Protocol:

Improved monitoring and prediction of clinical response and disease course during Golimumab therapy of patients with axial spondyloarthritis: The clinical utility of whole-body MRI, diffusion-weighted MRI, conventional MRI of sacroiliac joints and spine, and high-sensitive CRP and other soluble biomarkers of joint inflammation and damage.

Short English title: Novel MRI ANd biomarkers in GOlimumab-treated patients with axial spondyloarthritis (MANGO).

Danish titel: Videnskabeligt studie af nye MR- og biokemiske metoder til af følge og forudsige klinisk respons og sygdomsforløb hos patienter med rygsøjlegigt der påbegynder behandling med Golimumab

Name of protocol: MANGO
J. no. Scientific Committee: H1-2013-118
J.no. Danish Heath and Medicines Agency: Not considered a "Lægemiddelforsøg" (see section 30)
Region Hovedstaden: GLO-2013-33, GLO-2013-34
ClinicalTrials.gov no.: NCT02011386
Protocol version 4.1: 3 November 2016

An investigator initiated study

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1 CONTENT

2 APPROVAL OF CLINICAL STUDY PROTOCOL

Sponsor	Date and signature of approval:
Professor Mikkel Østergaard	_____

3 TIME LINE

The study is planned to start 1 December 2013 or as soon as possible thereafter, but not before it has been approved by the Scientific Committee and Authorities for Data Protection. The inclusion is planned to end July 2015. The last included patient is planned to have the last study visit performed July 2016. Evaluation of images, analyses of biomarkers and questionnaires including writing up manuscripts are expected to take up to a total of 5 years. A final report to the Ethical Committee and study participants will be send before July 2021.

4 ABBREVIATIONS

ADC	Apparent diffusion coefficient
AE	Adverse event
AHI	ASAS Health Index
AS	Ankylosing Spondylitis
ASDAS	Ankylosing Spondylitis Disease Activity Score
ASAS	Assessment of SpondyloArthritis International Society
ASAS20	Assessment of SpondyloArthritis International Society 20% response criteria
ASAS40	Assessment of SpondyloArthritis International Society 40% response criteria
ASAS5/6	Assessment of SpondyloArthritis International Society "5 out of 6" response criteria
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
BASDAI20	Change in BASDAI of ≥ 20%
BASDAI50	Change in BASDAI of ≥ 50%
BASDAI70	Change in BASDAI of ≥ 70%
BASFI	Bath Ankylosing Spondylitis Functional Index
BASMI	Bath Ankylosing Spondylitis Metrology Index
BMP	Bone morphogenetic protein
CTX-I	C-terminal cross-linking telopeptide of type I collagen
CTX-II	C-terminal crosslinking telopeptide of type II collagen
CRF	Case report form
CRP	C Reactive Protein
DeoxyPYD	Deoxypyridinoline
DANBIO	The Danish Rheumatological Database
DMARD	Disease-Modifying-Anti-Rheumatic-Drug
ELISA	Enzyme-linked immune-sorbent assays
FDA	US Food and Drug Administration
HLA-B27	Human Leukocyte Antigen B27
IL	Interleukin
IL-6	Interleukin-6
IL-22	Interleukin-22
IL-23	Interleukin-23
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IMP	Investigational Medicinal Product
MMP-3	Matrix Metalloproeinase 3
MRI	Magnetic Resonance Imaging
mSASSS	Modified Stoke Ankylosis Spondylitis Spine Score
MTX	Methotrexate;
NSAID	Non-Steroid Anti-Inflammatory Drug
P1NP	N-terminal propeptide of type 1 collagen
PACS	Picture archiving and communication system
Sc.	Subcutaneously
SI-joints	Sacroiliac joints
SJC	Swollen joint count
SpA	Spondyloarthritis
SAE	Severe Adverse Event
SUSARs	Suspected Unexpected Serious Adverse Reactions
TJC	Tender joint count
TMF	Trial master file
TNF	Tumor-Necrosis-Factor
TNFα	Tumor-Necrosis-Factor-alpha
VAS	Visual analogue scale
VEGF	Vascular Endothelial Growth Factor

5 AIM

5.1 Overall aim

To compare the ability of the following methods to monitor and predict response to Golimumab therapy in patients with axial spondyloarthritis (SpA):

- Whole-body MRI, diffusion-weighted MRI and conventional MRI of sacroiliac (SI) joints and spine.
- High-sensitive CRP and conventional CRP.
- Other soluble biomarkers of joint inflammation and damage.

5.1.1 Co-primary specific objectives

1. To investigate if whole-body MRI (respectively diffusion-weighted MRI) detect more patients with disease activity after 16 and 52 weeks of tumor-necrosis-factor-alpha (TNFα) inhibitor therapy than conventional MRI.
2. To investigate if patients with minimal signs of inflammation on baseline MRI are less likely to achieve a clinical response and are less likely to reach clinical remission than patients with high baseline MRI inflammation (conventional, diffusion-weighted and whole-body MRI will be applied).
3. To investigate if findings and changes in MRI and/or biomarkers early (at weeks 4 and 16) during TNFα inhibitor therapy will predict clinical response and clinical remission at 52 weeks.
4. To explore the relative predictive value of the matrix model[1] and whole-body MRI, diffusion-weighted MRI and conventional MRI (at weeks 0, 4 and 16) for clinical response and clinical remission at 52 weeks.

5.1.2 Secondary objectives

1. To investigate if circulating biomarkers of inflammation, cartilage and bone turnover detect more patients with disease activity after 16 and 52 weeks of TNFα inhibitor therapy than conventional MRI.
2. To investigate if patients with minimal baseline signs of inflammation as assessed by conventional CRP, high-sensitivity CRP and other experimental biomarkers of inflammation are less likely to achieve a clinical response and are less likely to reach clinical remission than patients with high baseline CRP, inflammation on whole-body MRI, diffusion weighted MRI and conventional MRI.
3. To investigate if changes in biomarkers early (at weeks 4 and 16) during TNFα inhibitor therapy will predict clinical response and clinical remission at 52 weeks.
4. To explore the relative predictive value of the matrix model[1] and circulting biomarkers of inflammation, cartilage and bone turnover (at weeks 0, 4 and 16) for clinical response and clinical remission at 52 weeks.

5.1.3 Tertiary objectives

1. To described baseline findings and changes in a novel questionnaire, the ASAS Health Index (AHI, in Danish ASAS Sundhedsindex), before and during TNFα inhibitor therapy.
2. To investigate the association between AHI and inflammation and structural findings on conventional and novel MRI sequences at baseline and during TNFα inhibitor therapy.
3. To investigate the association between AHI and conventional and experimental measures of disease activity (including CRP), function, quality of life, and association with sleep, fatigue and depression at baseline and during TNFα inhibitor therapy.
4. To investigate the responsiveness of AHI as compared to the variables mentioned above (2. and 3.).

6 HYPOTHESIS

6.1 Hypotheses in relation to co-primary specific objectives

1. Whole-body MRI (respectively diffusion-weighted MRI is more sensitive for detection of inflammation than conventional MRI in patients receiving TNFα inhibitor therapy.
2. Minimal inflammation on baseline whole body MRI (respectively baseline diffusion-weighted MRI and baseline conventional MRI) reduces the chance of clinical response and of clinical remission after 1 year of TNFα inhibitor therapy.
3. MRI findings and biomarkers early (4 weeks and/or 16 weeks) during TNFα inhibitor therapy can predict long-term (52 weeks) clinical response and clinical remission.
4. The matrix model (at weeks 0, 4 and 16) is equally predictive of clinical response and clinical remission at 52 weeks as whole-body MRI, diffusion-weighted MRI and conventional MRI.

6.2 Hypotheses in relation to secondary specific objectives

1. One or more selected biomarkers are more sensitive for detection of inflammation than conventional MRI in patients receiving TNFα inhibitor therapy.
2. Minimal inflammation as assessed by circulating biomarkers at baseline reduces the chance of clinical response and of clinical remission after 1 year of TNFα inhibitor therapy.
3. The concentration of circulating biomarkers early (4 weeks and/or 16 weeks) during TNFα inhibitor therapy can predict long-term (52 weeks) clinical response and clinical remission.
4. The matrix model (at weeks 0, 4 and 16) is equally predictive of clinical response and clinical remission at 52 weeks as by inflammatory biomarkers as by whole-body MRI, diffusion-weighted MRI and conventional MRI.

6.3 Hypotheses in relation to tertiary specific objectives

1. AHI is associated with conventional measures of disease activity, function, quality of life, sleep, fatigue and depression at baseline, and changes in AHI is associated with changes in these variables during TNFα inhibitor therapy.
2. AHI provides information on aspects of physical function, activity and participaton that is not entirely covered by the domains mentioned above.
3. AHI is associated both with inflammatory and structural findings on conventional MRI, and with inflammatory findings on novel MRI at baseline, and changes in relation to changes in inflammation during TNFα inhibitor therapy.
4. Although AHI is responsive, it is less responsive than conventional measures of disease activity including novel and conventional MRI and biochemical measures of inflammation during TNFα inhibitor therapy. This is based on that structural damage of the spine (ankylosis) will have negative impact on function, activity and participation, and therefore limit the responsiveness of the AHI as compared to other more direct measures of inflammation.

7 BACKGROUND

Axial sponyloarthritis (SpA) comprises a group of interrelated rheumatic diseases including ankylosing spondylitis (AS). The disease is characterized by inflammation in the sacroiliac (SI) joints and spine. Many of the patients also have peripheral arthritis and pain at enthesial sites. Axial spondyloarthritis is estimated to affect 1-2% of the Danish population, and has high costs for the society due to high frequency of sick leave and expensive treatment in form of tumor-necrosis-factor-alpha (TNFα) inhibitor therapy.

7.1.1 Prediction of treatment response

Currently, the response to TNFα inhibitor therapy in individual patients with ankylosing spondylitis (AS) and axial spondyloarthritis (SpA) cannot be reliably predicted. Serum concentration of C-reactive protein (CRP) and inflammation present on magnetic resonance imaging (MRI) have in a few studies been associated with the clinical response to a TNFα inhibitor[2-6]. Furthermore, CRP and findings by MRI of the spine and sacroiliac (SI) joints[2-6] have together with a matrix model[1], so far been the most promising parameters for this purpose. However, a clinical response can still occur despite normal CRP (as measured by the conventional method) and no MRI inflammation in the spine (on conventional MRI)[3;5].This may be caused by the fact that the current conventional methods are not sufficiently sensitive (CRP and MRI) or do not cover all inflamed areas (MRI)[7-11].

7.1.2 Remission in patients with axial SpA

Remission is increasingly becoming the goal of modern therapy in AS, but there is no consensus on how it should be defined[12;13]. The importance of obtaining remission in patients with axial SpA have recently been emphasized by an international group of experts in the Treat to Target (T2T) initiative[14]. However, the literature search of the group revealed that there are no clinical studies addressing the question. Currently, the criteria for disease activity and treatment response have been defined according to expert opinion. It is likly that remission criteria would benefit from including MRI measures and/or novel biomarkers. Exploration of the MRI/biomarker findings in patients in clinical remission, and in various definitions of MRI remissions, and their relation to concurrent and subsequent clinical outcomes, would be very relevant[12].

7.2 New MRI methods

Better methods than conventional CRP and MRI are now available. High-sensitive CRP assays, that measures CRP levels below the lower threshold of conventional CRP assays[15]. Novel experimental MRI-techniques include “head-to-toe” whole-body MRI[7;11;16;17] and an even more experimental method, such as diffusion-weighted MRI[18-20].

7.2.1 5.1.1 Whole-body MRI

Patients with axial SpA often have widespread disease activity outside the SI-joints and spine, and more comprehensive and objective methods for examination the disease burden are needed in the clinic. “Head-to-toe” whole-body MRI allows examination of peripheral and axial joints and entheses in one scan. This includes imaging of hip and shoulder joints and entheses or other more peripheral joints such as knee, ankles, feet, elbows wrists and hands. Furthermore, joints of the anterior chest wall and costo-transversal joints, which are not assessable by conventional SI joint/spine MRI is also assessed by whole-body MRI. To date, only one clinical trial has been published with ‘head-to-toe’ whole-body in patients with axial SpA treated with TNFα inhibitor[21]. This study showed that patients have more inflammation than expected and they have inflammation in areas that cannot assessed by clinical examination[22]. Department of Radiology, Herlev Hospital, earlier this year had a new MR-scanner that has a very high performance in making “head-to-toe” whole-body MRI i.e. with better image quality and shorter scan time. Thus scanner will be used in the study.

7.2.2 5.1.2 Diffusion-weighted MRI

Diffusion-weighted MRI depicts the free movements of water molecules (Brownian movements) in the interstitial space between the cells and outside the vessels[23]. The diffusion of water molecules is reduced if there is more cells or more proteins in the interstitial space, e.g. as if in inflammed, infected or infiltrated with cancer cells. Diffusion-weighted MRI is a new imaging modality in assessment of arthritis, which reveals other aspects of inflammation than conventional MRI[18-20], and it may be more sensitive for detection of inflammation in SI-joints and spine. Only few studies have

investigated diffusion-weighted imaging in patients with axial SpA. Patients with axial SpA have higher ADCs values in the SI-joints as compared to patients with back pain of other reasons and healthy subjects[24]. A very small study has shown that patients with axial SpA treated with TNFα inhibitor decreased significantly in ADC over 1 year as compared to patients treated with non-steroid-anti-inflammatory drugs or glucocorticoids[25]. We have performed a reliability study of diffusion-weighted MRI of the SI-joint and spine in patients with axial SpA (H-3-2012-085). The preliminary results show, that ADC is reproducible. It is possible that diffusion-weighted MRI can give a more sensitive measure of inflammation, and therefore have a future in the assessment of patients with axial SpA.

7.3 Novel biomarkers

7.3.1 New biomarkers for inflammation, cartilage and bone turnover

A range of novel circulating biomarkers for inflammation, cartilage and bone turnover may be of potential use for monitoring and predicting the response to TNFα inhibitor therapy and the disease course.

The biomarkers interlekin (IL)-6, IL-22 and IL-23 and vascular endothelial growth factor (VEGF) reflect inflammation[26;27] and the latter also neovascularization[28;29]. The C-terminal crosslinking telopeptide of type II collagen (CTX-II) is a biomarker of degradation of type II collagen, which is present in joint cartilage, and matrix metalloproteinase 3 (MMP-3) is a biomarker of extracellular matrix degradation in connective tissue[30;31]. Deoxypyridinoline (DeoxyPYD) and the C-terminal crosslinking telopeptide of type I collagen (CTX-I) are both biomarkers of bone degradation, whereas osteocalcin (OC) and N-terminale propeptide of of type I collagene (P1NP) are markers of bone formation[32;33]. Citrullinated vimentin has been proposed to be the degradation fragment of vimentin, which is a type III intermediate filament protein, which are important for the cytoskeleton[34]. Sclerostin is an inhibitor of the Wnt and bone morphogenetic protein (BMP) signaling pathway, and down-regulates new bone formation [35]. Periostin is predominantly expressed in collagen-rich fibrous connective tissues under constant mechanical stress such as bone and tendons, and it increases bone formation by inhibiting sclerostin[36].

Among the most promising biomarkers for monitoring and prediction of response treatment response are IL-6[15;37-39], VEGF[37;38;40;41], CTX-II[37;41-43], MMP-3[37;38;41;42;44], deoxypyridinoline[45], CTX-I [15;37;40;43;44], OC[15;37;40;46], PINP[46;47]. Furthermore, studies have shown that novels biomarkers as sclerostin[35;48-50] and citrullinated vimentin[34;51] may be of value to assess disease activity and treatment response in patients with ankylosing spondylitis. However, novel biomarkers of inflammation such as IL-22[52;53] and IL-23[26;54-58] and of regulation of bone formation such as periostin[36] may also be valuable for this purpose, but have not been investigated.

N-terminal peptide of procollagen type II (PIINP) reflects formation of type II collagen *[Munk HL, Gudmann NS, Christensen AF, Ejstrup L, Sorensen GL, Loft AG, et al. Cartilage collagen type II seromarker patterns in axial spondyloarthritis and psoriatic arthritis: associations with disease activity, smoking and HLA-B27. Rheumatol Int. 2016;36(4):541-9]*. MMP-derived type II collagen neoepitope (C2M) and MMP-derived type III collagen neoepitope (C3M) are degradation products of collagen type II and III *[Bay-Jensen AC, Wichuk S, Byrjalsen I, Leeming DJ, Morency N, Christiansen C, et al. Circulating protein fragments of cartilage and connective tissue degradation are diagnostic and prognostic markers of rheumatoid arthritis and ankylosing spondylitis. PLoS One. 2013;8(1):e54504]*.

All the above-mentioned biomarkers except for IL-22, IL-23 and periostin, which not have been investigated, have been shown either to change during treatment with TNFα inhibitor or to be possible independent predictors of structural damage progression. Nevertheless, they have been investigated in none respectively very few studies including imaging, and further investigations are needed. One or a panel of the mentioned bio- and MRI-markers could be useful for monitoring, and perhaps predicting, outcome.

7.4 ASAS Health Index

ASAS, an organisation of international SpA researchers, have recently developed a questionnaire called ASAS Health Index (AHI, ASAS Sundhedsindex), based on the core domains in the ICF i.e. the International Classification of Functioning, Disability and Health from the World Health Organisation (http://www.who.int/classifications/icf/en/). AHI is anticipated to reflect the patients' perception of their physical function, activity and participation, which is not covered by the currently used questionnaires that primarily covers disease activity and selected aspects of function. Currently, AHI is translated from English into different languages including Danish. Before the Danish version of AHI can be implemented in daily clinical practice, it is important to investigate its face and construct validity, and its responsiveness in relation to conventional measures of disease activity (including clinical examinations), function and quality of life, and more experimental measures of sleep and fatigue, and inflammatory and structural findings on MRI. Sleep disturbance and fatigue are often very prominent symptoms in patients with axial SpA, but not thoroughly assessed by use of the conventional questionnaires, and only very few studies have been performed including these measures.

7.5 The investigational medicinal product

The investigational medicinal product (IMP) in the study is Golimumab (Simponi®), which is a human monoclonal antibody directed against TNFα. In the study, the drug is applied as approved by the European and Danish authorities for patients with ankylosing spondylitis i.e. sc. 50 mg once every month (at the same date).
Currently, Golimumab is the first choice of treatment in Denmark for patients with axial spondyloarthritis with moderate to high disease activity, where other treatments have failed to show sufficient effect. This decision was made in 2012 by "Rådet for Anvendelse af Dyr Sygehusmedicin (RADS) for reumatologi, Danske Regioner", which included experts in rheumatology, pharmacology and health economics (http://www.regioner.dk/soeg?q=RADS). Golimumab was chosen as the first drug of choice for the years 2013 to 2015. Which TNFα inhibitor that will be the drug of choice from year 2016 is currently not known.
The study population is patients with axial spondyloarthritis including ankylosing spondylitis with moderate to severe disease activity, where other treatments have failed to show sufficient effect. The clinical indication for treatment with TNFα inhibitor in the study is the same as in the 'real' world, and follow the treatment recommendations from RADS and Dansk Reumatologisk Selskab.
For information on known and potential risks and benefits for the patients, see the copy of the package leaflet, in Appendices, section 31.

8 LITERATURE SEARCH

Information on the literature search performed in relation to this protocol is provided in section 31.

9 STUDY PLAN

9.1 Endpoints for the MRI and biomarker study

Below are mentioned the primary, secondary and tertiary endpoints for the statistical analyses.

9.1.1 Primary endpoint

1. Fulfillment of BASDAI50 (i.e. reduction of 50%) at week 52.

9.1.2 Secondary endpoints

1. Clinical assessments at week 16 and 52:
   a. BASDAI response defined as reduction in BASDAI of ≥20 mm or ≥50% (yes/no).
   b. ASDAS response defined as reduction in ASDAS>1.1 (yes/no).
2. MRI assessment at week 16:
   a. MRI remission defined as minimal (≤1 DVU affected) versus above-minimal (MRI activity in >1 DVU) MRI activity in the spine.
   b. MRI response defined as ≥ 50% reduction in conventional MRI spine score.

