at -80°C) to the prospective research biobank of the department of Rheumatology of Ghent University Hospital after the study has ended. All analysis on additional study samples will be performed by the laboratory attached to the department of Rheumatology of the Ghent University Hospital (Medical Research Building, MRB). Some analyses will be conducted by the Flemish institute for biotechnology (VIB – Vlaams Instituut voor Biotechnologie).

7. Randomisation/blinding

- Randomisation: not applicable.
- Blinding: the investigator and his team as well as the patient will be blinded for the results of the ileocolonoscopy until the patient is switched to golimumab. Only in case of major abnormalities necessitating medical intervention, the investigator will be made aware of the results of the ileocolonoscopy earlier.

8. Prior and concomitant medication

The subject will be excluded if he/she had/used:

- Full anti-inflammatory dose of NSAIDs for more than 4 weeks for the duration of the axSpA symptoms.

- Prior exposure to any biologic therapy with a potential therapeutic impact on SpA, including anti-TNF therapy.
- Exposure to disease-modifying drugs (DMARDSs; i.e. methotrexate and sulfasalazine) in the last 3 months before the ileocolonoscopy.
- Exposure to systemic corticosteroid treatment in the last 14 days before the ileocolonoscopy.
- Infection(s) requiring treatment with intravenous antibiotics/antivirals/antifungals within 30 days prior to the baseline visit or oral antibiotics/antivirals/antifungals within 14 days prior to the baseline visit.

During the trial there are no specific limitations for concomitant therapy, with exception of the use of DMARDS or other biologicals, while on therapy with golimumab.

9. Reporting adverse events

List of abbreviations

AE: Adverse Event

CA: Competent Authority

EC: Ethics Committee

SAE: Serious Adverse Event

SSAR: Suspected Serious Adverse Reaction

SUSAR: Suspected Unexpected Serious Adverse Reaction

Adverse events (AE)

The following information will be recorded:

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

AE's will be recorded from the first drug administration until the end of the trial.

Special attention will be given to those subjects who have discontinued the trial for an AE, or who experienced a severe or a serious AE.

Definitions of Adverse Event (AE)

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavorable and unintended sign (including

an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

Serious Adverse Avent (SAE)

Any untoward medical occurrence that at any dose:

- results in death;

- is life-threatening;

- requires inpatient hospitalization or prolongation of existing hospitalization;

- results in persistent or significant disability/incapacity;

or

- is a congenital anomaly/birth defect.

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

Unexpected adverse event

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

Life-threatening

Any event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

Associated with the use of the drug

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

<u>Attribution definitions</u>

Not related

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

Unlikely

An adverse event for which an alternative explanation is more likely - e.g. concomitant drug(s), concomitant disease(s), and/or the relationship in time suggests that a causal relationship is unlikely.

Possible

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

Probable

An adverse event which might be due to the use of the drug. The relationship in time is suggestive (e.g. confirmed by dechallenge). An alternative explanation is less likely - e.g. concomitant drug(s), concomitant disease(s).

Definitely

An adverse event which is listed as a possible adverse reaction and cannot be reasonably explained by an alternative explanation - e.g. concomitant drug(s), concomitant disease(s). The relationship in time is very suggestive (e.g. it is confirmed by dechallenge and rechallenge).

Reporting of adverse events

Adverse events will be reported between the first dose administration of trial medication and the last trial related activity.

All AEs and SAE's will be recorded in the patient's file and in the CRF. All SAE's will be reported as described below.

Medical events that occur between signing of the Informed Consent and the first intake of trial medication will be documented on the medical and surgical history section and concomitant diseases page of the CRF.

SAE's occurring within a period of 30 days following the last intake of trial medication will also be handled as such if spontaneously reported to the investigator.

All serious adverse events (SAE) and pregnancies occurring during clinical trials must be reported by the local Principal Investigator within 24 hours after becoming aware of the SAE to:

- The local EC;
- HIRUZ Clinical Trial Unit (CTU) of the University Hospital Ghent;
- The National Coordinating Investigator (in case of multicenter trials);

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

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

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

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

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

Contact details of HIRUZ CTU:

e-mail: hiruz.ctu@uzgent.be

tel.: 09/332 05 00

fax: 09/332 05 20

Contact details of the Principal/National Coordinating Investigator:

e-mail: dirk.elewaut@ugent.be, filip.vandenbosch@ugent.be

tel.: 09/332 50 74

fax: 09/332 47 87

Contact details MSD:

SAE reports and any other relevant safety information are to be forwarded by the National

Coordinating investigator to MSD GS

facsimile number: +1-215-993-1220

The investigator must provide the minimal information: i.e. trial number, subject's initials and date of birth, medication code number, period of intake, nature of the adverse event and investigator's attribution.