9.1.3 Tertiary endpoints

1. Clinical assessments at week 16 and 52.
   a. Clinical remission defined as
      i. Patient being in acceptable symptom state (PASS) (yes/no).
      ii. Reaching an ASAS20 response.
      iii. ASDAS <1.3.
   b. Clinical response defined as
      i. Patient reaching an acceptable symptom state (PASS).
      ii. BASDAI20, BASDAI50 and BASDAI70
      iii. Reduction in ASDAS ≥1.1.
      iv. ASAS20, ASAS40 and ASAS5/6.
2. MRI assessments at week 16 and 52:
   a. MRI remission defined as
      i. Inflammation in ≤2 consecutive SI-joint quadrants or ≤2 quadrants on the same image slice (i.e. the definition of a positive MRI for axial SpA by ASAS).
      ii. Minimal MRI inflammation in the spine (≤1 DVU affected) AND minimal MRI inflammation in the SI-joints (≤1 (eller 2) SI-joint quadrants involved in ≤ 1 slice)
   b. MRI response defined as
      i. ≥50% reduction in conventional SI-joint MRI score.
      ii. ≥50% reduction in conventional total spine MRI score.
      iii. ≥50% reduction in conventional combined spine and SI-joint MRI score.
      iv. ≥50% reduction in number of peripheral joints with inflammation on whole-body MRI.
      v. ≥50% reduction in number of axial joins with inflammation on whole-body MRI.
      vi. ≥50% reduction in number of entheses with inflammation on whole-body MRI.
      vii. ≥50% reduction in number of peripheral and axial joints and entheses with inflammation on whole-body MRI (i.e. total inflammatory load).
      viii. ≥50% reduction in SI-joint MRI score when assessed on diffusion weighted images.
      ix. ≥50% reduction in spine MRI score when assessed on diffusion weighted images.
      x. ≥50% reduction in combined SI-joints and spine MRI score when assessed on diffusion weighted images.

9.2 Endpoints for the ASAS HI sub-study

There are no specific endpoints for the ASAS HI study. ASAS HI is new questionnaire and no formal definitions high and low scores or for changes in scores are available. At the time for the statistical analyses the definitions that are available will be used.

9.3 Study design

The study is an open, longitudinal, 52-week observational cohort study of 50 patients with axial SpA, who starts treatment with Golimumab and are followed during treatment.

9.4 Study periods

The study is performed in three parts:

9.4.1 Part 1, week -2 to 0 (duration 0 to 2 weeks)

MRI and X-rays are performed as close as possible to the week 0 visit at not earlier than 2 weeks before. The medical and biochemal screening procedures before initiation of TNFα inhibitor therapy may be performed in this period, but they may also be performed before this period if they are not older than accepted by the local recommendations (typically 3 months). This will depend on, what is most practical for the participaring departments.

9.4.2 Part 2, week 0 to 16 (16 weeks)

All patients are treated with sc. Golimumab 50 mg every month (on the same date). Four injections are given in this period.

9.4.3 Part 3, week 16 to 52 (36 weeks)

Clinical responders (for definition, see section 9.1) continue sc. Golimumab 50 mg every month (on the same date). Eight injections are given in this period. At week 16, **clinical non-responders** change treatment at discretion of the treating rheumatologist, and they continue to be followed in the study if they are treated with TNFα inhibitor.

9.5 Methods to reduce/eliminate bias

There is no randomization, blinding or placebo in the study in relation to the IMP.
The study participants and the treating rheumatologists are blinded to all MRI information during the study besides to a brief description of the images performed before inclusion. The description of the screening MRI and X-ray is specifically made to support the decision of inclusion/not inclusion into the study i.e. guiding the diagnosis of axial SpA. The rheumatologists and radiologists can usually see the MRI scans that are stored in the PACS system. Scans performed in this study will be locked in PACS, and thus cannot be opened without a special request, which has to be made by the study coordinator.

9.6 Study treatment

- The patients are treated with sc. Golimumab 50 mg every month (on the same date).
- The study medication is provided as prefilled pens with Golimumab 50 mg dispensed in 0.5 ml. sterile water containing sorbitol (E420), L-histidin, L-histidin monohydrochlorid-monohydrat, polysorbat 80.
- The protection on the needle is made of latex.
- One package contains one injection pen.
- MSD will provide Golimumab pens for the first 7 injections (7 pens) and the participating departments will provide Golimumab pens for the last 5 injections (5 pens).
- The IMP from MSD is taken from the same supplies as the medicine sold to Danske Regioner.

9.7 Package

9.7.1 Information about the package

For copy of the print on the IMP package, see section 33.

- The IMP is delivered in packages, which have information and print identical to the packages sold to Danske Regioner.
- The IMP is in the study applied used as described on the package and package leaflet.

9.7.2 Information on the package

- Name, pharmaceutical dosage form, route of administration, quantity of dosage units, strength/potency.
- The batch and/or code number to identify the contents and packaging operation.
- Directions for use.
- Storage conditions.
- Period of use.
- "Keep out of reach of children".

9.8 Label

9.8.1 Information about the label

The label is shown in section 34.

- The label will measure 38 mm x 99 mm.
- The label will be applied on the blank/empty side of the package.
- All labels used in the study will be manufactured at "Videncenter for Reumatologi og Rygsydomme" and will be distributed to the participating departments.
- The packages provided by MSD will be labelled by the investigator before being distributed to the patient.
- Both sponsor and investigator will keep an accountability log for labels, see section 9.11.

9.8.2 Information on the label

The label is shown in section 34

- The information that is provided on the package is not mentioned on the label.
- Name, address and telephone number of the sponsor.
- Name, address and telephone number of the investigator is not provided on the package, but is provided on the patient card (see section 35).
- Name of trial and trial reference code.
- The trial subject identification number is provided.
- The visit number is not provided since it is not relevant.

9.9 Patient Card

The patient card is provided in section 35. The patient will be asked to carry the card at all times from week 0 (first injection of Golimumab) to week 52 (last study visit).

9.10 Storage of IMP

Special requirements in relation to the IMP (copy from Danish package leaflet)

- Opbevares utilgængeligt for børn.

- Brug ikke dette lægemiddel efter den udløbsdato, der står på etiketten og pakningen efter "EXP". Udløbsdatoen er den sidste dag i den nævnte måned.
- Opbevares i køleskab (2°C - 8°C). Må ikke nedfryses.
- Opbevar den fyldte pen i den ydre karton for at beskytte mod lys.
- Brug ikke dette lægemiddel, hvis De kan se, at væsken ikke er en klar til lys gullig farve, eller hvis den er grumset eller indeholder fremmede partikler.

9.11 Drug and label accountability

9.11.1 Sponsor

"Videncenter for Reumatologi og Rygsygdomme" (sponsor) will maintain an accountability log for the IMP received from MSD, which also will include the shipping receipts. They will also maintain an accountability log for the IMP and the labels they send to the participating centers. Sponsor has made standardized forms that fulfill the requirement of GCP.
Before study start, labels for all packages are printed i.e. 12 labels per patient plus one additional in case of injection failure etc. The packages with IMP provided by MSD will be send to the investigator with all lables, and investigator will lable the IMP before giving it to the patient. Furthermore, they will keep an accoutability log for the labels. Dedicated nurses who have experience with GCP will maintain both accountability logs.

9.11.2 Investigator

The investigators will maintain an accountability log for the IMP and labels they receive from sponsor and for the individual patient. Labels that are not used in the study are stored together with the accountability log for the IMP. The accountability log for the individual patient will include a detailed recording of injections performed at the center, no. of packages with IMP given to the patient for injection at home, and number of empty devices returned from the patient. Empty devices are stored until the patient has finalized the study. Before the empty devices are destroyed the information in the accountability log of the patient should be checked, and signed by the study nurse.

9.12 Safety procedures in relation to IMP

9.12.1 Receival of IMP and labelling procedure

At "Videncenter for Reumatology and Rygsygdomme", the staff that receives the IMP will include two persons of whom at least one will be a study nurse. Both persons are used to receive IMPs and comply with GCP and the required documentation. It is the same persons, who maintain the accountability log.
Shipment of IMP from "Videncenter for Reumatologi og Rygsygdomme" to the investigators will be planned in advance. At the investigators site, study nurses will maintain the accountability logs, and they will also label the IMP. The investigators study nurses are used to comply with GCP in pharmaceutical studies. The procedure for recieval of IMP, labelling and maintenance of accountability logs this study will be discussed at local meetings before at the centers before the study is initiated.

9.12.2 Storage of IMP

At sponsors site and the participating centers, the IMP is stored in refrigerators that are under continuous temperature surveillance connected to a central alarm in the hospital. In case, there is no electronic temperature surveillance, a thermometer showing the min/max. temperature will be place in the refrigerator. Sponsor and the centers keep a temperature log according to the

recommendations at the individual hospital, which fulfils the requirements of GCP. This may be either a manual log or an electronic readout.
At home, the patient store the IMP in his/her refrigerator. The study nurse routinely inform the patient about the importance of storage conditions at home and under transportation including at vacation. The patient also informed about the importance of having a thermometer in the refrigerator and check it regularly. The IMP is stored in a cooling bag under transportation from the hospital. This is all routine procedures in clinical practise.

9.12.3 Injection of IMP

The study nurses that participate in the study routinely inform and teach patients about how to inject the IMP. Furthermore, they are aware of patients that may need help or may benefit from having the injections performed at the hospital or by a nurse at home.
The first injection will be given at the centre once all study-related procedures have been performed and under the direct supervision of a study nurse. This supervision enables the study nurse to check that the correct technique for subcutaneous injection is used. If needed, the second injection can be given at the center. The injection technique is described on the package leaflet.
Each time the patients get new packages of IMP (every second month) they are routinely screened by the study nurses for problems with injection tecknique, adverse reactions in relation to the injection and for storage problems.

9.13 Randomization code and procedures for breaking the code

Not relevant for this study.

9.14 Source data

9.14.1 Definition of source data

Source documents are original records in which raw data are first recorded. These may include hospital records, X-rays, MRI scans, laboratory results, ECG or other printouts. If patient questionnaires are fill-in on paper and later entered into the e-CRF the paper based questionnaires are the source document.

9.15 Source data in this study

Source data will be defined before initiation of the study. A list will be available in the TMFs.
For information on variables and items included in the study, see section 15.

10 STUDY PARTICIPANTS

The study includes 50 patients with axial SpA or AS. The patients are recruited from the participating centers among the patients that are offered treatment with TNFα inhibitor due to moderate to high disease activity despite other treatment. Patients will not be recruited by use of advertisements.

11 RECRUITEMENT OF PATIENTS

The patients are recruited from the participting rheumatologic departments among their own patients. This is done without any use of advertisements etc. See section about information of the patients for further details (section 21

12 INCLUSION AND EXCLUSION CRITERIA

12.1 Inclusion criteria

1. Age >18 years and <85 years.
2. Spondyloarthritis according to the ASAS classification criteria for axial SpA (see section 37).
3. Sacroiliitis on conventional X-rays or MRI.
4. Disease activity assessed by BASDAI >40 mm despite treatment with NSAID.
5. Clinical indication for TNFα inhibitor treatment by the treating physician.
6. No contraindications for TNFα inhibitor treatment (see section 12.2.1).
7. No contraindications for MRI (see section 36).
8. Sufficient contraception for women (see section 12.2.2).
9. Capable of giving informed consent.
10. Capable of complying with the examination programme of the protocol.

12.2 Exclusion criteria

1. Pregnancy wish, pregnancy or breast-feeding.
2. Oral, intra-articular or intramuscular glucocorticoid within 4 weeks prior to inclusion.
3. DMARDs are allowed during the study, but the dose cannot be changed from 4 weeks before the first MRI scan and until week 16.
4. The use of other study drugs within 4 weeks prior to inclusion or less than 5 half-lives of the study drug before inclusion if this is more than 4 weeks.
5. The use of suspected disease-modifying or immunosuppressive drugs within 4 weeks before to inclusion.
6. Previous treatment TNFα inhibitor.
7. Contraindications for TNFα inhibitor treatment (see section 7).
8. Contraindications for MRI (see section 36).
9. Known recent drug or alcohol abuse.
10. Failure to provide written consent.
11. Incapable of complying with the examination programme for physical or mental reasons.

12.2.1 Contraindications to TNFα inhibitor treatment

The patients are asked about previous and current diseases, with focus on the following conditions and circumstances that may influence the decicion of starting TNFα inhibitor treatment:

1. Active infections or persistent chronic infections that have required treatment with intravenous drugs within 30 days, or oral drugs within 14 days, before the start of TNFα inhibitor.
2. Immunosuppressive conditions or new HIV infection.
3. Active or chronic Hepatitis B and/or C virus infection.
4. Persons with latent tuberculosis (TB) (Quantiferon test and/or chest X-ray indicating TB) or other risk factors for activation of latent TB must undergo TB prophylaxis starting 4 weeks before the first administration of golimumab. The prophylactic treatment follows the guidelines of the treating department.
5. Severe, uncontrolled medical disease, such as uncontrolled diabetes with documented previous repeat infections, unstable heart disease, heart failure or recent cerebrovascular event.
6. Neurological symptoms indicative of demyelinating disease of the central nervous system, e.g. multiple sclerosis.
7. Heart failure (NYHA group 3 and 4).

8. Malignant diseases except well-treated non-metastatic squamous or basal cell skin carcinoma and/or carcinoma in situ cervix uteri.
9. New SLE or SLE-like disease.
10. Current and/or imminent wish to become pregnant.
11. Postive serum HCG.

In case of contraindications to the treatment with TNFα inhibitor the patient cannot be included in the study.

12.2.2 Sufficient contraception for women

Copy of text from http://laegemiddelstyrelsen.dk.

Det skal I indeværende forsøg sikres, at fertile kvinder ikke er gravide inden indtræden i forsøget (negativ graviditetstest forud for indgåelse i forsøget), samt at der benyttes sikker antikonception.

Sundhedsstyrelsen anser følgende svangerskabsforebyggende midler som sikker antikonception i forbindelse med lægemiddelforsøg: Spiral eller hormonel antikonception (p-piller, implantat, transdermal depotplastre, vaginalring eller depotinjektion). I visse tilfælde kan steril fast partner eller brug af dobbeltbarriere findes acceptabelt. Dette forudsætter en gyldig begrundelse i særlige forhold omkring forsøgsdesign, præparatkarakteristika og/eller patientpopulationen. Ved dobbeltbarriere forstås kondom kombineret med pessar.

Fertile kvinder, som inkluderes i forsøg, skal således anvende svangerskabsforebyggende midler i overensstemmelse med ovenstående i hele forsøgsperioden og efter forsøgsophør i en periode på 6 måneder (information fra MSD).

Sterile eller infertile forsøgsdeltagere er fritaget for kravet om brug af antikonception. For at betragtes som steril eller infertil må man almindeligvis være kirurgisk steriliseret (vasektomi/bilateral tubektomi, hysterektomi og bilateral ovarektomi) eller være postmenopausal, defineret som udebleven menstruation i mindst 12 måneder før studie indrullering.

Der kan for enkelte individer eller særlige populationer være forhold, som taler imod brug af ovenstående metoder. Eksempler kan være alvorligt svækkede hospitaliserede patienter eller ikke seksuelt aktive fertile børn. En sådan vurdering tages af investigator og er dennes ansvar. Begrundelsen for afvigelsen skal nedskrives (f.eks. i CRF), og skal ikke indsendes til Sundhedsstyrelsen, men kunne dokumenteres ved en eventuel fremtidig inspektion.

12.3 Withdrawal criteria for an individual patient

Investigators should contact study coordinator whenever possible to discuss the withdrawal of a subject in advance.

Reasons for withdrawal:

1. Development of an illness that interferes with continued treatment with TNFα inhibitor (i.e. TNFα inhibitor stopped permanently and no new TNFα inhibitor initiated).
2. Withdrawal of Golimumab treatment before week 16.
3. Non-compliance with study procedures including the treatment in the opinion of the investigator.
4. Withdrawal of informed consent for any reason and at any time.
5. Confirmation of a pregnancy during the study, as evidenced by a positive pregnancy test.
6. If sponsor or a regulatory agency requests withdrawal of the patient.

In case of withdrawal from the study, the subject should have the Withdrawal Visit (Eksklusionsbeøg) performed.

Withdrawn subjects will not be replaced with new patients in the study.

12.4 Reasons for stopping the trial

- Golimumab has been used since 2009 in US and Europe for treating patients with rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis. It belongs to a group of drugs, the TNFα inhibitors, which has been used since year 2000 all over the world. Although there are differences in the biochemistry, farmacokineics etc. the clinical response, frequence of adverse events etc. appear similar. Therefore, we do not expect the study to stopped before time due to unexpected drug reaction etc.
- Should the MRI scanner used in the study go down it is usually repaired within a few days. However, in case of a longer break down, there are other MRI scanners at the Department of Radiology at Herlev Hospital, which can make the same type of sequences.
- If requested by a regulatory agency.

12.5 Treatment

Week 0 to 16: Patients are treated with sc. Golimumab 50 mg every month (on the same date)

Week 16 to 52: Clinical responders continue sc. Golimumab 50 mg every month (on the same date). Clinical non-responders change treatment according to the treating rheumatologist. At week 16, clinical non-responders change treatment at discretion of the treating rheumatologist, and they continue to be followed in the study if they are treated with TNFα inhibitor.

12.6 Treatment response

Treatment response is evaluated at week 16 and 52. A clinical response is defined as a reduction in BASDAI of ≥ 20 mm or ≥ 50%.

12.7 Concomitant treatment

12.7.1 Prohibited concomitant treatments during the study

The following treatments are not allowed during the study.

- Other drugs with a potential disease-modifying effect (except DMARDs).
- Other study drugs.

12.7.2 Permitted under special circumstances and in certain time intervals only

- Glucocorticoids. At specific time points during the study, intraarticular or intramuscular injection with glucocorticoid are allowed.
    - Before week -4 before the MRI scans
    - From week 4 after all study procedures have been performed and until week 8
    - From week 16 after all study procedures have been performed and until week 20
    - From week 28 after all study procedures have been performed and until week 32
    - From week 40 after all study procedures have been performed and until week 44
- Oral and intravenous glucocorticoids are not allowed at any time point.

12.7.3 Permitted concomitant treatment during the study

The following treatments are allowed during the study, and the use should be recorded in the CRF at each visit.

- Paracetamol.
- NSAIDs (if taken, dose must be fixed from 2 weeks before the first MRI scans through week 4 after completion of examination programme).
- Tramadol.
- DMARDs (dose must be fixed from 4 weeks before the first MRI scan to week 16).

In case of lack of improvement in disease activity during the study despite paracetamol, NSAID and/or tramadol treatment the patient must not be excluded before contact with the study coordinator, so that another effective treatment may be initiated.
Collectively, paracetamol and tramadol are also referred to as rescue medication.

12.8 Treatment after end of the study

Clinical responders at week 52 continue with sc. Golimumab 50 mg once every month (at the same date). In case of insufficient treatment effect, treatment will be changed in accordance with the guidelines of the department concerned and at discreation of the treating rheumatologist.

12.9 Surveillance of compliance to treatment

The first and eventually the second injection of Golimumab will be given at the participating center under supervision of a study nurse. All other doses can be given outside the center. To document compliance, all pens (pre-filled pens given to the patient, empty pens returned used or unused from the patient) have to be counted and documented in the accountability log for the individual patient.

13 ASSESSMENT OF EFFICACY

13.1 Specification and justification of efficacy parameters

The criteria for inclusion in this study regarding diagnosis and clinical disease activity (point 2. and 4.) and all contraindications to TNFα inhibitor are the same as is used in clinical practice.
The primary treatment response used in the study (BASDAI response) is the treatment response that also is used in clinical practice as the primary treatment response. Of the other criteria used in the study, ASAS and ASDAS response criteria are primarily used in studies.
PASS is an overall subjective measure of disease activity that has only been investigated in few studies of patients with axial SpA. MRI is used in clinical practice for diagnosing axial SpA, but is at the moment not routinely recommended for assessment of treatment response, due to the lack of definitions of response and remission criteria.

13.2 Methods and time points for assessment and recording of efficacy parameters

For information on analyses of the efficacy parameters, see section 13.
For an overview over time points for assessment of the efficacy parameters, see flowchart section 28.
For an overview of the acceptable time window for all the study visits, see flowcart section 28.

14 ASSESSMENT OF SAFETY

14.1 Specification and justification of safety parameters

The safety assessments performed before treatment initiation in the study are the same as used in daily clinical practise. The participating departments of rheumatology have different levels of safety

assessment during treatment with TNFα inhibitor. During the study, the centers will follow their own recommendations in supplement to those described below.

14.1.1 Methods and time points for assessment of safety parameters before week 0

Safety assessments before initiation of the IMP include a screening for previous and current diseases (see section 14.1). This is done by review of the patient's medical record, interview with the patient, and clinical, biochemical and imaging assessments. The biochemical screening can be performed within 3 months before initiation of the IMP - the same period as is used in clinical practice, except for infections, and liver and kidney dysfunctions, which should be re-assessed at the week 0 visit together with the urine test, and the blood tests, which not should be more than 1-2 weeks old.
The screening visit in the study can be performed within 4 weeks before the inclusion visit (week 0) or it can be performed together with the inclusion visit, if all screenings procedures have been performed within the acceptable time frames (see above and below) and all tests all are normal.

History of TB exposure
The rheumatologist asks the patients to previous exposure for TB, which includes an anamnesis of previous travels and living in other countries than Denmark, TB among family, friends and collegues etc. Calmette vacination status.

Chest X-ray
To screen for tuberculosis a radiological chest examination is performed before inclusion. A previous examination can be used provided it has been performed within 3 months before treatment initiation.

Quantiferon tests
Quantiferon test is carried out with-in 3 months before treatment initiation. The Quantiferon test (QFT-G) detects the release of interferon-gamma (IFN-γ) in fresh heparinised whole blood from sensitised patients when incubated with mixtures of synthetic peptides representing 2 proteins (early secretory antigenic target-6 (ESAT-6) and culture filtrate protein-10 (CFP-10)), which are present in M Tuberculosis. Direct comparisons have shown that the sensitivity of QFT-G was not statistically different from Tuberculin Skin Test (TST) in terms of detecting an infection in persons with untreated culture-positive tuberculosis. According to the US Centres for Disease Control and Prevention, QFT-G can be used for the same groups of persons as TST, including screening for TB. (http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5415a4.htm).

Electrocardiogram (ECG)
A 12-lead electrocardiogram has to be performed within 3 months before treatment initiation.

Hepatitis and HIV
All patients are screened for hepatitis B and C (HBsAg, anti-HBs, anti-HCV) and HIV within 3 months before treatment initiation.

Pregnancy test
Women of childbearing potential will be tested for pregnancy (sHCG) before inclusion into the study. The samples are analysed at the biochemical department where they are collected.

Physical examination
Before the start TNFα inhibitor treatment the patient undergoes a physical examination. The general physical examination includes an assessment of the general condition, oral cavity, lymph node status, auscultation of heart and lungs, abdominal examination, musculoskeletal conditions, skin and neurology.

Vital signs
Pulse and blood pressure are measured at week 0 and 52 and at exclusion, and besides that only if necessary.

Safety blood and urine samples
Before the start of the TNFα inhibitor treatment the following blood and urine, samples are collected:
Haemoglobin, CRP, leukocytes, differentials, platelets, albumin, ALAT or ASAT, LDH, alkaline phosphatase, creatinine at every study visit. ANA screening is performed at week 0 and 52.
The urine is analysed for haemoglobin, albumin, glucose, leukocytes and nitrite and is performed at week 0 and 4 and whenever clinically indicated, or recommended locally at the centre.

14.2 Methods and time points for assessment, registration and analyses of safety parameters

For methods and time points for assessment of safety parameters, see flowchart section 28.
The values of the safety parameters are not recorded in the CRF, but only indirectly in a checklist to assure that the treating rheumatologist have seen the results and the patients can continue treatment with the IMP (or after week 16 with the other TNFα inhibitor) in the study. Only if the safety parameter is considered an adverse event, it should be recorded exactly as a part of the report to the Danish Health and Medicines Authorities.
None of the safety parameters is included in the source data if not reported as an adverse event.

14.3 Procedures to avoid and treat complications

The participating centers are all used to treat patients with axial SpA with the IMP used in the study and with other TNFα inhibitors, and they have implemented care programs to avoid complications. These care programs are based on international and national recommendations for screening for contraindications before initiation of TNFα inhibitor, and for screening for complications during this treatment. The rheumatologists that treat patients in the study are either rheumatologic specialists, and if not, they treat the patients in the study under close supervision of rheumatologic specialists.

14.4 Follow-up time in relation to complications

SAE and SUSARs are followed until the first coming annual rapport the Ethical Committee and for the last included patient until the closure of study letter to the Ethical Committee. Assessemt and reporting of adverse events

14.5 Depression screening

14.6 ***The results of the depression screening (CES-D) will be provided to the treating physician in the eCRF. The results will be provided in five categories as defined by CES-D i.e. "no clinical significance", "subthreshold depression symptoms", "possible major depressive episode", "probable major depressive episode", or "meets criteria for major depressive episode". The treating rheumatologist is responsible making a clinical judgement of the patient as it is performed in daily clinical practise, and to document it in the patient record if there is any suspicion of depression. Furthermore, the treating rheumatologist is responsible for taking action according to his/her individual clinical judgment of the patient, and refer the patient to his/her general practisioner or a psychiatrist.*** **Adverse events (AE) and adverse reactions (AR)**

14.6.1 Definition Adverse Event (AE)

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

14.6.2 Definition Adverse Reaction (AR)

All noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions. The phrase "responses to a medicinal product" means that a causal relationship between a medicinal product and an adverse event is at least a possibility (refer to ICH E2A). A reaction, in contrast to an event, is characterized by the fact that a causal relationship between the drug and the occurrence is suspected. If an event is spontaneously reported, even if the relationship is unknown or unstated, it meets the definition of an adverse drug reaction.

14.6.3 Recording of Adverse Events (AE) and Adverse Reacstions (AR)

AE and AR are not recorded in the study.

14.7 Pre-malignant conditions

- MSD has special focus on pre-malignant conditions, which should be reported as such under Adverse Events in the CRF.
- At the end of the study, the investigator will submit a complete line listing of all Adverse Events that have been captured throughout the study to MSD. MSD will review this for possible premalignant conditions. If any are reported, MSD will contact the Investigator with a dedicated follow-up request to be completed. In case a pre-malignant condition has progressed to a malignancy, the Investigator will need to complete the Malignancy Follow-Up Questionnaire, according to the above procedure.

14.8 Serious adverse event (SAE), serious adverse reaction (SAR) and suspected unexpected serious adverse reaction (SUSAR)

14.8.1 Definition of Serious Adverse Event (SAE)

Any untoward medical occurrence or effect that at any dose.

- Results in death.
- Is life threatning.
- Requires hospitalisation or prolongation of existing inpatients' hospitalisation.
- Results in persistent or significant disability or incapacity.
- Is a congenital anomaly or birth defect.
- Cancer.
- Overdose.

Other important medical events that may jeopardize the patient or may require intervention to prevent one of the outcomes listed previously should also be considered "serious".

14.8.2 Reporting of Suspected Unexpected Serious Adverse Reaction (SUSAR) and Suspected Unexpected Adverse Reaction

All suspected adverse reactions related to an IMP and comparators that are both unexpected and serious or non-serious are subject to expedited reporting.

14.8.3 Definition of Unexpected Event – and specification of the reference document used in the study

Any event that is not included in the appropriate Reference Safety Information (Investigator's Brochure) or one that is more severe or more specific, than what is included in the Reference Safety Information.
In this study, the reference document used for defining an unexpected event is the Investigator's Brochure. There will be copy of the Investigator's Brochure in the TMF.

14.9 Time frames for reporting SUSARs and Suspected Unexpected Adverse Reaction

Investigator must report all SUSARs and Suspected Unexpected Adverse Reactions within 24 hours to sponsor, who will take care of the reporting to the authorities and MSD. The sponsor must ensure that all relevant information about

- **SUSARs that are fatal or life threatening** should be reported to the health authorities as soon as possible and in no case later than 7 days after such a case has come to the sponsor's knowledge. Relevant follow-up information is subsequently communicated within additional 8 days. MSD has to be informed within 48 hours.
- **All other SUSARs** must be reported to the Danish Health and Medicines Agency as soon as possible, no later than 15 days from the sponsor's first knowledge of such reactions. The Etical Committee has to be informed within 7 days. MSD has to be informed within 48 hours.
- **Suspected Unexpected Adverse Reaction** must be reported to the health authorities as soon as possible, no later than 15 days from the sponsor's first knowledge of such reactions. MSD will be informed within 48 hours.

SAE, SUSAR and Suspected Unexpected Adverse Reactions are reported to the Danish Health and Medicines Authorities, the Ethics Committee and MSD within the time periods mentioned above (see also table below).

14.10 How to report SUSARs and Suspected Unaxpected Adverse Reactions

Each report should be submitted on a CIOMS-form (the form used in DANBIO). Each report should also include the study number and accompanied by comments on any possible consequences for the trial. The investigator must complete all fields in the CIOMS form. CIOMS-forms filled in in the eCRF, and paper-based back-ups are present in the paper CRF.
All patients with SAEs, SUSARs and Unexpected Adverse Reactions must be followed up for outcome, and this will be done by sponsor in relation to the annual report to the Ethics Committee and MSD.

14.11 Additional information on malignancy to MSD

As part of a US Food and Drug Administration (FDA) requirement for all TNFα inhibitor agents, all malignancies occurring in patients 30 years of age or younger who received golimumab (Simponi) must be reported to MSD within 48 hours using the same method described above for SAE reporting. MSD will follow-up with the Investigator by sending a dedicated Malignancy Follow-up Questionnaire that has to be completed by the Investigator(s) and submitted to MSD within 2 weeks of receipt, using the same method described above for SAE reporting. The Investigator must make at least two attempts to contact the patient or guardian to complete the Malignancy Follow -up Questionnaire. If the attempts are not successful, the reason
for each unsuccessful attempt must be documented (e.g., patient lost-to-follow-up, patient refuses to supply the additional information, etc.).

14.12 Annual report on SAE, SUSARs and Suspected Unexpected Adverse Reactions

The investigator must once yearly throughout the entire trial period submit an annual report to and the Independent Ethics Committee.

The investigator agrees to submit to the Danish Health and Medicines Authority and MSD all information concerning participants' safety; SAE/SUSAR/pregnancy reports & annual report to:

- Att. Pharmacovigilance by fax +45 4439 5004

14.13 Practical procedures for reporting of AEs, ARs, SAEs, SARs, SUSARs

The following table provides an overview of responses/reactions that must be reported.

	REQUIRED REPORTING OF AE			PRACTICAL PROCEDURES FOR REPORTING ADVERSE EVENT FOR	
Type of adverse event	**MSD**	**SST Afdeling for Lægemiddel-overvågning og Medicinsk Udstyr**	**Independent Ethics Committee (IEC)**	**INVESTIGATOR**	**SPONSOR**
Expected AR and AE	No	No	No	No	No
Unexpected Non-serious AR	Yes	Yes	No	Report immediately to SST via DANBIO, and e-mail letter to sponsor	• Fax to MSD within 48 hours
Serious AE (SAE)	Yes	Yes	Yes	Report immediately to SST via DANBIO, and e-mail letter to sponsor	• Fax to MSD within 48 • Letter to IEC within 7 days
Suspected Unexpected Serious Adverse Reactions (SUSAR)	Yes	Yes	Yes	Report immediately to SST via DANBIO, and e-mail letter to sponsor	• Fax to MSD • Letter to IEC within 7 days
Sponsor to submit an annual report	Yes	No	Yes	NA	• Letter to IEC on SAE and SUSAR

15 VARIABLES INCLUDED IN THE STUDY

Different variabels are included in the study. These are either directly related to the aims of the study or indirectly by providing other types of information, which are important for the study e.g. fulfillment of inclusion and not exclusion criteria, contraindications for TNFα inhibitor, time frames for study visits etc.
Below as listed the variables that are considered the core variables in the study, which are collected by the investigator. For patient questionnaires, see separate file with these.

15.1 Screening

When the visit is not performed together with the inclusion visit.

- Informed consent.
- Patient ID.
- Date.
- Name of rheumatologist.
- Gender.
- Height and weight.
- HLA-B27.
- Symptom duration.
- Disease duration.

- Tobacco and alcohol consumption.
- Clincal history incl. past medical history (medical and surgical diseases).
- Presence of benign diseases/conditions that is associated with increased development of cells in the bone marrow (i.e. being blood donor, anemia, infections etc.).
- ASAS classification criteria (see section 37).
- Contraindications for TNFα inhibitor (see section 12.2.1).
- Inclusion criteria (see section 12.2.1).
- Exclusion criteria (see section 12.2).
- BAS questionnaire: Pain, patient global assessment, BASDAI and BASFI.
- HAQ questionnaire
- BASMI.
- Physician global assessment.
- Blood pressure and pulse.
- General clinical assessment.
- Clinical assessments in relation to eligibility for TNFα inhibitor.
- MRI scans and conventional radiography
- Radiological assessments in relation to eligibility for TNFα inhibitor.
- Biochemical assessments in relation to eligibility for TNFα inhibitor.
- ANA test.
- Conventional blood tests (see section 14.1).
- Conventional urine tests (see section 14.1).

15.2 Inclusion

When the visit is not performed together with the screening visit.

- Patient ID.
- Date.
- Name of rheumatologist.
- Clincal history incl. past medical history (medical and surgical diseases).
- Presence of benign diseases/conditions that is associated with increased development of cells in the bone marrow (i.e. being blood donor, anemia, infections etc.).
- Contraindications for TNFα inhibitor (see section 12.2.1).
- Inclusion criteria (see section 12.2.1).
- Exclusion criteria (see section 12.2).
- Target joints (axial and peripheral) and entheses.
- BAS questionnaire: Pain, patient global assessment, BASDAI and BASFI.
- HAQ questionnaire
- Other patient questionnaires (see separate file).
- BASMI.
- Examination of 66/68 periperal joint (tender/swollen).
- Examination of 35 entheses (tender).
- BASMI.
- Physician global assessment.
- Blood pressure and pulse.
- General clinical assessment.
- Treatment after the study visit.
- Concomitant medication (also in relation to all other diseases).
- Accountability log for the IMP.
- Check that MRI scans and radiography of the SIJs and spine have been perfomed.

- Check that radiological assessments in relation to eligibility for TNFα inhibitor have been performed.
- Check that biochemical assessments in relation to eligibility for TNFα inhibitor have been performed.
- Conventional blood tests (see section 14.1).
- Conventional urine tests (see section 14.1).
- Experimental biomarkers.

15.3 Screening and inclusion (when performed together)

When the visits are performed together.

- Informed consent.
- Patient ID.
- Date.
- Name of rheumatologist.
- Gender.
- Height and weight.
- HLA-B27.
- Symptom duration.
- Disease duration.
- Tobacco and alcohol consumption.
- Clincal history incl. past medical history (medical and surgical diseases).
- Presence of benign diseases/conditions that is associated with increased development of cells in the bone marrow (i.e. being blood donor, anemia, infections etc.).
- ASAS classification criteria (see section 37).
- Contraindications for TNFα inhibitor (see section 12.2.1).
- Inclusion criteria (see section 12.2.1).
- Exclusion criteria (see section 12.2).
- Target joints (axial and peripheral) and entheses.
- BAS questionnaire: Pain, patient global assessment, BASDAI and BASFI.
- HAQ questionnaire
- Other patient questionnaires (see separate file).
- Examination of 66/68 periperal joint (tender/swollen).
- Examination of 35 entheses (tender).
- BASMI
- Physician global assessment
- Blood pressure and pulse.
- General clinical assessment including assessment in relation to eligibility for TNFα inhibitor.
- Treatment after the study visit.
- Concomitant medication (also in relation to all other diseases).
- Accountability log for the IMP.
- Check that MRI scans and radiography of the SIJs and spine have been perfomed.
- Check that radiological assessments in relation to eligibility for TNFα inhibitor have been performed.
- Check that biochemical assessments in relation to eligibility for TNFα inhibitor have been performed.
- Conventional blood tests (see section 14.1).
- Conventional urine tests (see section 14.1).
- Experimental biomarkers.

15.4 Specific for week 4

- Patient ID.
- Date.
- Name of rheumatologist.
- Presence of benign diseases/conditions that is associated with increased development of cells in the bone marrow (i.e. being blood donor, anemia, infections etc.).
- Target joints (axial and peripheral and including entheses).
- BAS questionnaire: Pain, patient global assessment, BASDAI and BASFI.
- HAQ questionnaire
- Other patient questionnaires (see separate file).
- Examination of 66/68 periperal joint (tender/swollen).
- Examination of 35 entheses (tender).
- Physician global assessment
- Treatment after the study visit.
- Concomitant medication (also in relation to all other diseases).
- Accountability log for the IMP.
- Registration SAE, SUSARs and Suspected Unexpected Adverse Reactions.
- Pregnancy obtained in the study after initation of TNFα inhibitor.
- MRI scans and conventional radiography.
- Conventional blood tests (see section 14.1).
- Conventional urine tests (see section 14.1).
- Conclusion conventional blood tests (see section 14.1).
- Experimental biomarkers.

15.5 Specific for week 16

- Patient ID.
- Date.
- Name of rheumatologist.
- Presence of benign diseases/conditions that is associated with increased development of cells in the bone marrow (i.e. being blood donor, anemia, infections etc.).
- Target joints (axial and peripheral and including entheses).
- BAS questionnaire: Pain, patient global assessment, BASDAI and BASFI.
- HAQ questionnaire
- Other patient questionnaires (see separate file).
- Examination of 66/68 periperal joint (tender/swollen).
- Examination of 35 entheses (tender).
- Physician global assessment.
- Treatment response i.e. reduktion i BASDAI ≤20 mm or ≤50%).
- Treatment after the study visit.
- Concomitant medication (also in relation to all other diseases).
- Accountability log for the IMP.
- Registration SAE, SUSARs and Suspected Unexpected Adverse Reactions.
- Pregnancy obtained in the study after initation of TNFα inhibitor.
- MRI scans.
- Conventional blood tests (see section 14.1).
- Conventional urine tests (see section 14.1).
- Conclusion conventional blood and urine tests (see section 14.1).
- Experimental biomarkers.

15.6 Specific for week 52 and exclusion visit

- Patient ID.
- Date.
- Name of rheumatologist.
- ”End of study” i.e. reasons for if the patient has not followed the study protocol).
- Presence of benign diseases/conditions that is associated with increased development of cells in the bone marrow (i.e. being blood donor, anemia, infections etc.).
- Target joints (axial and peripheral and including entheses).
- BAS questionnaire: Pain, patient global assessment, BASDAI and BASFI.
- HAQ questionnaire
- Other patient questionnaires (see separate file).
- Treatment response i.e. reduktion i BASDAI ≤20 mm or ≤50%).
- Examination of 66/68 periperal joint (tender/swollen).
- Examination of 35 entheses (tender).
- Physician global assessment.
- Blood pressure and pulse.
- General clinical assessment.
- Treatment after the study visit.
- Concomitant medication (also in relation to all other diseases).
- Accountability log for the IMP.
- Registration SAE, SUSARs and Suspected Unexpected Adverse Reactions.
- Pregnancy obtained in the study after initation of TNFα inhibitor.
- MRI scans and conventional radiography.
- Conventional blood tests (see section 14.1).
- Conventional urine tests (see section 14.1).
- Experimental biomarkers.

15.7 All other study visits

- Patient ID.
- Date.
- Name of rheumatologist.
- Presence of benign diseases/conditions that is associated with increased development of cells in the bone marrow (i.e. being blood donor, anemia, infections etc.).
- BAS questionnaire: Pain, patient global assessment, BASDAI and BASFI.
- HAQ questionnaire
- Examination of 66/68 periperal joint (tender/swollen).
- Treatment after the study visit.
- Concomitant medication (also in relation to all other diseases).
- Accountability log for the IMP.
- Registration SAE, SUSARs and Suspected Unexpected Adverse Reactions.
- Pregnancy obtained in the study after initation of TNFα inhibitor.
- Conventional blood tests (see section 14.1).

15.8 Patient questionnaires used in the study

The patient completes different questionnaires covering disease activity, functional ability, pain and the overall effect of the arthritis in everyday life. The individual components of the questionnaires are described below.

- Patient Acceptable Symptom State (PASS) (see separate file).

- The BAS (Bath Ankylosing Spondylitis) questionnaire, which includes pain, patient global assessment, BASDAI and BASFI (see separate file).
- The HAQ (Health Assessment Questionnaire) including 5 additional questions (2 catagories) with relation to axial SpA (see separate file)
- The ASAS Health Index (ASAS HI) including contextual factors (see separate file).
- Quality of life: Short-Form-36 (SF-36), EuroQol and 15D
- Fatigue: Multidimensinal Fatigue Inventory (MFI) (see separate file) and the Bristol Rheumatoid Arthritis Fatigue MultiDimentionelt Queationnaire, (BRAF-MDQ and BRAF-NRS) (see separate file).
- Sleep: Pittsburgh Sleep Quality Index (PSQI) (see separate file).
- Depression: Center for Epidemiologic Studies Depression Scale (CES-D) (see separate file).

Pain
On a horizontal visual analogue scale (VAS scale), the patient indicates the degree of pain. The scale is divided into an area from "no" to "intolerable" pain. The scale is a horizontal 100 mm line and the distance (in mm) from "no" is recorded.