This report of a serious adverse event by telephone must always be confirmed by a written, more detailed report. For this purpose the appropriate SAE form will be used. Pregnancies occurring during clinical trials are considered immediately reportable events. They must be reported as soon as possible using the same SAE form. The outcome of the pregnancy must also be reported.

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

Annual Safety Reporting

HIRUZ CTU will ask the National Coordinating Investigator for an annual report containing an overview of all SSARs (Suspected Serious Adverse Reaction) and a summary regarding the safety of the trial subjects. HIRUZ CTU will send this report to the Central EC and the CA within the timelines as defined in national legislation. The National Coordinating Investigator will pass this annual report to all local Principal Investigators.

10. Analysis of the study

10.1 Calculation of the sample size

This estimation is based on a pilot study evaluating Ankylosing Spondylitis Disease Activity Score (ASDAS) response to anti-TNFα in axSpA patients with and without gut inflammation [Cypers H, unpublished data]. Based on these proportions, we estimate that the sample size necessary for detecting a significant difference (95% confidence interval) in ASDAS category (ASDAS < 2.1 yes/no) after golimumab treatment between patients with versus without gut inflammation would be 55 per group i.e. 110 patients in the golimumab arm, for a power of 80%.

10.2 Analysis of the images and the samples

Central reading will be performed by the departments Rheumatology and Radiology of the Ghent University Hospital (dr. M. de Hooge and prof. dr. Lennart Jans). Radiological images of patients enrolled at Reuma Institute Hasselt (Center 02) and at Imelda hospital Bonheiden (center 03), will be pseudonymized and uploaded on an electronic device (eg. external HDD). At the end of the trial, the electronic device with all the pseudonymized images will be send by secured postal mail to the Rheumatology department of Ghent University Hospital to allow for central reading.

The blood samples, stool samples and gut biopsies will finally all be stored in the prospective research biobank of the department of rheumatology of the Ghent University Hospital ("Biobank van menselijk lichaamsmateriaal van patiënten met reumatische en/of musculoskeletale aandoeningen en gezonde controles", EC 2019/0314, medical administrator: prof. dr. Dirk Elewaut). For the Imelda Hospital in Bonheiden (Center 03) these biological samples will first be stored on site as part of the prospective research biobank of the department of rheumatology of the Ghent University Hospital and shipped regularly in batch to the Gent University Hospital. The gut biopsies from patients recruited at the Reuma Institute Hasselt (Center 02) will be collected at Jessa Hospital, will be registered and stored (temporarily) in the Jessa Biobank (medical administrator: dr. Jean-Luc Rummens – no processing required except for immediate freezing) and will be transferred at once (cooled transport at -80°C) to the prospective research biobank of the department of Rheumatology of Ghent University Hospital after the study has ended. Subsequently all samples will be analysed by the laboratory attached to the department of Rheumatology of the Ghent University Hospital (Medical Research Building, MRB) and by the VIB. These are to investigate e.g. the serum and fecal calprotectin levels and to perform in depth immunophenotyping (flow cytometry). Reuma Institute Hasselt, Jessa Ziekenhuis Hasselt nor Imelda hospital Bonheiden is expected to perform any analyses on any of the additionally collected study samples.

10.3 Statistical analysis

The statistical analysis will be performed by the department of Rheumatology of the Ghent University Hospital in collaboration with the department of Biostatistics of the Ghent University.

11. Insurance

Faultless liability Ghent University.

12. Publication policy

The results of this trial will be published in an A1-journal. The privacy of the participants will be respected at all times.

PART 2: GENERAL PART OF THE PROTOCOL

13. Independent Ethics Committee (IEC) / Institutional Review Board (IRB)

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

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

Amendments should not be implemented without prior review and documented approval/favorable opinion from the IEC/IRB except when necessary to eliminate an immediate hazard to trial subjects or when the change involves only logistical or administrative aspects of the trial. At the end of the trial, the investigator will notify the IEC/IRB about the trial completion.

14. ICH/GCP guidelines

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

15. Subject information and informed consent

Prior to entry in the trial, the investigator must explain the procedure of the trial and the implication of participation to potential subjects or their legal representatives. Subjects will be informed that their participation is voluntary and that they may withdraw consent to participate at any time. Participating subjects will be told that competent authorities and authorized persons may access their records without violating the confidentiality of the subject, to the extent permitted by the applicable law(s) and/or regulations. By signing the Informed Consent Form (ICF), the subjects or legally acceptable representatives are authorizing such access. After this explanation and before entry to the trial, written, dated and signed informed consent should be obtained from the subject or legally acceptable representative. The ICF should be provided in a language sufficiently understood by the subject. Subjects must be given the opportunity to ask questions. The subject or legally acceptable representative will be given sufficient time to read the ICF and to ask additional questions. After this explanation and before entering the trial, consent should be appropriately recorded by means of either the subject's or his/her legal representative's dated signature or the signature of an independent witness who certifies the subject's consent in writing. After having obtained the consent, a copy of the ICF must be given to the subject. In case the subject or legally acceptable representative is unable to read, an impartial witness must attest the informed consent.