Patient global
The patient's general assessment of the influence of the disease on life is indicated on a VAS scale (0-100 mm) as descriebed above (see separate file).

BASDAI (Bath Ankylosing Spondylitis Disease Activity Index)
On VAS scales (0 to 100 mm) the patient indicates the severity of six types of discomfort related to disease activity[59]. A BASDAI index is calculated based on the patient's replies to the six questions (see separate file).

BASFI (The Bath Ankylosing Spondylitis Functional Index)
The patient indicates on VAS scales (0 to 100 mm) the ability to perform 10 actions or movements[60]. The questions are primarily related to axial arthritis. A BASFI index is calculated (see separate file).

HAQ (Health Assessment Questionnaire)
The patient's functional status is assessed using a questionnaire with 20 questions that assesses how difficult it is for the patient to perform eight functions. The questions are primarily related to arthritis in peripheral joints. A score (HAQ score) is calculated (see separate file). The questionnaire is extended so it includes 5 additional questions (2 catagories) with relation to axial SpA.

ASDAS (Ankylosing Spondylitis Disease Activity Score)
A new compositive measure of disease activity based on four answers from BASDAI in the BAS questionnaire and CRP [61].

Patient Acceptable Symptom State (PASS)
Includes essentially a single question about the patient find the current state of disease acceptable (yes/no) [62]. However, methodologic researchers has developed several different versions of the question, which may lead to different answers. Three of the questions will be used in the study (see separate file).

ASAS Health Index
Furthermore, a Danish translation of the ASAS Health Index will be applied in the study. ASAS Health Index is a new 17 item questionnaire that covers patients' perception of their physical function, activity and participation[63]. The questionnaire includes 9 additional questions, which are

believed to constitute important contextual factors, which also should be assessed (see separate file).

The patient's assessment of health related quality of life
The patients complete three different questionnaires to assess their own health related quality of life: SF36[64], EuroQol [65] and 15D[66]. These questionnaires assess different aspects of health related quality of life (see separate file).

The Multidimensional Fatigue Inventory (MFI)
The Multidimensional Fatigue Inventory (MFI)[67] includes 20 questions. It was primarily invented for cancer patients, but today it is regarded a generic instrument for assessment of fatigue. MFI is included to have a conventional measure of fatigue (see separate file)..

The Bristol Rheumatoid Arthritis Fatigue Scale (BRAF)
The Bristol Rheumatoid Arthritis Fatigue Scale (BRAF)[68] is a new questionnaire, that includes 23 questions related to fatigue in patients with rheumatoid arthritis. Only few studies have used the BRAF questionnaire, and none of these have included patients with axial SpA, who often complain of fatigue (see separate file).

The Pittsburgh Sleep Quality Index (PSQI)
Sleep quality is assessed by the Pittsburgh Sleep Quality Index (PSQI)[69]. This questionnaire includes 9 questions, and is one of the most used sleep quality questionnaires (see separate file).

The Center for Epidemiologic Studies Depression Scale (CES-D)
The Center for Epidemiologic Studies Depression Scale (CES-D)[70] is a screening instrument for depression in epidemiologic studies. In this study it is included because depression is a well-known confounder for fatigue and sleep disturbances, and it may also affect physical function, activity and participation, which is assessed by ASAS HI (see separate file).

15.9 Physical examinations

The physical examination includes both a general physical examination and an assessment of the presence of spondyloarthritis-related diseases and co-morbidities. If possible, the same rheumatologist perform all the examinations of an individual patient.

General physical examination
Performed at weeks 0, and 52, and when necessary. The general physical examination includes an assessment of the general condition, fidings in oral cavity, lymph node status, auscultation of heart and lungs, abdominal examination, musculoskeletal conditions, skin and neurology.

The Bath Ankylosing Spondylitis Metrology Index (BASMI)
The treating rheumatologist performs five measurements, where the results for each conventionally is transformed to a scale from 0 to 2 and the BASMI 0-2 score is subsequently calculated. In this study the exact result of the 5 measurements are recorded so different version of BASMI can be calculated i.e. the conventional BASMI 0-2 and the linear BASMI 0-10. Performed at all study visits (see separate file).

Thorax expansion
Thorax expansion is measured at maximum inspiration following a maximum expiration corresponding to the fourth intercostal space in men and just below the breast in women. Performed at weeks 0, 4, 16, 28, 40 and 52.

Assessment of joints

In total 66 joints are examined for swelling and 68 joints for tenderness. The following joints are examined: Right and left temperomandibular joint, sternoclavicular joint, acromioclavicular joint, humeral articulation, elbow joint, wrist, midtarsal joint, ankle joint, knee joint, hip joint (for tenderness only) as well as carpometacarpal joint, 10 MCP-joints, 10 PIP-joints, 10 DIP-joints in the hands and 10 MTP-joints, great toe joints, PIP-toe joints. The result of the joint examination should be stated on a separate joint examination sheet. All patients are examined whether or not they have symptoms in the joints. Performed at all study visits.

Assessment of entheses

The following entheses will be assessed clinically: Medial and lateral epicondyle of humerus, supraspinatus tendon insertion into the greater tuberosity of humerus, 1st and 7th costochondral joint, iliac crest, anterior superior iliac spine, posterior superior iliac spine, spinous process of L5, tuber ishiadici, greater trochanter of femur, medial and lateral femur condyle, quadriceps tendon at the insertion into patella, the patella ligaments insertion into patella and tibia, Achilles tendon and fascia plantaris at the insertion into calcaneus. From these different enthesis indices will be calculated: Berlin [71], San Francisco[72], Leeds [73], SPARCC [74], and MASES[75]. Performed at weeks 0, 4, 16 and 52. The assessment of enthesitis on whole-body MRI will include the above mentioned entheses and other entheses e.g. at pelvis, which cannot be examined clinically due to their location in the body.

Assessment of other co-morbidities (uveitis and psoriasis)

The patient is asked about signs of uveitis and if necessary the patient is referred to an ophthalmologist. The patient is also asked about signs of psoriasis, and if present, the patient is examined. Performed at all study visitis.

The physician's assessment of disease activity

Should be stated on both BAS and HAQ. This is a subjective assessment on a 100 mm VAS scale. Performed at all study visits.

15.10 Imaging

MRI

Whole-body MRI, diffusion weighted MRI and conventional MRI of the sacroiliac joints and spine will be performed on all patients before inclusion as well as at weeks 4, 16 and 52. The MRI in connection with screening should be performed as close to week 0 as possible, and in any case not earlier than 4 weeks before. The MRIs are performed on the same 3T MRI maschine.

The duration of the MRI scans will be less than 60 minutes. A final scan protocol will be available before study start. All MRIs are performed on the same scanner.

The MRI protocol is under development and will be available before the first patient is included in the study. There will not be used any intravenous MRI contrast in the study.

Conventional radiography

X-rays of the SI-joints and the total spine (lumbar, thoracic and cervical spine) will be will performed on all patients prior to inclusion as well as at week 52.

15.10.1 Evaluation of X-ray and MR images

A trained SpA expert assesses X-rays and conventional MRI of SI-joints and spine obtained before inclusion. The results regarding presence of sacroilitis and radiological SpA diagnosis are send to the department. The first whole-body MRI is reviewed by a radiologist for unexpected changes (e.g. in the organs) that should prompt further investigation. The scans are only reviewed and no detailed description is given. The remaining MRI scans including whole-body MRI are not described while

the project is going on, and will only in special circumstances be descriebed. The scans are not evaluated for clinical practise after the study, but if there are a special clinical indication it may be possible to have a description of the conventional MRI performed at week 52.
After the end of the study the X-rays and MRI scans will be anonymised and evaluated in accordance with international guidelines at the time of evaluation and by use of validated MR-scores. The readers are experienced with MRI and conventional radiography in SpA. Those who evaluate the MRI images will be blinded for clinical, biochemical and other imaging data as well as in relation to the chronology of the images.

15.11 Biochemical analyses

Conventional biochemical and urinary analyses
At the screening visit and at all other scheduled study visits the following blood samples will be performed: Haemoglobin, CRP, leukocytes, differentials, platelets, albumin, ALAT, LDH, alkaline phosphatase, creatinine. The urine is analysed for haemoglobin, albumin, glucose, leukocytes and nitrite. All above-mentioned samples are analysed at the local biochemical department. ANA screening is performed at screening and week 52. The volume comprise 11 ml. at the inclusion and week 52 study visit and 7 ml. at all other visits.
The urine is analysed for haemoglobin, albumin, glucose, leukocytes and nitrite at screening, inclusion and at week 4, and therafter only when considered clinically necessary.

Experimental biochemical analyses
The following experimental biomarkers will be measured by central research laboratories experienced in these types of analysis. Commercial methods for analyses will be used such as ELISA technique, gene and microRNA arrays and PCR. Since the methods improves all the time, the methods used for the analyses of the experimental biomarkers in this study will not be decided before the analyses are performed.

Blood and urine samples for analyses of experimental biomarkers are obtained at weeks 0, 4, 16 and 52, and stored at -80C° and -2C°, respectively. A detailed description of the acquisition, handling and storage of these samples are provided in the laboratory manual, see Appendices section 38. The blood and urine volumn for analyses of experimental biomarkers comprise 254 ml and 40 ml, respectively, for all 4 study visits.

The following biomarkers are measures

- Conventional CRP and high sensitivity (hs-) CRP
- Biomarkers of inflammation: IL-6, IL-22, IL-23 and VEGF
- Biomarkers of cartilage and extracellular matrix formation and degradation: CTX-II, MMP-3, N-terminal peptide of procollagen type II (PIINP), MMP-derived type II collagen neoepitope (C2M), and MMP-derived type III collagen neoepitope (C3M)
- Biomarkers of bone turnover: DeoxyPYD, CTX-I, OC, PINP, sclerostin and periostin
- Citrullinated vimentin
- HLA-B27

It is to be expected that new potential biomarkers (proteins, genes, mRNA, mikroRNA, metabolittes) including genetic markers for assessment of disease activity, treatment response and prognosis in patients with axial SpA will be discovered within the next 5-10 years. Therefore blood and urine samples will be stored in a research biobank until December 2019, and thereafter the samples will be moved to a biobank dedicated for future research. For further information on the biobank, see section below. Before biochemical analyses not included in this protocol are performed, the steering committee has to apply the Ethical Committee for permission. The gene analyses that may be performed later on, will NOT include a substantial analyses of the genome (in

Danish: omfattende kortlægning af individets arvemasse), but will be performed only to identify the presence of pre-specified genes, that may contribute to an improved assessment of clinical disease activity, treatment response or prognostication for patients with axial SpA including AS.

15.12 Oprettelse af forskningsbiobank (section in Danish)

Blodprøverne vil blive taget ved inklusion, 4, 16, og 52 uger og ved evt. eksklusion. Projekt- og rutineblodprøver tages samtidigt. Projektblodprøverne udgør 77 ml ved det første besøg og derefter 59 ml ved de øvrige 3 besøg svarende til i alt 254 ml. over 52 uger. Blodprøver mærkes i "anonymiseret" form (patientnummer, initialer og dato).
Blodprøverne opbevares i en minus 80 ^{o}C fryser i "Videncenter for Reumatologi og Rygsygdomme", i det forskningslaboratorium, der hører under professor Mikkel Østergaard. Urinprøverne opbevares ved minus 20 ^{o}C. Såvel blod- og urinprøver opbevares i en aflåst fryser i et aflåst lokale geografisk adskilt fra Reumatologisk Ambulatorium. Fryseren er under kontinuerlig central elektroniske overvågning døgnet rundt i forhold til temperaturændringer. Separat herfor opbevares en liste med den "nøgle", som kobler patientnummer til CPR-nummer. Denne liste bruges alene i forbindelse med, at prøvesvar kobles til kliniske oplysninger og MR-fund, som led i dataanalyse i projektet. Kun Susanne Juhl Pedersen og bioanalytiker Teresa Rozenfeld og evt. andre personer, som har fået tilladelse hertil af Region Hovedstaden/Glostrup Hospital, vil have adgang til disse lister. Listerne opbevares på separat netværks drev, iht. databehandlingsaftalen med Region Hovedstaden og Glostrup Hospital.
Biobankens styregruppe udgøres af læge, ph.d. Susanne Juhl Pedersen, professor Mikkel Østergaard, overlæge ph.d. Inge Juul Sørensen. Blodprøverne samt de tilhørende kliniske data vil blive gjort tilgængelige for andre forskere med interesse for patienter med aksial SpA efter skriftlig aftale med styregruppen.
Eksterne samarbejdspartnere i ind- og udland, der måler på blodprøverne, vil få disse tilsendt i anonymiseret form og i afmålte voluminer, og evt. overskydende materiale returneres til forskningsbiobanken. De fleste af blod- og urinprøverne analyseres af bioanalytiker ansat på Glostrup Hospital. Der foreligger aktuelt ingen aftaler med eksterne samarbejdspartnere herunder udenlandske samarbejdspartnere, og det kan derfor ikke på nuværende tidspunkt oplyses, hvem der evt. vil blive samarbejdet med. Den gældende lovgivning for udlevering af biologisk materiale og data følges.
Bestemmelse af andre biomarkører end dem, der er beskrevet i denne protokol, skal godkendes styregruppe og derefter separat af Videnskabsetisk Komité. Forud for blodprøvetagningen giver patienten informeret samtykke til afgivelse af blod, der indsamles og opbevares i en forskningsbiobank til analyse af forudbestemte prøver, der er nævnt i indeværende protokol og til senere analyse af nye biomarkører som omfatter proteiner, gener, mRNA, mikroRNA og metabolitter med relation til sygdomsaktivitet, behandlingsrespons og prognose hos patienter med axial SpA inkl. AS.
Prøverne vil befinde sig i forskningsbiobanken indtil og med december 2019. Herefter overgår blod- og urinprøverne til en biobank mhp. fremtidig forskning. Blodprøverne opbevares ialt i 25 år fra studiets afslutning dvs. frem til december 2041, hvorefter materialet destrueres. Lov om behandling af personoplysninger vil blive overholdt.

16 STATISTICS

16.1.1 Statistical plan for primary objective

The plan for the statistical analyses for the primary objective is provided below.

The primary analysis set will be the intention-to-treat (ITT) population, which comprises all included patients. An additional Per Protocol (PP) analysis will be done as a robustness analysis.

Included patients will be divided into:

1. Clinical non-responders versus clinical responders at week 16 and 52 (based on BASDAI response respectively on ASDAS response (delta-ASDAS>1.1). Fulfilment (yes/no) of BASDAI50 improvement (=reduction in BASDAI of ≥50% or 20 mm) at week 52 is the primary clinical endpoint.
2. MRI remission versus MRI non-remission: Minimal (≤1 DVU affected; equalling MRI-remission) versus above-minimal (MRI activity in >1 DVU) MRI activity at week 16
3. MRI-responders (50% reduction in conventional MRI spine score at week 16.

The statistical analyses will include:
Descriptive statistics for all patients, responders and non-responders (number, median/mean/range of conventional and experimental data).

- Comparison between groups mentioned above (responders vs. non-responders, MRI-remission vs. MRI non-remission)
  - Changes in biomarkers, imaging and clinical parameters
    - Changes within the groups: Paired T-test (in case of normal distribution), Wilcoxon-Pratt test (in case of non-normal distribution)
    - Comparison between the groups – unpaired T-test (normal distribution) or Mann Whitney test (non-normal distribution).
  - Week 0 (baseline), week 4, week 16, week 52 and AUC (area under the curve) values for biomarkers as well as imaging and clinical parameters
    - Unpaired T-test or Mann-Whitney test (see above)
- Correlation analysis
  - Test for correlation (Pearson's test if normal distribution, Spearman's if non-normal distribution) between:
    - Changes in biomarkers, clinical and imaging parameters between baseline and week 4, 16 and 52
    - Absolute values for biomarkers, clinical and imaging parameters both at baseline and week 4, 16 and 52

Furthermore, clinical and MRI outcomes at week 52 will be compared between patients with and without clinical and MRI response at weeks 4 and 16 and between patients with and without MRI-remission at week 4 and 16, and the correlation between the image parameters internally and with clinical parameters will be assessed by unpaired T-tests/Mann-Whitney tests, correlation analysis and logistic regression (to assess predictive value).

Finally, as a secondary analysis, the predictive value of the MRI parameters will be compared to the predictive value of the matrix model developed by Vastesaeger et al[1]
Finally, the variation between the evaluators will be assessed upon repeated blind evaluation of imaging data, and the smallest demonstrable difference (SDD) calculated. Based on SDD, the number of definitive cases of improvement/worsening for the individual measures will be calculated.

For secondary and tertiary outcome measures, an analysis plan will be developed before start of the analyses. This is reasonable since there within the the next few years will be publications with relation to ASAS HI and maybe also some of the experimental biomarkers, which are important for the planning of the analyses.

16.2 Sample size calculation

16.2.1 Sample size calculation for the primary objective

The calculation of power in this study is based on the following:

a. Concerning the sensitivity of conventional versus whole-body MRI to detect inflammation in patients treated with TNFα inhibitor therapy: the expected proportion of patients who has a "conventional MRI minimal disease activity" at week 16 is assumed to be 0.5 (based on Braun et al, Ann Rheum Dis, 2012[76]), whereas the assumed proportion of patients with "a minimal WBMRI MRI disease activity" is 0.25. With a risk of type 1 error of 5% (α=0.05) and a power of 70% (ß=0.30), 37 patients will be needed to test a difference between the sensitivities of the 2 methods.
b. Concerning MRI response at week 16 predicting clinical response at week 52: 60% of patients are expected to have an "MRI response" (defined as 50% reduction in conventional MRI activity) at week 16. Among MRI responders at week 16, the expected proportion of patients who have a clinical response at week 52 is 80%, whereas 40% among MRI-non-responders at week 16. With a risk of type 1 error of 5% (α=0.05) and a power of 70% (ß=0.30), 38 patients will be needed to test the predictive value of early MRI response for clinical response at week 52.
c. Concerning "MRI remission" at week 16 predicting clinical response at week 52: 50% of patients are expected to be in "conventional MRI remission" (defined as ≤ 1 DVU with MRI inflammation) at week 16. The expected proportion of patients who have a clinical response at month 52 is 80% among patients with "conventional MRI remission" at week 16 and 40% among those without "conventional MRI remission" at week 16. With a risk of type 1 error of 5% (α=0.05) and a power of 70% (ß=0.30), 46 patients will be needed to test the predictive value of early MRI remission for clinical response at week 52.

Experience shows that a dropout of at least 4 patients (app. 10%) can be expected. On this basis a sample size of 50 patients has been decided.
It is not possible to calculate the exact number of patients, who have to complete the study to ensure a high power in the statistical analysis of biomarkers, since the variation of the biomarkers is unknown.

16.2.2 Sample size calculation for secondary and tertiary obejectives

Since there is no studies published on ASAS HI and only few studies published for many of the biomarkers, little is known about the variation in these and therefore it is not possible to calculate the sample size. Thus, this part of the study can be considered a 'pilot' study. It is anticipated, that the study population has a sufficient size to perform a later assessment of the variation.

16.3 Criteria for ending the trial

There are no statistical criteria for ending the trial.

16.4 Procedures for missing data and data not used etc.

Details of imputation for missing data due to protocol deviation or premature withdrawal will be pre-specified a detailed plan of the statistical analyses before these are performed.

16.5 Access to source data and other documents

The Investigator will permit study-related audits by the study coordinator and inspections by the Scientific Commetee after reasonable notice. The main purposes of an audit or inspection are to confirm that the rights and well-being of the subjects enrolled have been protected, that enrolled

subjects (i.e. signing consent and undergoing study procedures) are appropriate for the study, and that all data relevant for the evaluation of the investigational medicinal product have been processed and reported in compliance with the planned arrangements, the protocol, investigational site, Ethical Committee and rules for GCP. The Investigator will provide direct access to all study documents, source records, and source data. If an inspection by a regulatory authority is announced, the Investigator will immediately inform Mikkel Østergaard.

16.6 Handling, processing and storage of data

16.6.1 Practical handling of source documents

All source documents (paperbased or electronic) must be accurate, clear, unambiguous, permanent, and capable of being audited. The primary CRF in this study will be an electronic CRF, with a paper based back-up.
The paper CRF should be filled-in with some permanent form of recording. Corrections are made according to the GCP. Changes should not be obscured by correction fluid or have temporary attachments such as removable self-stick notes. Photocopies of CRFs are not considered acceptable source documents. Any change or correction to the paper CRF should be dated, initialed, and explained (if necessary) and should not obscure the original entry. Use of correction fluid is not permitted. For the e-CRF, for all data entry and changes it should be possible to track who entered/changed data, time points, and the original data if changed. Detailed instructions will be provided in the CRF Completion Guidelines.
The investigator will maintain a list of personnel authorized to enter data into the paper and e-CRF.

16.6.2 Storage of source documents

Source documents on paper should be kept in a secure, limited access area at the centers according to the Danish Legislation. Sponsor store the orginal paper CRF, whereas investigator store a copy of the paper CRF. The e-CRF is located in the DANBIO database (https://danbio-online.dk/Danbio-yearly-report-2007-eng.pdf/view), where data are stored also according to Danish Legislation i.e. 10 years. If data is entered directly into the e-CRF at the visit, the e-CRF is the sorce document.

17 ETISKE FORHOLD (SECTION IN DANISH)

17.1 Generelle etiske forhold

Forsøget vil blive gennemført i overensstemmelse med anbefalinger vedrørende biomedicinsk forskning med mennesket som forsøgsperson, som vedtaget af den 18. World Medical Assembly, Helsinki, Finland, juni 1964 og senere revisioner.
God klinisk praksis kræver, at den kliniske protokol, alle protokolændringer, informeret samtykkeerklæring, og alle andre former for deltagerinformation (f.eks. annoncer til rekruttering af deltagere) samt alle andre nødvendige dokumenter skal vurderes af den Videnskabssetiske Komité. Der vil blive indhentet godkendelse af protokollen, den informerede samtykkeerklæring, al information til deltagerne og/eller eventuelle annoncer fra Lægemiddelstyrelsen og Videnskabssetiske Komité før påbegyndelse af forsøget.
I løbet af forsøget skal sponsor straks udlevere skriftlige rapporter til Lægemiddelstyrelsen og Videnskabsetiske Komité vedrørende enhver ændring, som har betydning for udførelsen af forsøget og/eller øger risikoen for deltagerne. Det er ligeledes sponsors ansvar at holde Lægemiddelstyrelsen informeret om enhver alvorlig utilsigtet hændelse i henhold til lovgivningen.

17.2 Etiske forhold vedr. denne undersøgelse

17.2.1 Etiske forhold til behandling

De patienter, der tilbydes inklusion i forsøget, er alle patienter med vedvarende moderat til høj sygdomsaktivitet, der i daglig klinisk praksis er kandidater til behandling med TNFα inhibitor. Der inkluderes ikke patienter, der under normale forhold ikke ville blive tilbudt denne behandling. Golimumab blev sammen med tre andre TNFα inhibitorer sidste år vurderet af et ekspertpanel under Rådet for Anvendelse af Dyr Sygehusmedicin (RADS), der fandt, at de alle var ligeværdige i forhold til effekt og bivirkninger til behandling af axial SpA. Efter en udbudsrunde blev Golimumab valgt som førstevalgspræparat til denne patientgruppe til og med år 2015. Da der derfor ingen etiske overvejelser ved valget af behandlingen i forsøget, da patienterne uden for forsøget vil blive tilbudt den samme behandling. Golimumab gives i forsøget i den rekommanderede dosis. Hvilken TNFα inhibitor behanding, der bliver første valgsbehanding i næste udbudsrunde vides aktuelt ikke.
Såfremt patienterne forud for inklusion dagligt behandles med NSAID (non-steroide-anti-inflammatoriske stoffer, gigtmedicin), skal denne behandling så vidt muligt fastholdes i de første 4 uger af forsøget. En del patienter er dog ophørt med NSAID grundet manglende behandlingseffekt, eller fordi de ikke tåler NSAID, og de skal ikke tage NSAID i forsøget. Ligeledes skal patienter, der er i behandling med DMARDs (f.eks. methotrexate eller salazopyrin) grundet perifer ledinvolvering forblive i denne behandling til og med uge 16. Dosis fastholdes fra 4 uger inden inklusion til uge 4 eller så længe der er behov herfor. I daglig klinisk praksis vil man normalt før vælge at trappe ud af DMARD behandling efter at man har sikret sig, at der er et tilstrækkeligt behandlingsrespons på Golimumab. Efter uge 4 må patienterne tage NSAID ved behov og efter eget ønske, og patienter i behandling med DMARDs kan evt. reducere eller ophøre med behandlingen efter aftale med den behandlende læge.

17.2.2 Etiske forhold til MR-skanning og røntgenundersøgelse

Udsættelse for MR-skannerens radiobølger og magnetfelt er uden bivirkninger, og giver ikke nogle skadelige følger på kortere eller længere sigt. MR-skanningerne udføres uden anvendelse af intravenøst kontrastmiddel. En MR-skanning indebærer ingen røntgenbestråling.
Da tidligere studier omfattende patienter med SpA og reumatoid arthritis har vist, at signifikante ændringer i MR-inflammations score kan observeres efter 4 til 6 ugers behandling med TNFα inhibitor, er det i forsøget valgt at gennemføre den første opfølgningsskanning efter 4 uger, da behandling med Golimumab gives hver måned (på den samme dato).
Ved helkrops MR-skanningen fokuseres der på såvel perifere led som rygsøjlens led. Det betyder, at de indre organer kun fremstilles som mørke skygger. Undersøgelsen kan derfor ikke anvendes som screening for sygdomme i de indre organer, og resultaterne vedr. leddene må betragtes som eksperimentelle, da helkrops MR-skanning ved gigtsygdomme er et helt nyt videnskabeligt forskningsområde. Der foreligger en lille risiko for, at helkrops MR-skanningen afslører ikke forventede forandringer i de indre organer. Dette vil medføre yderligere billeddiagnostiske og evt. biokemiske undersøgelser, der kan opleves som en psykisk belastning. Omvendt kan deltagelse i studiet også potentielt medføre, at nogle få patienter får diagnosticeret en behandlingskrævende sygdom tidligere end ellers med forbedret prognose til følge. Den første helkrops MR-skanning vil blive set igennem af en erfaren radiolog mhp. dette.
Diffusionsvægtet MR-skanning er en ny skanningsmetode, der kun er blevet udersøgt i få studier. Det vides endnu ikke om skanningen kan finde klinisk anvendelse og der gives derfor ikke svar på denne skanning, der heller ikke vurderes i forbindelse med patientens inklusion i studiet.
I dag kendes værdien af MR-skanning til vurdering af behandingseffekt og prognose hos patienter med aksial SpA ikke, og den anvendes derfor ikke rutinemæssigt i den kliniske dagligdag. For at kunne vurdere betydningen af fund på MR-skanning mest optimalt, vil alle fraset studiekoordinator være blindet for MR-skanningerne udført under studiet. Der vil blive udsendt et skriftligt svar på

skanningen udført forud for inklusion, men ikke på de øvrige skanninger. MR-skanningen vil ellers kunne blive anvendt til vurdering af behandlingseffekt på et ikke evidensbaseret grundlag, hvilket vil kunne medføre en skævvridning af studiets resultater (bias) i studiet, der dermed ikke vil kunne genere valide resultater.
Ved røntgenundersøgelserne af sacroiliacaled og rygsøjle udsættes patienten for røntgenstråling svarende til den naturlige baggrundsstråling over 1 år. Røntgenundersøgelse af rygsøjle og sacroiliacaled i daglig klinisk praksis er standardundersøgelser i forhold til klassifikation af sygdommen og for vurdering af sygdomsprogression, og de billeder der tages i forsøget erstatter de undersøgelser, der ellers ville blive taget i daglig klinisk praksis. Efter studiets afslutning vil billederne blive tilgængelige for klinisk brug.

17.2.3 Etiske forhold til blodprøvetagning

Det forudgående screeningsprogram, og de gentagne rutineblod- og urinprøver, der tages af sikkerhedsmæssige årsager svarer i indhold og hyppighed til daglig klinisk praksis. Projektblodprøverne vil blive taget ved inklusion, 4, 16, og 52 uger og ved evt. eksklusion. Projekt- og rutineblodprøver tages samtidigt. Projektblodprøverne udgør 76 ml ved det første besøg og derefter 58 ml ved de øvrige 3 besøg svarende til i alt 254 ml. over 52 uger, hvilket ikke påvirker patientens blodprocent eller helbred i øvrigt. Klinisk vil patienterne traditionelt blive vurderet ved læge mindst 6-7 gange i det første år. Det betyder i praksis, at deltagelse i studiet ikke medfører ekstra konsultationer på reumatologisk afdeling end som i den kliniske dagligdag.
Undersøgelsen forventes at kunne bidrage med ny væsentlig viden om anvendelsen af MR-skanning til monitorering og forudsigelse af behandlingsrespons. De potentielle patientfordele skønnes derfor etisk at retfærdiggøre de ulemper, som undersøgelsen medfører for patienterne i form af gener i forbindelse med gentagne kliniske, biokemiske og billeddiagnostiske undersøgelser, samt for de deltagende afdelinger i form af øget ressourceforbrug.

17.2.4 Etiske forhold til spørgeskemaer

Patienterne besvarer en lang række spørgeskemaer i studiet vedr. sygdomsaktivitet og livskvalitet, hvilket de også rutinemæssigt gør i daglig klinisk praksis via den landsdækkende reumatologiske database, DANBIO (www.danbio-online.dk). Derud får de studiet et nyt spørgeskema omhandlende fysisk funktion, aktivitet og deltagelse, som er udarbejdet særligt til denne patientgruppe (ASAS Sundhedsindex). Spørgsmålene vedr. fysisk aktivitetsniveu og spørgeskemaerne vedr. udmattethed (fatigue), søvn og depression er medtaget for at kunne analysere besvarelserne af ASAS HI mest optimalt. Flere af disse spørgeskemaer er eksperimentelle, da de ikke tidligere har været anvendt på denne patientgruppe. Den behandlende læge vil have adgang til oplysninger om, hvorvidt alle de ikke traditionelt anvendte spørgeskemaer er blevet besvaret, men ikke til selve besvarelsen af disse ud over for depressionsscreeningen (CES-D).
For depressionsscreeningen vil den behandlende læge kunne se hvilken svargruppe, som patienten tilhører jfr. definitionerne i spørgeskemaet. For patienter, der har iht. spørgeskemaet har en "possible major depressive episode", "probable major depressive episode", eller "meets criteria for major depressive episode", vil den behandlende reumatolog vurdere om patienten har en depression. Dette gøres på samme måde ved en almindelig konsultation i reumatologisk ambulatorium, og det dokumenteres på tilsvarende vis i patientjournalen. Det er kendt at screeningsspørgeskemaer ikke altid diagnosticerer patienterne korrekt, herunder vil nogle fejlagtigt blive screenet positivt for depression uden at have det og vice versa. Da flere af symptomerne, der ses ved axial SpA også ses ved depression (f.eks. natlig opvågning), så er dette af og til en differentialdiagnostisk overvejelse i klinisk praksis, og indgår i vurderingen af patienten. Patienter, der i hht. spørgeskemaet viser tegn på depression, vil blive vurderet af den behandlende reumatolog og ved behov henvist til videre udregning og behandling hos egen læge eller psykiater. Det skønnes derfor ikke at udgøre et etisk problemstilling at anvende spørgeskemaet for depression i forsøget.

Det skønnes, at de resultater som forsøget vil kunne generere, langt overstiger ulemperne ved det forøgede tidsmæssige forbrug for de deltagende patienter og personale, samt de ricisi og belastninger, der i øvrigt er forbundet med deltagelse i forsøget.

18 RISICI, BIVIRKNINGER OG ULEMPER (SECTION IN DANISH)

18.1.1 Risici, bivirkninger og ulemper til behandling

Patienten vil i forsøget modtage samme behandling som uden for forsøget, da den anvendte behandling er den samme, som den anbefalede behandling iht. retningslinjerne fra Rådet for Anvendelse af Dyr Sygehusmedicin (RADS) til og med år 2015. Fra år 2016 og fremefter vides det ikke, hvilken TNFα hæmmer som vil blive førstevalgsbehandling. I forsøget gives Golimumab i samme dosis og med samme tidsinterval, som det er recommenderet. Forsøget inklusionskriterier for opstart af behandling er de samme, som dem der anvendes i den kliniske dagligdag. Da forsøget kun omfatter patienter, der under alle omstændigheder ville blive tilbudt behandlingen, så udsættes ingen patienter for en risiko for bivirkninger, som de ikke ville bllive udsat for. Kontrolforanstaltningerne i forsøget de samme, som i den kliniske dagligdag.

18.1.1 Risici, bivirkninger og ulemper til MR-skanning og røntgenundersøgelse

Der er ingen kendte bivirkninger på kortere eller længere sigt ved gennemførelse af MR-skanning, når blot eksklusionskriterierne overholdes. Der skal ikke tages andre forholdsregler ved MRI i 3.0 T magnetfelt end i et 1.5 T magnetfelt, hvorfor der anvendes de samme eksklusionskriterier, og hvorfor f.eks. brugen af spiral (intrauterin device) ikke har nogen betydning for deltagelse. Den anvendte 3.0 T MR-skanner anvendes i daglig klinisk praksis på Herlev Hospital. Forud for inklusion i forsøget sikres det, at der ikke er kontraindikationer for MR-skanning. Dette gøres rutinemæssigt ved der udfyldes et skema vedr. disse når skanning bestilles. Disse retningslinjer er fælles for Region Hovedstadens. Desuden gennemgår radiograferne skemaet med forsøgsdeltageren lige før skanningen. Der anvendes ikke intra-venøst kontraststof ved forsøget. MR-skanningerne i alt maksimalt tage 60 min., hvilket patienterne erfaringsmæssigt finder acceptabelt. Det er muligt at indlægge en pause midtvejs i skanningen.
Der gennemføres en traditionel røntgenundersøgelse af columna totalis og sacroiliacaled 2 gange i løbet af studiet. Ved denne undersøgelse udsættes patienten for røntgenstråling svarende til 1 og 2.5 mSv, hvilket svarer til den naturlige baggrundsstråling over ca. 1 år (www.sundhed.dk). Der er en ganske lille stråledosis, der skønnes at udgøre en meget lille risko. Det skønnes at denne dosis kan øge livstidsrisikoen for cancer med 1 ud at 100.000 til 1 ud af 10.000. Dette skal ses i lyset af at livstidsricikoen for at få cancer er ca. 25%.

18.1.1 Risici, bivirkninger og ulemper til blodprøvetagning

Under projektet vil der blive udtaget 318 ml. fuldblod (heraf anvendes de 254 ml. til analyse af projektblodprøver og 64 ml til analyse af rutineblodprøver), hvilket ikke vil indebære nogen risiko for blodmangel. Der er en ubetydelig risiko for infektion og hæmatom (lille blodansamling uden for venen), hvilket skønnes til mindre en 1 ud af 10.000. Begge er forbigående og giver kun anledning til minimale gener.
De potentielle patientfordele på længere sigt i form af mere følsomme metoder til opfølgning og forudsigelse af sygdomsforløbet ved SpA skønnes klart etisk at retfærdiggøre de risici, bivirkninger og ulemper som deltagelse i studiet kan medføre.

18.1.2 Ricisi, bivirkninger og ulemper til spørgeskemaerne

En ulempe for patienterne er, at det tager tid at udfylde spørgeskemaerne, men vi skønner at den ekstra tid det tager, er rimelig i forhold til gevinsten af de resultater, der opnås, da aktuelt ikke

foreligger nogen viden om ASAS HI. Der foreligger i øvrigt heller ikke megen viden om udmattethed, søvn mv. hos denne patientgruppe, der har store problemer med forstyrret nattesøvn gr. sygdomsaktivitet. Det kan ikke udelukkes, at der er enkelte spørgsmål i ASAS HI og de øvrige spørgskemaer, som nogle patienter vil synes er for personlige til at de vil besvare, men vi skønner dog, at de vil udgøre en fåtal og derfor ikke udgøre et problem for undersøgelsen.
Det er kendt at screeningsspørgeskemaer ikke altid får diagnosticeret patienterne korrekt, herunder vil nogle fejlagtigt blive screenet positive for depression uden at have det og vice versa. Derfor er selve besvarelsen af spørgeskemaet ikke det samme som en diagnose, der skal behandles. Den behandlende reumatolog vil for alle patienter, lige som de gør i daglig klinisk praksis vurdere om patienten har symptomer på depression, og såfremt der er mistanke herom henvise vedkommende til egen læge eller psykiater mhp. yderligere vurdering og behandling. Reumatologens vurdering baseres på et lægeligt skøn ud fra kendskabet til patienten og faglig vurdering på samme måde som i daglig klinisk praksis. Patienter, der har tegn på depression jfr. svarkategorierne (" possible major depressive episode", "probable major depressive episode" og "meets criteria for major depressive episode") iht. besvarelse af spørgeskemaet, vil blive vurderet for depression af den behandlende reumatolog på samme måde som i daglig klinisk praksis, og henvist til videre vurdering og behandling hos egen læge eller psykiater efter behov og efter aftale med patienten. For patienter, der har en depression, kan det såvel på kortere som på længere sigt kun være en fordel at få stillet diagnosen depression.
Det skønnes, at de resultater som forsøget vil kunne generere, lagt overstiger ulemperne ved det tidsmæssige forbrug for de deltagende patienter og personale, samt de ricisi og belastninger, der i øvrigt er forbundet med deltagelse i forsøget.

19 RESPEKTEN FOR FORSØGSPERSONERNERS FYSISKE OG MENTALE INTEGRITET SAMT PRIVATLIVETS FRED (SECTION IN DANISH)

Oplysningerne om forsøgspersonen beskyttes efter lov om behandling af personoplysninger og sundhedsloven. Projektet anmeldes til Region Hovedstaden IMT og Glostrup Hospital, der varetager "paraply"-anmeldelse af alle forskningsprojekter til Datatilsynet. Lov om behandling af personoplysninger vil blive overholdt.

20 TILGÆNGELIGHEDEN AF OPLYSNINGER FOR FORSØGSPERSONEN (SECTION IN DANISH)

Patienten informeres mundligt og skriftligt om navn, adresse, kontakt telefonnummer til den reumatolog, der behandler dem under studiet. De vil af vedkommende kunne få adgang til flere oplysninger om projektet. Ligeledes kan studiekoordinator Susanne Juhl Pedersen kontaktes per telefon eller e-mail adresse.

21 INFORMATION AF PATIENTERNE (SECTION IN DANISH)

21.1 Særlige forhold vedr. afgivelse af deltagerinformation i indeværende studie

- Den første kontakt til forsøgspersonen vil foregå i relation til en ambulant kontrol i det reumatologiske ambulatorium på en af de deltagende afdelinger. Der anvendes ikke opslag.
- Den mundtlige information i indeværende forsøg vil blive givet af den behandlende reumatolog ved eller i relation til en ambulant kontrol i reumatologisk ambulatorium.
- Den skriftlige information kan udleveres før den mundlige information gives og vice versa. Det vil afhænge af de lokale forhold.

- Det sikres at informationssamtalen foregår uforstyrret ved at forsøgsdeltageren gives informationen ved en konsultation i reumatologisk ambulatorium. Såfremt, der foretages telefonisk kontakt spørges forsøgsdeltageren, om tidspunktet for kontakten er passende, og tilbydes i øvrigt en tid til samtale i reumatologisk ambulatorium.
- Det sikres at forsøgspersonen får mulighed for at få en bisidder med ved informationssamtalen ved at gøre opmærksom på denne mulighed såvel skriftligt som mundtligt, og ved at forsøgspersonen tilbydes en ekstra informationssamtale, hvor bisidderen kan være tilstede.
- Der vil mindst være en betænkningstid på 2-3 dage mellem den mundtlige/skriftlige information og den senere underskrift på samtykkeerklæringen. Typisk vil der være endnu længere tid og oftest et par uger.
- Samtykket søges indhentet når en patient på afdelingen bliver kandidat behandling med TNFα hæmmer. Inden patienten kan tilbydes behandlingen har vedkommende betænkningstid vedr. om de ønsker behandlingen, og det skal på fælleskonference besluttes at afdelingen vil tilbyde han/hende behandlingen. I forbindelse med dette forløb informeres vedkommende om muligheden for at deltage i forsøget. Der vil derfor være en klar sammenhæng mellem stillingtagen til samtykket i relation til at informationen omkring forsøget er givet.

21.2 Generelle forhold vedr. informtion til patienten før, under og efter forsøget

Inden informationssamtalen:
- Skal der træffes aftale om tid og sted for samtalen.
- Skal det oplyses, at der er tale om en forespørgsel om deltagelse i et sundhedsvidenskabeligt forskningsprojekt.
- Skal der gøres opmærksom på, at det er muligt at medbringe en bisidder til samtalen.
- Skal der oplyses, om retten til betænkningstid efter informationen. Betænkningstiden afhænger af forsøgets karakter. Som udgangspunkt må denne være mindst et døgn.
- Skal forsker have overvejet retten til at frabede sig viden om nye væsentlige helbredsoplysninger i projektet.