16. Case Report Forms

The source documents are to be completed at the time of the subject's visit. The CRFs are to be completed within reasonable time after the subject's visit. The investigator must verify that all data entries in the CRFs are accurate and correct. If certain information is Not Done, Not Available or Not Applicable, the investigator must enter "N.D." or "N.AV." or "N.AP", respectively in the appropriate space.

17. Direct access to source data/documents

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

18. Data handling and record keeping

The investigator essential documents will be retained for at least 20 years. At that moment, it will be judged whether it is necessary to retain them for a longer period, according to applicable regulatory or other requirement(s).

19. References

1. Dougados M, Baeten D. Spondyloarthritis. Lancet 2011;377(9783):2127-37.

2. Mielants H, Veys EM, Cuvelier C et al. HLA-B27 related arthritis and bowel inflammation. Part 2. Ileocolonoscopy and bowel histology in patients with HLA-B27 related arthritis. J Rheumatol 1985;12-294-8.

3. Van Praet L, Van den Bosch F, Jacques P et al. Microscopic gut inflammation in axial spondyloarthritis: a multiparametric predictive model. Ann Rheum Dis 2013;72:414-417.

4. Van Praet L, Van den Bosch F, Mielants H, Elewaut D. Mucosal inflammation in spondyloarthritides: past, present and future. Curr Rheumatol Rep 2011;13(5):409-15.

5. Mielants H, Veys EM, Cuvelier C, De Vos M. Course of gut inflammation in spondyloarthropathies and therapeutic consequences. Baillieres Clin Rheumatol 1996;10(1):147-64.

6. Mielants H et al. The evolution of spondyloarthropathies in relation to gut histology. III. Relation between gut and joint. J Rheumatol 1995;22(12):2279-84.

7. De Vos M, Mielants H, Cuvelier C, Elewaut A, Veys E. Long-term evolution of gut-inflammation in patients with spondyloarthropathy. Gastroenterology 1996;110(6):1696-703.

8. Cypers H, Van Praet L, Varkas G, Elewaut D. Relevance of the gut/joint axis for the management of spondyloarthritis in daily clinical practice. Curr Opin Rheumatol 2014;26(4):371-6.

9. Van Praet L et al. Degree of bone marrow edema in sacroiliac joints of patients with axial spondyloarthritis is linked to gut inflammation and male sex: results from the GIANT cohort. Ann Rheum Dis 2014;73(6):1186-9.

10. Baert F et al. Mucosal healing predicts sustained clinical remission in patients with early-stage Crohn's disease. Gastroenterology 2010;138(2):463-8.

11. van der Heijde D, Sieper J, Maksymowych W, Dougados M, Burgos-Vargas R, Landewé R et al. 2010 Update of the international ASAS recommendations for the use of anti-TNF agents in patients with axial spondyloarthritis. Ann Rheum Dis 2011;70:905-8.

12. Paccou J, Flipo RM. An appraisal of golimumab in the treatment of severe, active nonradiographic axial spondyloarthritis. Drug Des Devel Ther 2016;10:2255-62.

13. Toussirot E, Vauchy C, Binda D, Michel F. Golimumab in radiographic and nonradiographic axial spondyloarthritis: a review of clinical trials. Drug Des Devel Ther 2016;10:2087-94.

14. Sandborn W, Feagan B, Marano C, Zhang H, Strauss R, Johanns J et al. Subcutaneous golimumab induces clinical response and remission in patients with moderate-to-severe ulcerative colitis. Gastroenterology 2014;146:85-95.

15. Inman RD et al. Efficacy and safety of golimumab in patients with ankylosing spondylitis: results of a randomized, double-blind, placebo-controlled, phase III trial. Arthritis Rheum 2008;58(11):3402-12.

16. Sieper J et al. A randomized, double-blind, placebo-controlled, sixteen-week study of subcutaneous golimumab in patients with active nonradiographic axial spondyloarthritis. Arthritis Rheumatol 2015;67(10):2702-12.

17. Gossec et al. Preliminary definitions of ‘flare’ in axial spondyloarthritis, based on pain, BASDAI and ASDAS-CRP: an ASAS initiative. Ann Rheum Dis 2016;75(6):991-6.

Signature page

Investigator:

Name: Prof. Dr Dirk Elewaut

Title: Head of department Reumatologie – Principal Investigator

Signature:

Date: _____

Investigator:

Name: Prof. Dr. Filip Van den Bosch _____

Title: Principal Investigator

Signature:

Date: _____