Informationssamtalen:
- Skal være nøje planlagt.
- Skal foregå i uforstyrrede rammer og uden afbrydelser.
- Skal tilrettelægges så forsøgspersonerne har tilstrækkelig tid til at læse den skriftlige information, lytte til den mundtlige information og stille spørgsmål.
- Skal indeholde en forståelig fremstilling af forskningsprojektet uden brug af tekniske eller værdiladede vendinger, og gives på en hensynsfuld måde tilpasset modtagerens individuelle forudsætninger m.h.t. alder, modenhed, erfaring m.v.
- Skal indeholde oplysning om eventuelle forudsigelige risici, bivirkninger, komplikationer og ulemper, samt at der kan være uforudsigelige risici og belastninger knyttet til deltagelse i et sundhedsvidenskabeligt forskningsprojekt.
- Skal indeholde oplysninger om andre behandlingsmetoder, jf. § 5, stk. 3 i bekendtgørelse om anmeldelse og information, såfremt forskningsprojektet også har et behandlingsmæssigt sigte, samt om der i forbindelse med projektet indhentes oplysninger fra forsøgspersonens patientjournal.
- Skal indeholde en beskrivelse af det informerede samtykkes omfang, herunder at samtykket omfatter adgang til videregivelse og behandling af nødvendige oplysninger om forsøgspersonens helbred, øvrige rent private forhold og andre fortrolige oplysninger som led i den kvalitetskontrol og monitorering, som en sponsor og eventuel monitor er forpligtede til at udføre, jf. § 5, stk. 5, i bekendtgørelse om anmeldelse og information.
- Skal indeholde oplysninger om forhold, som forsøgspersonen i øvrigt skønnes at være uvidende om, men som har betydning for forsøgspersonens stillingtagen, fx at vederlag til deltagerne er skattepligtige.

Efter informationssamtalen:

- Skal forsøgspersonen informeres, såfremt der under gennemførelsen af forsøget fremkommer nye oplysninger om effekt, risici, bivirkninger, komplikationer eller ulemper.
- Skal den forsøgsperson, der fortsat er aktivt med i forsøget, informeres, såfremt forskningsprojektets forsøgsdesign ændres væsentligt i forhold til forsøgspersonens sikkerhed.
- Skal forsøgspersonen informeres, såfremt der under gennemførelsen af forskningsprojektet fremkommer væsentlige oplysninger om forsøgspersonens helbredstilstand, medmindre forsøgspersonen utvetydigt har givet udtryk for, at den pågældende ikke ønsker dette, jf. bekendtgørelse om anmeldelse og information, § 14.
- Skal den forsøgsansvarlige, eller den informerende sundhedsperson, ved projektets afrapportering informere forsøgspersonen om de resultater, der er opnået samt om eventuelle konsekvenser for den enkelte. Dette forudsætter, at det er praktisk muligt og forsøgspersonen ønsker dette.Hvis forsøget afbrydes, skal forsøgspersonen informeres om årsagen hertil.

22 ØKONOMI (SECTION IN DANISH)

Undersøgelsen er en investigator-initieret undersøgelse i gang sat af en gruppe reumatologer bestående af Mikkel Østergaard og Susanne Juhl Pedersen. MSD støtter studiet med i alt 2.513.231 kr. og leverer medicin til 7 af de 12 måneder.

Følgende budgetaftale er indgået:

Løn til studiekoordinator	86.250 kr.[1]
Løn til central bioanalytiker	37.375 kr.[2]
Minus 80 grader fryser (ca. 50% af prisen)	32.488 kr.
Statistiker	30.015 kr.
Gebyr ansøgning SST	5.750 kr.
Monitorering, eCRF og dataindtastning	115.000kr.
Ekstra til justering for prisstigninger	113.928 kr.
Per patient per studiebesøg	
Screeningsbesøg	0,00 kr.
Inklusionsbesøg[3]	2.012,00 kr.
Besøg uge 4[3]	1.437,00 kr.
Besøg uge 16[3]	1.437,00 kr.
Besøg uge 28	862,00 kr.
Besøg uge 40	862,00 kr.
Afsluttende studiebesøg[4]	2.012,00 kr.
Eksklusionsbesøg	862,00 kr.
Per patient pr udført ydelse	
Analyse af eksperimentelle biomarkører	1.765,25 kr.
MR-skanning (udførelse, blinding og evaluering billeder)	5.750,00 kr.
Røntgenundersøgelse (udførelse, blinding og evaluering billeder)	1.150,00 kr.

De enkelte afdelinger indgår selv aftaler med deres lokale laboratorier om tagning af experimentelle blodprøver, opbevaring og forsendelse af disse, og betaler selv for disse ydelser. Beløbet per studiebesøg, hvor der indgår eksperimentelle blodprøver er forøget for at kompensere herfor, om end det ikke nødvendigvis dækker de fulde omkostninger. Beløbet, der udbetales for de kliniske besøg omfatter også alle øvrige udgifter i forbindelse med forsøget herunder aflønning af personale for selve besøget, initeringsmøde, modtagelse og håndtering af medicin mv.
MSD overfører alle beløb vedr. studiet til en forskningskonto på Glostrup Hospital. MSD overfører midlerne iht. en aftale vedr. datoer for opnåelse af "milestones". Mikkel Østergaard overfører

midler til de deltagende afdelingers forskningskontier. De deltagende afdelinger afregner selv med deres respektive laboratorier. De deltagende afdelinger får samlet udbetalt midler når den sidst inkluderede patient har gennemført sidste studiebesøg.

De deltagende afdelinger bidrager med medicin til de sidste 5 måneder i studiet.
Den forsøgsansvarlige modtager ikke vederlag for studiet.
Evt. overskydende beløb vil blive anvendt til dækning af andre udgifter i forbindelse med studiet herunder forsendelse af studiemedicin fra sponsor til investigator, løn til studentermedhjælp til fremstilling og fotokopiering af CRFer og TMFs mv. Desuden vil der formentlig være behov for yderligere midler til finaciering af biomarkørdelen af studiet.

[1] Til skrivning af protokol, udarbejdelse af eCRF og papir CRF, TMFs, initieringsmøder og løbende arbejde f.eks. kontakt til afdelingerne osv., beløbet svarer til ca. 1.7 måneds overenskomstmæssig løn).
[2]Indsamling af blodprøver, varetagelse af biobank.
[3]Besøg, hvor der tages eksperimentelle blodprøver.

Den forsøgsansvarlige og studiekoordinator har ingen privat eller økonomisk tilknytning til private virksomheder, fonde mv. som har interesser i det pågældende projekt.

23 VEDERLAG ELLER ANDRE YDELSER TIL FORSØGSPERSONER (SECTION IN DANISH)

Der ydes ikke vederlag eller andre ydelser til forsøgspersoner. Der ydes ikke transport godtgørelse eller tabt arbejdsfortjeneste.

24 PUBLIKATIONSPLAN (SECTION IN DANISH)

Det forventes muligt at indsende et abstrakt til European League Against Rheumatism (EULAR) kongressen i år 2018, og efterfølgende kongresser som f.eks. American College of Rheumatology (ACR). Hovedstudiet og delprojekter vil forsøges publiceret i velestimerede reumatologiske tidsskrifter som f.eks. Annals of the Rheumatic Diseases eller Arthritis and Rheumatism. Såvel positive, negative eller inkonklusive undersøgelsesresultater vil blive publiceret. Offentliggørelsen vil finde sted så hurtigt, som det er muligt, fagligt forsvarligt og i overensstemmelse med lov om behandling af personoplysninger. Såfremt studie ikke kan blive publiceret på anden vis, så vil det blive offentliggjort på anden vis enten via afdelingens hjemmeside eller www.clinicaltrials.gov.

25 RETNINGSLINJER FOR MEDFORFATTERSKAB (SECTION IN DANISH)

Projektets styregruppe består af studiekoordinator læge ph.d. Susanne Juhl Pedersen, professor Mikkel Østergaard og overlæge, ph.d. Inge Juul Sørensen, Reumatologisk Klinik, alle fra "Videncenter for Reumatologi og Rygsygdomme", Glostrup Hospital.
Manuskripter tilsigtes publiceret i engelsksprogede internationale tidsskrifter med medlemmer af styregruppen som første, anden og sidste forfattere, med mindre styregruppen internt har truffet beslutning om andet. De deltagende afdelinger opnår ét medforfatterskab for hver seks patienter, der gennemfører undersøgelsen, hvor medforfatteren yderligere deltager i analyser og diskussion af resultater samt artikelskrivning. Andre personer, som har ydet et stort bidrag, herunder mindst én repræsentant fra den deltagende radiologiske afdeling, kan være medforfattere. Ved uenighed træffes den endelige beslutning herom af styregruppen.

Oplæg til manuskripter vedrørende hovedstudiet udfærdiges af styregruppen i fællesskab, og de forelægges øvrige deltagere i projektet til kommentarer og revision.
Delprojekter og tillægsprojekter, der ikke er omfattet af indeværende protokol kan eventuelt analyseres af de for disse forsøg ansvarlige forskere og publiceres med disse forskere som førsteforfattere. Forinden skal der foreligge en skriftlig aftale mellem disse forskere og styregruppen. Øvrige forfatterskaber på del- og tillægsprojekter afhænger af tillægsprojektets karakter, men såfremt der anvendes kliniske data indsamlet af de deltagende afdelinger, vil disse blive kreditteret med medforfatterskab. Forfatterlisten skal beskrives i den omtalte skriftlige aftale og vil generelt, udover personer substantielt involveret i tillægsprojektet, omfatte de mest substantielt bidragende investigatorer i grundprojektet, herunder styregruppens medlemmer. Økonomiske sponsorer herunder MSD har ingen indflydelse på eller involvering i dataanalysen eller i udarbejdelsen af manuskripter herunder abstrakts. Økonomiske sponsorer vil i alle publikationer blive anerkendt for at have støttet forsøget.

26 APPENDICES

The file ”Andre relevante bilag” contains all appendices in relation to this protocol i.e.

27 RELEVANTE KLAUSULER I KONTRAKTEN MELLEM SPONSOR OG FORSØGSSTEDET (SECTION IN DANISH)

Udvalgte passager fra kontrakten mellem professor Mikkel Østergaard, Videncenter for Reumatologi og Rygsygdomme, Glostrup Hospital og MSD med relevans for Videnskabsetisk Komite er vedlagt følgebrevet.

References

28 FLOWCHART

Visit number	**S**	**1**	**2**	**3**	**4**	**5**	**6**	**E**
Week number	**-2#**	**0#**	**4***	**16***	**28**	**40**	**52**	
Allowed time shift (+/- days)	**14**	**0**	**3**	**7**	**10**	**10**	**10**	**7**
Screening for TNFα inhibitor eligibility								
Screening for TNFα inhibitor eligibility	X							
Quantiferon test for TB	X							
Chest X-ray (if older than 3 months)	X							
ECG	X							
Hepatitis B and C screening and HIV	X							
HCG (women only)	X							
Study related procedures								
Informed consent	X							
Clinical history incl. past medical and surgical history	X							
Inclusion and exclusion criteria	X	X						
Clinical procedures								
BAS questionnaire (pain, global, BASDAI, BASFI)	X	X	X	X	X	X	X	X
HAQ questionnaire (HAQ, pain, global)		X	X	X	X	X	X	X
Patient Acceptable Symptom State (PASS)		X	X	X			X	X
ASAS Health Index		X	X	X			X	X
Health-related Quality of Life (SF-36, 15D, EuroQol)		X	X	X			X	X
Questionnaires sleep, fatigue and depression		X	X	X			X	X
Questionnaires physical activity		X	X	X			X	X
BASMI incl. thorax expansion		X	X	X	X	X	X	X
Swollen/tender joint counts (66/68)		X	X	X	X	X	X	X
Enthesitis indices		X	X	X			X	X
Physician global		X	X	X	X	X	X	X
ASDAS		X	X	X	X	X	X	X
Detailed physical examination	X						X	X
Vital signs (blood pressure and hart rate)	X						X	X
Adverse event registration			X	X	X	X	X	X
Imaging procedures								
MRI scans of SI-joints and spine (whole-body, diffusion weighted, conventional)		X	X	X			X	
X-rays of SI-joints and spine		X					X	
Laboratory procedures								
HLA-B27	X							
ANA	X						X	
Routine blood tests	X	X	X	X	X	X	X	X
Urine	X	X	X					
Blood and urine samples to be stored (experimental biomarkers)		X	X	X			X	X

#Screening and week 0: The visits can be performed simultaneously if the patient has had a recent clinical examination and the screenings test have been checked before the MRI scans and X-rays are performed.

*Week 4 and 16: Injection with Golimumab not allowed before the examination program has been completed.

Patients will be asked to complete examination program, even if Golimumab therapy is stopped.

E: Exclusion visit to be performed, if possible before other therapies are initiated, in patients who are to be excluded of study.

29 APPENDICES

30 LÆGEMIDDELSTYRELSEN VURDERING AF FORSØGET

Fra: Zainab Nawar Ajina - 9154 [ZNA@DKMA.DK]
Sendt: 29. august 2013 08:21
Til: Susanne Juhl Pedersen
Emne: Vedr. forespørgsel om anmeldelsespligtigt forsøg

Kære Susanne Juhl Pedersen

Der skal hermed kvitteres for din mail af 19-08-2013, hvori der fremsendes projektbeskrivelse med henblik på vurdering af anmeldelsespligten.

Efter gennemlæsning af protokollen, "Improved monitoring and prediction of clinical response and disease course during Golimumab therapy of patients with axial spondyloarthritis: The clinical utility of whole-body MRI, diffusion-weighted MRI, conventional MRI of sacroiliac joints and spine, and high-sensitive CRP and other soluble biomarkers of joint inflammation and damage", kan det oplyses, at studiet **ikke** er vurderet til at være anmeldelsespligtigt efter Lægemiddelloven § 88, stk. 1 og skal derfor **ikke** anmeldes til Sundhedsstyrelsen.

Denne vurdering er baseret på, at forsøget har til formål undersøge **MR-scanningernes** evne til overvågning og forudsigelse af respons til Golimumab, dvs. der er tale om et observationsstudie med metodeudvikling og ikke en undersøgelse af Golimumabs effekt.

Den endelige afgørelse vedrørende projektet skal derfor gives af den Videnskabsetiske komité, hvilket De selv anmodes om at meddele komiteen.

For så vidt angår registrering og anden behandling af personoplysninger i undersøgelsen henviser vi til Datatilsynet, som fører tilsyn hermed.

Sagsnummer **2013082500** bedes meddelt ved en eventuel henvendelse.

Venlig hilsen

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Lægemiddeludvikling og -evaluering
Danish Health and Medicines Authority
Medicines Development and Clinical Trials
T +45 72 22 74 00
sst@sst.dk

31 SEARCH STRATEGY PUBMED

Performed July 2013

#1	SpA ord	"Spondylarthropathy OR spondylarthropathies OR spondyloarthr* OR spondylarthr* OR spondylitides OR ankylosing spondylitis OR bechterew OR bechterew* OR bekhterev OR Strumpell OR spondylitis OR Struempell OR ankylopoetica OR ankylopoietica" 29420 references
#2	MRI ord	"MRI OR magnetic resonance imaging" 363441 references
#3	Remission	107480 references
#4	Low disease activity	34264 references
#1 AND #2 AND #3		23 of which 2 are of relevance
#1 AND #2 AND #4		42 of which 4 are of relevance
#5	ASAS Health Index	44 references, none of relevance (abstracts containing the three words)
#6	Assessment of SpondyloArthritis International Society health index	8 references of which 1 is relevant
#7	BRAF-MDQ	3 references of which 0 is relevant (3 RA studies)
#8	Bristol Rheumatoid Arthritis Fatigue Scales	7 references of which 0 are relevant
#9	Patient Acceptable Symptom State	74 references of which 10 is about SpA or AS
#10	Sleep	128552 references
#11	infliximab OR adalimumab OR etanercept OR golimumab OR certolizumab pegol (i.e. TNFα inhibitors)	12770 references
#1 AND #10 AND #11		5 references of which 4 is relevant
#12	Pittsburgh Sleep Quality Index	1330 references
#1 AND #12		5 references of which 4 is of relevance
#1 AND #11 AND #12		0 references
#13	Fatigue "in title"	16383 references
#1 AND #13		44 references
#1 AND #11 AND #13		3 references, all relevant
#14	Multidimensional Fatigue Inventory	343 references
#1 AND #14		5 reference of which all are relevant
#1 AND #11 AND #14		0 references
#15	Center for Epidemiologic Studies Depression Scale	3896 references
#1 AND #15		3 references, none of relevance
#16	IL-6 OR IL6 OR interleukin 6 OR interleukin-6	79696 references
#1 OR #16		213 references
#1 OR #11 OR #16		31 references
#17	IL-22 OR IL22 OR interleukin 22 OR interleukin-22	1195 references
#1 OR #17		17 references
#1 OR #11 OR #17		1 references

#18 Interleukin 23 OR IL-23 OR IL23	3486 references
#1 OR #19	129 references
#1 OR #11 OR #19	7 references
#19 VEGF OR vascular endothelial growth factor	60404 references
#1 OR #19	43 references
#1 OR #11 OR #19	12 references
#20 CTX-II OR CTXII OR cross-linking telopeptide of type II collagen	193 references
#1 AND #20	6 references
#1 AND #11 AND #20	2 references
#21 MMP-3 OR "MMP 3" OR Metalloproteinase 3 OR Stromelysin 1	35905 references
#1 OR #21	82 references
#1 AND #11 AND #21	25 references
#22 DeoxyPYD	17887 references
#1 OR #22	19 references
#1 AND #11 AND #22	1 reference
#23 CTX-I OR CTXI OR telopeptide of type I collagen	2621 references
#1 OR #23	20 references
#1 AND #11 AND #23	5 references
#24 Osteocalcin OR OC	24795 references
#1 AND #24	55 references
#1 AND #11 AND #24	8 references
#25 Propeptide of type I procallagen OR PINP	1378 references
#1 AND #25	6 references
#1 AND #11 AND #25	2 references
#26 Sclerostin	489 references
#1 AND #26	12 references
#1 AND #11 AND #26	0 references
#27 Periostin	450 references
#1 AND #27	0 references
#28 Citrullinated vimentin	147 references
#1 AND #28	16 references
#1 AND #11 AND #28	1 reference

32 COPY OF PACKAGE LEAFLET

Indlægsseddel: Information til brugeren

Simponi® 50 mg injektionsvæske, opløsning i en fyldt pen
Golimumab

Læs denne indlægsseddel grundigt inden De begynder at tage dette lægemiddel, da den indeholder vigtige oplysninger.
- Gem indlægssedlen. De kan få brug for at læse den igen.
- Spørg lægen, apotekspersonalet eller sundhedspersonalet, hvis der er mere, De vil vide.
- Lægen har ordineret Simponi til Dem personligt. Lad derfor være med at give det til andre. Det kan være skadeligt for andre, selvom de har de samme sygdomstegn, som De har.
- Tal med lægen, apotekspersonalet eller sundhedspersonalet, hvis en bivirkning bliver værre, eller De får bivirkninger, som ikke er nævnt her.

Deres læge har også givet Dem et patientinformationskort, der indeholder informationer om sikkerhed, som De skal være opmærksom på før og under behandling med Simponi.

Oversigt over indlægssedlen:

1. Virkning og anvendelse

Simponi indeholder det aktive stof golimumab.

Simponi tilhører en medicingruppe kaldet "TNF-blokkere", som bruges til voksne til behandling af følgende betændelsessygdomme:
- Reumatoid artrit
- Psoriasisartrit
- Ankyloserende spondylit

Simponi virker ved at blokere virkningen af et protein, der hedder 'tumornekrosefaktor alfa' (TNF_{α}). Dette protein er involveret i kroppens betændelsesprocesser, og blokering af proteinet kan mindske betændelsen i Deres krop.

Reumatoid artrit
Reumatoid artrit (kronisk leddegigt) er en betændelsessygdom i leddene. Hvis De har aktiv reumatoid artrit, vil De i første omgang blive behandlet med andre lægemidler. Hvis De ikke reagerer godt nok på disse lægemidler, vil De få Simponi, som De skal tage sammen med et andet lægemiddel, der hedder methotrexat, for at:
- Reducere sygdomstegn og symptomer på Deres sygdom.
- Nedsætte hastigheden af beskadigelse af Deres knogler og led.

- Forbedre Deres fysiske funktionsevne.

Psoriasisartrit
Psoriasisartrit er en betændelsessygdom i leddene, almindeligvis ledsaget af psoriasis, som er en betændelsessygdom i huden. Hvis De har aktiv psoriasisartrit, vil De først få andre lægemidler. Hvis De ikke reagerer godt nok på disse lægemidler, vil De få Simponi for at:
- Reducere sygdomstegn og symptomer på Deres sygdom.
- Nedsætte hastigheden af beskadigelse af Deres knogler og led.
- Forbedre Deres fysiske funktionsevne.

Ankyloserende spondylit
Ankyloserende spondylit er en betændelsessygdom i rygraden. Hvis De lider af ankyloserende spondylit, vil De først få andre lægemidler. Hvis De ikke reagerer godt nok på disse lægemidler, vil De få Simponi for at:
- Reducere sygdomstegn og symptomer på Deres sygdom.
- Forbedre Deres fysiske funktionsevne.

2. Det skal De vide, før De begynder at tage Simponi

De må ikke tage Simponi:
- hvis De er overfølsom (allergisk) over for golimumab eller et af de øvrige indholdsstoffer i dette lægemiddel (anført under pkt. 6).
- hvis De har tuberkulose (TB) eller en anden alvorlig infektion.
- hvis De har hjertesvigt i moderat eller svær grad.

Hvis De er i tvivl, om noget af ovenstående gælder for Dem, så tal med Deres læge, apoteketspersonalet eller sundhedspersonalet, før De får Simponi.

Advarsler og forsigtighedsregler
Kontakt lægen, apoteket eller sundhedspersonalet, før De tager Simponi.

<u>Infektioner</u>
Fortæl straks Deres læge, hvis De har en infektion eller har symptomer på infektion under og efter behandling med Simponi. Tegn på infektion inkluderer feber, hoste, åndenød, influenzalignende symptomer, diarre, sår, tandproblemer eller en brændende smerte, når De lader vandet.
- De kan muligvis lettere få infektioner, når De er i behandling med Simponi.
- Disse infektioner kan udvikle sig hurtigere og være mere alvorlige end ellers. Derudover kan tidligere infektioner dukke op igen.

Tuberkulose (TB)
Fortæl det straks til Deres læge, hvis De får tegn på TB under eller efter behandlingen. Symptomer inkluderer vedvarende hoste, vægttab, træthedsfølelse, feber eller nattesved.
- Der er set tilfælde af TB hos patienter i behandling med Simponi, i sjældne tilfælde er TB også set hos patienter, som har været i behandling for TB. Lægen vil undersøge, om De har TB. Lægen vil notere disse undersøgelser på Deres patientinformationskort.
- Det er meget vigtigt, at De fortæller det til Deres læge, hvis De nogensinde har haft TB, eller hvis De har været i tæt kontakt med en person, som har eller har haft TB.
- Hvis Deres læge tror, at De har risiko for at få TB, kan De blive behandlet med lægemidler mod TB, inden De får Simponi.

Hepatitis B-virus (HBV)

- Inden De får Simponi, skal De fortælle Deres læge, hvis De er bærer af, eller hvis De har eller har haft HBV.
- Fortæl det til Deres læge, hvis De tror, at De har en risiko for at få HBV.
- Deres læge skal teste Dem for HBV.
- Behandling med TNF-blokkere, såsom Simponi, kan medføre, at HBV igen bliver aktiv hos patienter, som bærer denne virus. Dette kan i nogle tilfælde være livstruende.

Invasive svampeinfektioner
Fortæl det straks til Deres læge, hvis De har boet eller rejst i et område, hvor infektioner forårsaget af særlige svampetyper (kaldet histoplasmose, kokcidioidomykose eller blastomykose), som kan påvirke lungerne eller andre dele af kroppen, er almindelige. Spørg Deres læge, hvis De ikke ved, om disse infektioner er almindelige i det område, De har boet eller rejst i.

Kræft og lymfom
Fortæl det til Deres læge, før De får Simponi, hvis De har eller nogensinde har haft lymfom (en type blodkræft) eller enhver anden form for kræft.
- Behandling med Simponi eller andre TNF-blokkere kan øge Deres risiko for at udvikle lymfom eller anden form for kræft.
- Patienter med alvorlig reumatoid artrit og andre betændelsessygdomme, og som har haft sygdommen i lang tid, kan have en større risiko end gennemsnittet for at udvikle lymfom.
- Nogle børn og teenagere, som har fået TNF-blokkere, har udviklet kræft inklusive usædvanlige typer kræft, som i visse tilfælde har været dødelige.
- Patienter med svær vedvarende astma, kronisk obstruktiv lungesygdom (KOL), eller patienter som er storrygere, kan have øget risiko for kræft ved behandling med Simponi. Hvis De har svær astma, KOL eller er storryger, bør De tale med Deres læge, om hvorvidt TNF-blokkere er passende for Dem.
- Nogle patienter, der er blevet behandlet med golimumab, har udviklet visse former for hudkræft. Hvis der opstår forandringer i hudens udseende eller svulster på huden under eller efter behandlingen, skal De fortælle det til lægen.

Hjertesvigt
Fortæl det straks til Deres læge, hvis De får nye eller forværrede tegn på hjertesvigt. Symptomer på hjertesvigt inkluderer åndenød eller hævelse af fødderne.
- Nyt eller forværret hjertesvigt er set hos patienter i behandling med TNF-blokkere.
- Hvis De har mildt hjertesvigt, og De er i behandling med Simponi, skal De nøje overvåges af Deres læge.

Sygdom i nervesystemet
Fortæl det straks til Deres læge, hvis De nogensinde har haft eller udvikler symptomer på en demyeliniserende sygdom såsom multipel sklerose. Symptomer inkluderer synsændringer, muskelsvaghed i Deres arme eller ben eller følelsesløshed eller prikken et sted i kroppen. Deres læge skal vurdere, om De skal i behandling med Simponi.

Operationer eller tandbehandling
- Fortæl Deres læge, hvis De skal have foretaget en operation eller en tandbehandling.
- Fortæl kirurgen eller tandlægen, som foretager indgrebet, at De er i behandling med Simponi ved at vise dem patientinformationskortet.

Autoimmun sygdom
Fortæl det til Deres læge, hvis De udvikler symptomer på en sygdom kaldet lupus. Symptomer inkluderer vedvarende udslæt, feber, ledsmerter og træthed.

- I sjældne tilfælde har patienter behandlet med TNF-blokkere udviklet lupus.

Blodsygdomme
Hos nogle patienter kan kroppen ikke producere nok blodceller, som kan hjælpe med at bekæmpe infektioner eller hjælpe med at stoppe blødning. Kontakt straks Deres læge, hvis De udvikler feber, der ikke forsvinder, nemt får blå mærker, bløder eller ser meget bleg ud. Deres læge kan beslutte at stoppe behandlingen.

Hvis De er i tvivl, om noget af ovenstående passer på Dem, skal De tale med Deres læge eller apoteket, før De tager Simponi.

Vaccinationer
Tal med Deres læge, hvis De er blevet eller planlægger at blive vaccineret.
- De må ikke få visse (levende) vacciner, mens De er i behandling med Simponi.
- Visse vaccinationer kan forårsage infektioner. Hvis De var i behandling med Simponi, mens De var gravid, kan Deres barn have en øget risiko for at få en sådan infektion i op til ca. 6 måneder efter, De fik Deres sidste dosis under graviditeten. Det er vigtigt, at De fortæller barnets læge og andet sundhedspersonale om Deres behandling med Simponi, så de kan afgøre, hvornår Deres barn kan blive vaccineret.

Allergiske reaktioner
Fortæl det omgående til Deres læge, hvis De oplever symptomer på en allergisk reaktion efter De er startet i behandling med Simponi. Symptomer på en allergisk reakation kan være hævet ansigt, læber, mund eller hals, hvilket kan gøre det svært at synke eller trække vejret, hududslæt, nældefeber, hævede hænder, fødder eller ankler.
- Nogle af disse reaktioner kan være alvorlige eller i sjældne tilfælde, livstruende.
- Nogle af disse reaktioner forekom efter den første injektion af Simponi.

Børn og teenagere
Simponi frarådes til børn og unge (under 18 år), fordi det ikke er blevet undersøgt i denne aldersgruppe.

Brug af anden medicin sammen med Simponi
- Fortæl altid lægen eller på apoteket, hvis De bruger anden medicin eller har gjort det for nylig, herunder medicin til behandling af reumatoid artrit, psoriasisartrit eller ankyloserende spondylit.
- De må ikke tage Simponi sammen med lægemidler, der indeholder de aktive stoffer anakinra eller abatacept. Disse lægemidler anvendes til behandling af reumatoide sygdomme.
- Fortæl Deres læge eller apoteket, hvis De bruger anden medicin, der påvirker Deres immunsystem.
- De må ikke få visse (levende) vacciner, mens De tager Simponi.

Hvis De er i tvivl, om noget af ovenstående passer på Dem, skal De tale med Deres læge eller apoteket, før De tager Simponi.

Graviditet og amning
Tal med Deres læge, før De tager Simponi, hvis:
- De er gravid eller planlægger at blive gravid, mens De er i behandling med Simponi. Virkningen af dette lægemiddel er ukendt hos gravide. Simponi frarådes til gravide kvinder. De skal undgå at blive gravid ved at anvende sikker prævention, mens De er i behandling med Simponi og mindst 6 måneder efter den sidste Simponi-injektion.

- De har i sinde at amme Deres barn. Før De starter med at amme, skal det være mindst 6 måneder siden, De fik Deres sidste behandling med Simponi. De skal stoppe med at amme, hvis De skal i behandling med Simponi.
- De var i behandling med Simponi under Deres graviditet, da Deres barn kan have en øget risiko for at få en infektion. Det er vigtigt, at De fortæller barnets læge og andet sundhedspersonale om Deres behandling med Simponi, før barnet bliver vaccineret (se punktet om vaccination for mere information).

Hvis De er gravid eller ammer, har mistanke om, at De er gravid, eller planlægger at blive gravid, skal De spørge Deres læge eller apoteket til råds, før De tager dette lægemiddel.

Trafik- og arbejdssikkerhed
Simponi kan i mindre grad påvirke Deres evne til at køre bil og betjene værktøj eller maskiner. Der kan opstå svimmelhed, efter De har brugt Simponi. Hvis dette sker, må De ikke køre bil eller betjene nogen form for maskiner.

Simponi indeholder latex og sorbitol
Overfølsomhed over for latex
En del af den fyldte pen, beskyttelseshætten til nålen, indeholder latex. Tal med Deres læge inden De anvender Simponi, hvis De eller Deres hjælper/plejer er allergisk over for latex, da latex kan forårsage alvorlige allergiske reaktioner.

Sorbitol-intolerans
Simponi indeholder sorbitol (E420). Kontakt lægen, før De tager denne medicin, hvis lægen har fortalt Dem, at De ikke tåler visse sukkerarter.

3. Sådan skal De tage Simponi

Brug altid dette lægemiddel nøjagtigt efter lægens eller apotekspersonalets anvisning. Er De i tvivl, så spørg lægen eller på apoteket.

Den sædvanlige dosis
- Den anbefalede dosering er 50 mg (indholdet af 1 fyldt pen) en gang om måneden på den samme dag hver måned.
- Tal med Deres læge, før De tager den 4. dosis. Deres læge vil beslutte, om De skal fortsætte behandlingen med Simponi.
- Hvis De vejer mere end 100 kg, kan dosis øges til 100 mg (indholdet af 2 fyldte penne) en gang om måneden på den samme dag hver måned.

Sådan får De Simponi
- Simponi gives som indsprøjtning under huden (subkutant).
- I begyndelsen vil Deres læge eller sygeplejerske indsprøjte Simponi. De og Deres læge kan dog beslutte, at De selv kan indsprøjte Simponi. I dette tilfælde vil De blive trænet i, hvordan man selv indsprøjter Simponi.

Tal med Deres læge, hvis De har spørgsmål angående indsprøjtningerne. Der er en detaljeret "Brugsvejledning" i slutningen af denne indlægsseddel.

Hvis De har brugt for meget Simponi

Kontakt straks Deres læge eller apoteket, hvis De har brugt eller har fået for meget Simponi (enten ved at indsprøjte for meget en enkelt gang eller ved at indsprøjte for ofte). Tag altid den ydre karton med Dem, også selvom den er tom.

Hvis De har glemt at tage Simponi
Indsprøjt den glemte dosis, så snart De husker det, hvis De har glemt at tage Simponi på den planlagte dato.

De må ikke tage en dobbeltdosis som erstatning for den glemte dosis.

Hvornår skal den næste dosis indsprøjtes:
- Indsprøjt den glemte dosis hurtigst muligt og fortsæt Deres oprindelige plan, hvis De er mindre end 2 uger forsinket.
- Indsprøjt den glemte dosis hurtigst muligt og tal med Deres læge eller apoteket om hvornår De skal tage den næste dosis, hvis De er mere end 2 uger forsinket.

Spørg lægen eller på apoteket, hvis der er noget, De er i tvivl om.

Hvis De holder op med at tage Simponi
Tal med lægen eller apoteket hvis De overvejer at stoppe Simponi behandling.

Spørg lægen, på apoteket eller sundhedspersonalet, hvis De har yderligere spørgsmål om brugen af dette lægemiddel.

4. Bivirkninger

Dette lægemiddel kan som al anden medicin give bivirkninger, men ikke alle får bivirkninger. Nogle patienter kan få alvorlige bivirkninger, der skal behandles. Risikoen for at få visse bivirkninger er større ved en dosis på 100 mg sammenlignet med en dosis på 50 mg. Bivirkninger kan opstå i flere måneder efter sidste indsprøjtning.

Fortæl det straks til Deres læge, hvis De bemærker noget af følgende alvorlige bivirkninger med Simponi:
- **Allergiske reaktioner, der kan være alvorlige eller i sjældne tilfælde livstruende (sjælden).** Symptomer på en allergisk reaktion kan være hævelse af ansigt, læber, mund eller svælg, som kan forårsage besvær med at synke eller trække vejret, kløende udslæt, nældefeber, hævede hænder, fødder eller ankler. Nogle af disse reaktioner forekom efter første Simponi-dosis.
- **Alvorlige infektioner (inklusive TB, bakterieinfektioner, herunder alvorlige blodinfektioner og lungebetændelse, alvorlige svampeinfektioner og andre opportunistiske infektioner (ikke almindelige).** Symptomer på en infektion kan være feber, træthed, (vedvarende) hoste, åndenød, influenzalignende symptomer, vægttab, nattesved, diarré, sår, tandproblemer eller en brændende fornemmelse, når De lader vandet.
- **Tilbagevendende hepatitis B-infektion, hvis De er smittebærer af hepatitis B-virus eller tidligere har haft hepatitis B (sjælden).** Symptomerne kan være gulfarvning af hud og øjne, mørkebrun urin, smerte i højre side af maven, feber, kvalme og opkastning eller udpræget træthed.
- **Sygdom i nervesystemet såsom multipel sklerose (ikke almindelig).** Symptomer på sygdom i nervesystemet kan omfatte synsændringer, muskelsvaghed i arme eller ben, følelsesløshed eller prikken/snurren et eller andet sted på kroppen.

- **Kræft i lymfeknuderne (lymfom) (sjælden).** Symptomer på lymfom kan være hævede lymfeknuder, vægttab eller feber.
- **Hjertesvigt (ikke almindelig).** Symptomer på hjertesvigt kan være åndenød eller hævede fødder.
- **Tegn på en sygdom i immunsystemet, kaldet lupus (sjælden).** Symptomer kan være ledsmerter eller et udslæt på kinder eller arme, som er følsomt over for sol.
- **Blodsygdom.** Symptomer på blodsygdom kan være vedvarende feber, blå mærker, eller at De bløder meget nemt eller ser meget bleg ud.

Fortæl det straks til Deres læge, hvis De bemærker nogen af ovennævnte symptomer.

Følgende yderligere bivirkninger er observeret med Simponi:

Meget almindelige bivirkninger (kan forekomme hos flere end 1 ud af 10 patienter):
- Øvre luftvejsinfektioner (i næse, svælg og luftrør), ondt i halsen eller hæshed, løbende næse

Almindelige bivirkninger (kan forekomme hos mellem 1 og 10 ud af 100 patienter):
- Unormale levertal (stigning i leverenzymer) ved blodprøver, som tages af Deres læge
- Svimmelhed
- Hovedpine
- Overfladisk svampeinfektion
- Bakterielle infektioner (såsom betændelse i hudens bindevæv)
- Nedsat antal røde blodceller
- Positiv blodprøve for lupus
- Søvnbesvær
- Depression
- Forstoppelse
- Hårtab
- Allergiske reaktioner
- Udslæt og kløe på huden
- Fordøjelsesbesvær
- Mavesmerter
- Kvalme
- Følelsesløshed eller en prikkende følelse
- Influenza
- Bronkitis
- Bihulebetændelse
- Forkølelsessår
- Højt blodtryk
- Feber
- Reaktioner på indsprøjtningsstedet (inklusive rødme, hårdhed, smerte, blå mærker, kløe, prikken og irritation)
- Svaghedsfølelse
- Nedsat heling
- Ubehag i brystet

Ikke almindelige bivirkninger (kan forekomme hos mellem 1 og 10 ud af 1.000 patienter):
- Infektioner i led eller omkring liggende væv
- Nyreinfektioner
- Byld
- Kræft, inklusive hudkræft og ikke-kræftagtige svulster eller knuder, inklusive modermærker
- Psoriasis (også på håndflader og/eller fodsåler og/eller i form af blærer på huden)

- Lavt antal blodplader
- Lavt antal hvide blodceller
- Kombineret nedsat antal blodplader, røde og hvide blodceller
- Lidelser i skjoldbruskkirtlen
- Øget blodsukker
- Øget kolesteroltal
- Balanceforstyrrelser
- Smagsforstyrrelser
- Synsforstyrrelser
- Følelse af uregelmæssig hjerterytme
- Forsnævring af blodkar i hjertet
- Blodpropper
- Smerte og misfarvning af fingre og tæer
- Rødmen
- Astma, kortåndethed, hvæsen
- Mave- og tarmlidelser inkl. betændelse i mavens slimhinde og tyktarmen, som kan give feber
- Sure opstød
- Smerter og sår i munden
- Galdesten
- Leverlidelser
- Blærelidelser
- Brystlidelser
- Menstruationsforstyrrelser
- Knoglebrud
- Betændelse i blodkarrene i huden, hvilket resulterer i udslæt

Sjældne bivirkninger (kan forekomme hos mellem 1 og 10 ud af 10.000 patienter):
- Kronisk betændelsestilstand i lungerne
- Nyrelidelser
- Betændelse i blodkarrene i de indre organer
- Leukæmi
- Melanom (en type hudkræft)
- Grov afskalning af huden
- Immunsygdomme der kan påvirke lunger, hud og lymfekirtler (hyppigst visende sig som sarkoidose)

Bivirkninger med ukendt hyppighed:
- Knoglemarv der ikke kan producere blodceller
- Merkelcellekarcinom (en type hudkræft)

Tal med lægen, apotekspersonalet eller sundhedspersonalet, hvis De får bivirkninger, herunder bivirkninger, der ikke fremgår af denne indlægsseddel.

5. Opbevaring

- Opbevares utilgængeligt for børn.
- Brug ikke dette lægemiddel efter den udløbsdato, der står på etiketten og pakningen efter "EXP". Udløbsdatoen er den sidste dag i den nævnte måned.
- Opbevares i køleskab (2°C - 8°C). Må ikke nedfryses.
- Opbevar den fyldte pen i den ydre karton for at beskytte mod lys.

- Brug ikke dette lægemiddel, hvis De kan se, at væsken ikke er en klar til lys gullig farve, eller hvis den er grumset eller indeholder fremmede partikler.
- Spørg Deres læge eller på apoteket, hvordan De skal bortskaffe medicinrester. Af hensyn til miljøet må De ikke smide medicinrester i afløbet, toilettet eller skraldespanden.

6. Pakningsstørrelser og yderligere oplysninger

Simponi indeholder
Det aktive stof er: Golimumab. En 0,5 ml fyldt pen indeholder 50 mg golimumab.
De øvrige indholdsstoffer er: Sorbitol (E420), L-histidin, L-histidin monohydrochloridmonohydrat, polysorbat 80 og vand til injektionsvæsker.

Udseende og pakningsstørrelser
Simponi leveres som injektionsvæske i en fyldt pen til engangsbrug. Simponi er tilgængelig i en pakke indeholdende 1 fyldt pen og en multipakning indeholdende 3 (3 pakker a 1) fyldte penne.

Begge pakningsstørrelser er ikke nødvendigvis markedsført.

Opløsningen er klar til let opaliserende (en perlelignende glans), farveløs til lysegul og kan indeholde få, små halvgennemsigtige eller hvide partikler af protein. Anvend ikke Simponi hvis opløsningen er misfarvet, uklar eller hvis den indeholder fremmede partikler.

Indehaver af markedsføringstilladelsen og fremstiller
Janssen Biologics B.V.
Einsteinweg 101
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Hvis De vil have yderligere oplysninger om Simponi, skal De henvende Dem til den lokale repræsentant:

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Denne indlægsseddel blev senest ændret: Marts 2013

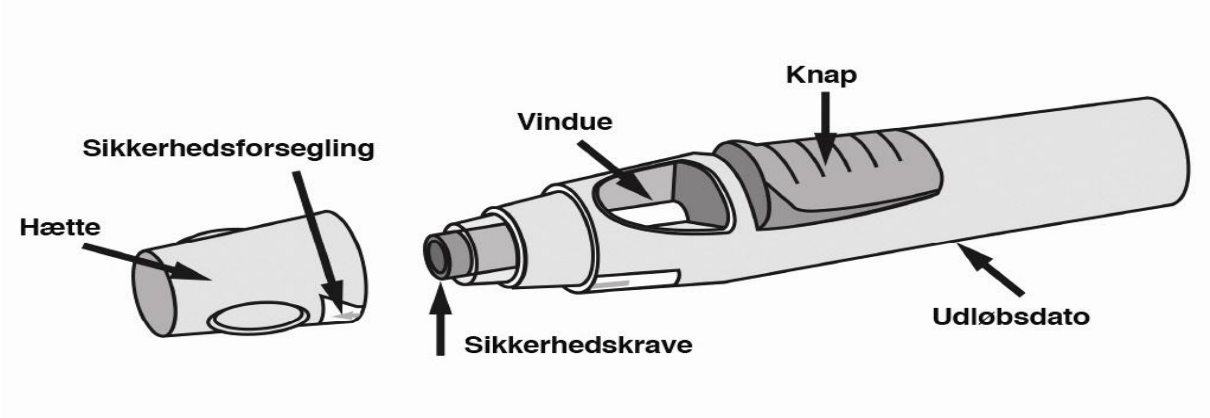
De kan finde yderligere information om dette lægemiddel på Det Europæiske Lægemiddelagenturs hjemmeside http://www.ema.europa.eu/.

BRUGSVEJLEDNING

Hvis De ønsker selv at indsprøjte Simponi, skal De først oplæres af sundhedsfagligt personale i, hvordan De forbereder og giver Dem selv indsprøjtningen. Kontakt Deres læge, sygeplejerske eller apoteket for at aftale en træningskonsultation, hvis De ikke er blevet oplært.

I denne brugsvejledning:
1. Forberedelse til anvendelse af pennen
2. Valg og forberedelse af indsprøjtningssted
3. Indsprøjtning af medicinen
4. Efter indsprøjtningen

Diagrammet nedenfor (se figur 1) viser, hvordan "SmartJect" fyldt pen ser ud. I denne pjece omtales "SmartJect" fyldt pen som "pen".



Figur 1

1. Forberedelse til anvendelse af pennen
- Ryst på intet tidspunkt pennen.
- Fjern ikke hætten fra pennen, før det er nødvendigt.

Tjek udløbsdato
- Tjek udløbsdato (angivet som "EXP") på pennen.
- De kan også tjekke udløbsdatoen på æsken.

Anvend ikke pennen, hvis udløbsdatoen er passeret. Udløbsdatoen er den sidste dag i den nævnte måned. Kontakt Deres læge eller apoteket.

Tjek sikkerhedsforsegling
- Tjek sikkerhedsforseglingen rundt om hætten på pennen.

Anvend ikke pennen, hvis forseglingen er brudt. Kontakt Deres læge eller apoteket.

Vent 30 minutter, så pennen opnår stuetemperatur
- Læg pennen ved stuetemperatur uden for æsken i 30 minutter utilgængeligt for børn for at sikre en ordentlig indsprøjtning.

Varm ikke pennen på andre måder (for eksempel må den ikke varmes i en mikrobølgeovn eller i varmt vand).
Fjern ikke pennens hætte, mens den får lov til at nå stuetemperatur.

Klargøring af resten af udstyret

Mens De venter, kan De klargøre resten af udstyret, som inkluderer en alkoholserviet, en vatrondel eller gaze og en nålebeholder.

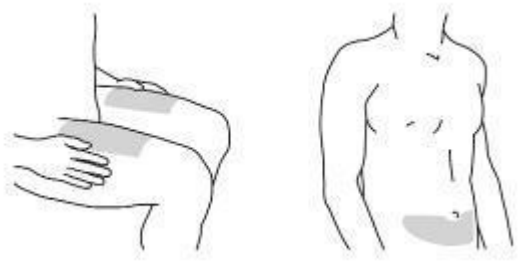
Tjek væsken i pennen

- Se igennem vinduet for at sikre, at væsken i pennen er klar til en anelse opaliserende (en perlelignende glans) og farveløs til lysegul. Injektionsvæsken kan benyttes, selv om den indeholder nogle få små, halvgennemsigtige eller hvide partikler af protein.
- De vil også bemærke en luftboble, hvilket er normalt.

Anvend ikke pennen, hvis injektionsvæsken har en forkert farve, er uklar eller indeholder fremmede partikler. Tal med Deres læge eller på apoteket, hvis dette sker.

2. Valg og forberedelse af indsprøjtningssted (se figur 2)

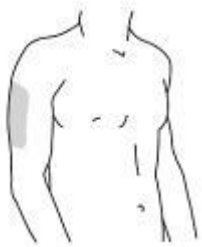
- De kan som regel indsprøjte medicinen på den øvre side af lårene.
- De kan også foretage indsprøjtningen på maven (abdomen) under navlen, undtagen i området ca. 5 cm lige under navlen.
- De må ikke indsprøjte i områder, hvor huden er øm, rød, skællet, hård, eller hvor der er blå mærker, ar eller strækmærker.



Figur 2

Valg af indsprøjtningssted for hjælpere/plejere (se figur 3)

- Hvis plejepersonale giver Dem indsprøjtningen, kan det ydre område af overarmen også anvendes.
- Alle de nævnte områder kan anvendes uanset Deres kropstype eller størrelse.



Figur 3

Forberedelse af indsprøjtningssted

- Vask hænderne grundigt med sæbe og varmt vand.
- Tør indsprøjtningsstedet med en alkoholserviet.
- Lad huden tørre inden injektion. Lad vær med at vifte eller blæse på det rene område.

Rør ikke dette område igen før indsprøjtningen gives.

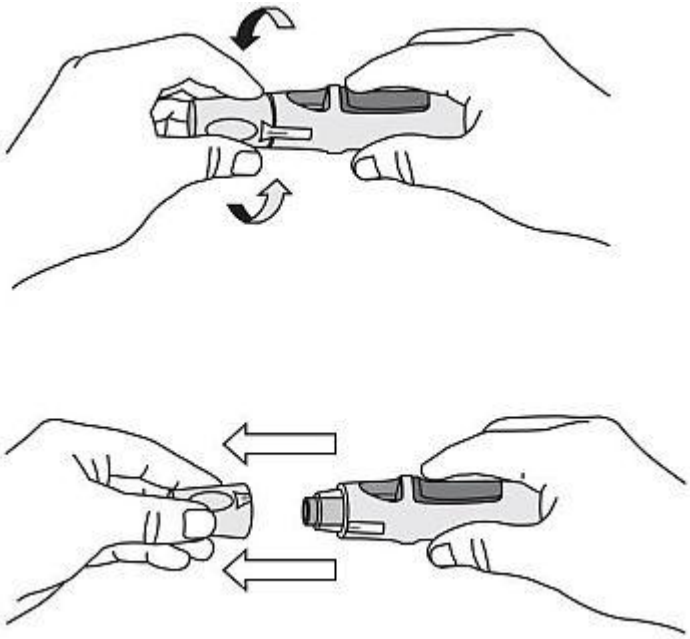
3. Indsprøjtning af medicinen

Hætten bør ikke fjernes, før De er klar til at indsprøjte medicinen. Medicinen skal indsprøjtes inden for 5 minutter efter, at hætten er fjernet.

Fjern hætten (figur 4)

- Når De er klar til at indsprøjte, skal De vride hætten en anelse, så sikkerhedsforseglingen brydes.
- Træk hætten af og smid den ud efter indsprøjtningen.

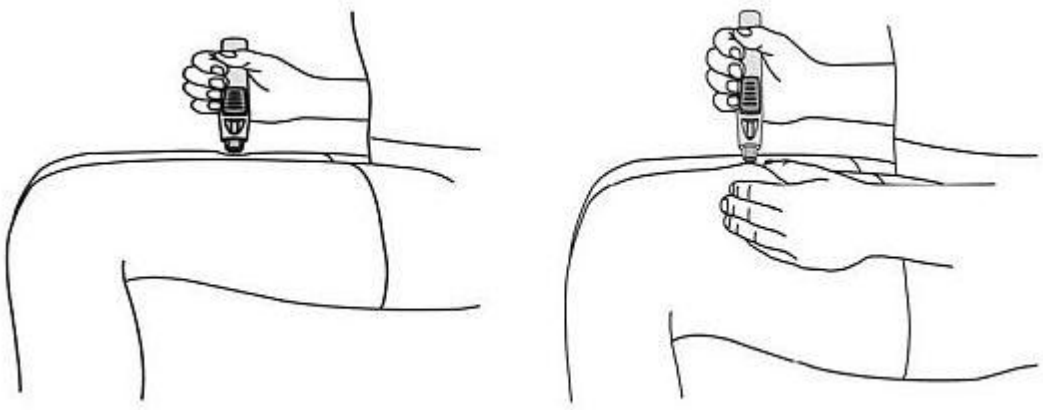
Sæt ikke hætten på igen, da den kan ødelægge nålen indeni pennen. Anvend ikke pennen hvis den tabes uden hætten. Kontakt Deres læge eller apoteket, hvis dette sker.



Figur 4

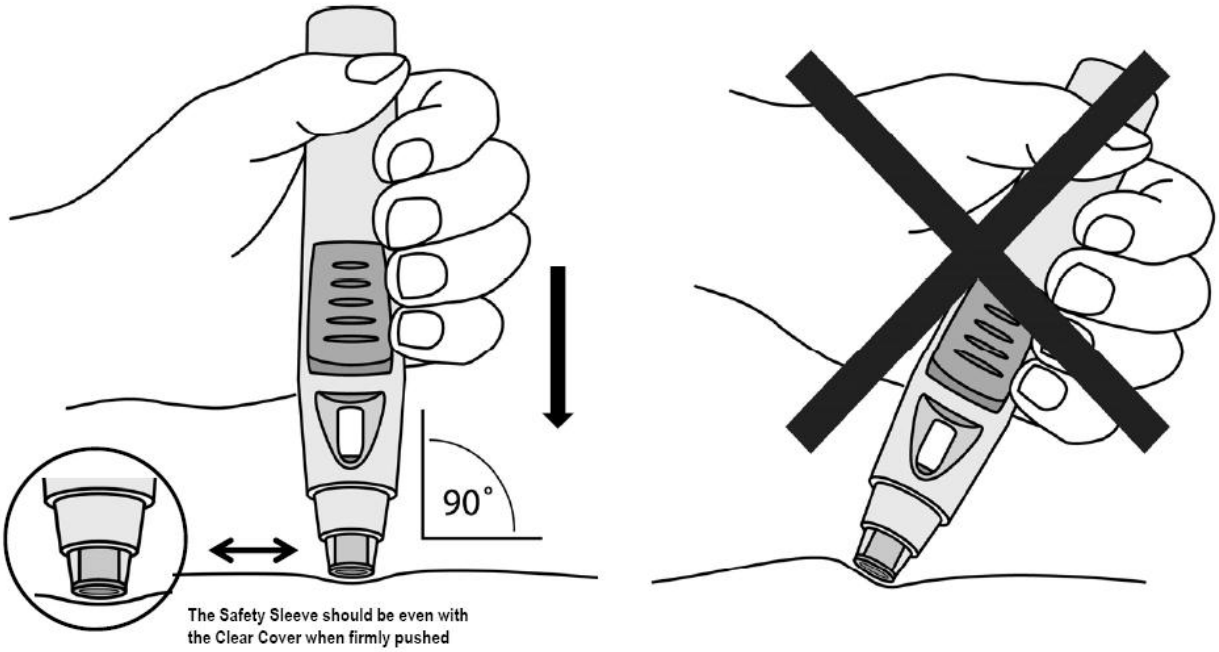
Pres pennen fast mod huden (se figur 5 og 6)

- Hold pennen behageligt i Deres hånd. Tryk **IKKE** på knappen endnu.
- De kan vælge mellem to injektionsmetoder. Det anbefales at foretage indsprøjtningen uden at klemme huden sammen (figur 5a). Men hvis De foretrækker det, kan De klemme huden sammen for at danne en fast overflade til indsprøjtningen (figur 5b).
- Pres den åbne ende af pennen fast mod huden i en ret vinkel (90 grader), indtil sikkerhedshætten glider helt ind i Clear Cover (figur 6).



Figur 5a

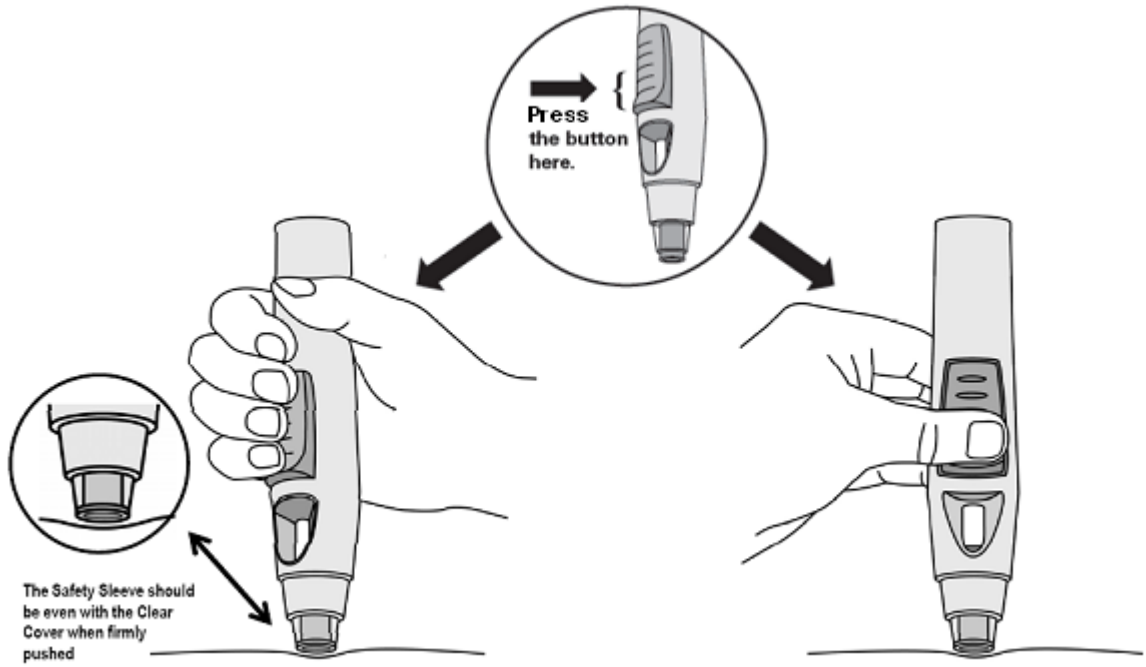
Figure 5b



Figur 6

Tryk på knappen for indsprøjtning (se figur 7)

- **Bliv ved med at presse pennen mod Deres hud og tryk på knappen med Deres fingre eller tommelfinger.** De vil ikke kunne trykke knappen ind, medmindre pennen er **presset fast mod huden,** og sikkerhedshætten glider ind i Clear Cover.
- Så snart knappen er trykket ind, vil den forblive inde, så det er ikke nødvendigt fortsat at trykke på den.



Figur 7

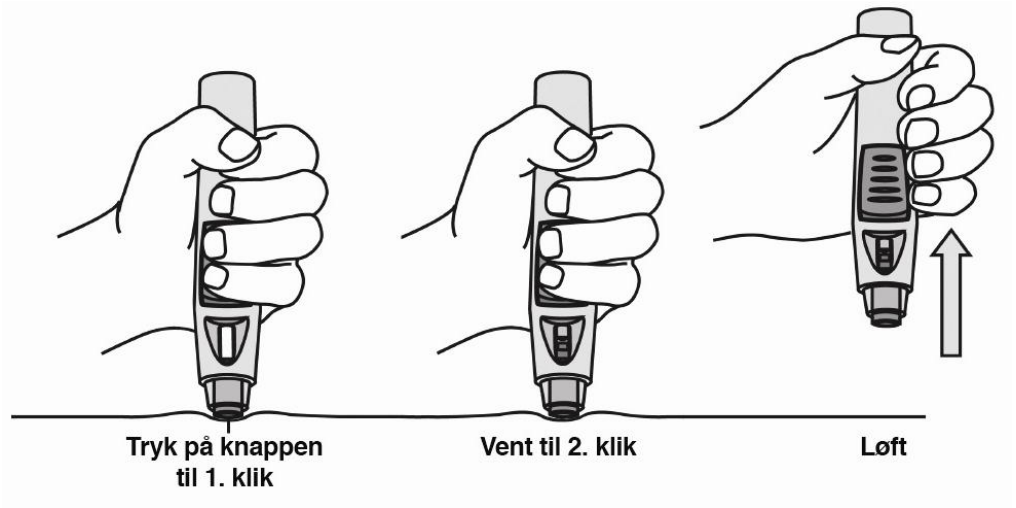
- **De vil høre et "klik" – bliv ikke urolig.** Det første "klik" betyder, at nålen er ført ind, og indsprøjtningen er startet. De vil muligvis mærke et nålestik.

Løft ikke pennen væk fra huden. Hvis pennen løftes fra huden, vil De muligvis ikke få fuld dosis.

Fortsæt med at holde indtil det andet "klik" (se figur 8)

- **Fortsæt med at holde pennen fast mod huden, indtil De hører et nyt "klik". Det varer som regel 3-6 sekunder, men det kan tage op til 15 sekunder, før De hører det andet "klik".**
- Det andet "klik" betyder, at indsprøjtningen er færdig, og at nålen igen er tilbage i pennen.
- Løft pennen fra indsprøjtningsområdet.

Tæl 15 sekunder fra tidspunktet De trykker på knappen, til De løfter pennen fra indsprøjtningsområdet, hvis De er hørehæmmet.



Figur 8

4. Efter indsprøjtningen

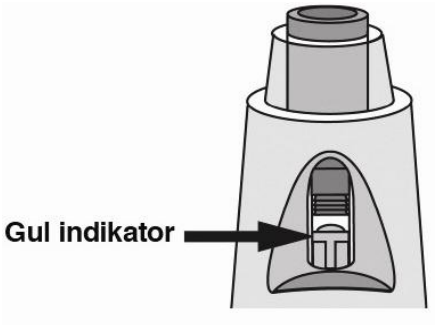
Anvend vatrondel eller gaze

- Der kan være en smule blod eller væske ved indsprøjtningsområdet. Dette er normalt.
- De kan presse en vatrondel eller gaze på indsprøjtningsområdet i 10 sekunder.
- Hvis det er nødvendigt, kan De dække indsprøjtningsområdet med et lille stykke plaster.

Gnid ikke på huden.

Tjek vinduet - en gul indikator bekræfter rigtig håndtering (se figur 9)

Tal med Deres læge eller apoteket, hvis den gule indikator ikke er synlig i vinduet, eller hvis De har mistanke om, at De ikke har fået den fulde dosis. Tag ikke en ny dosis uden at have spurgt Deres læge.

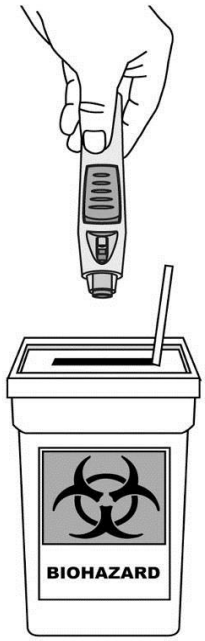


Figur 9

Smid pennen væk (se figur 10)

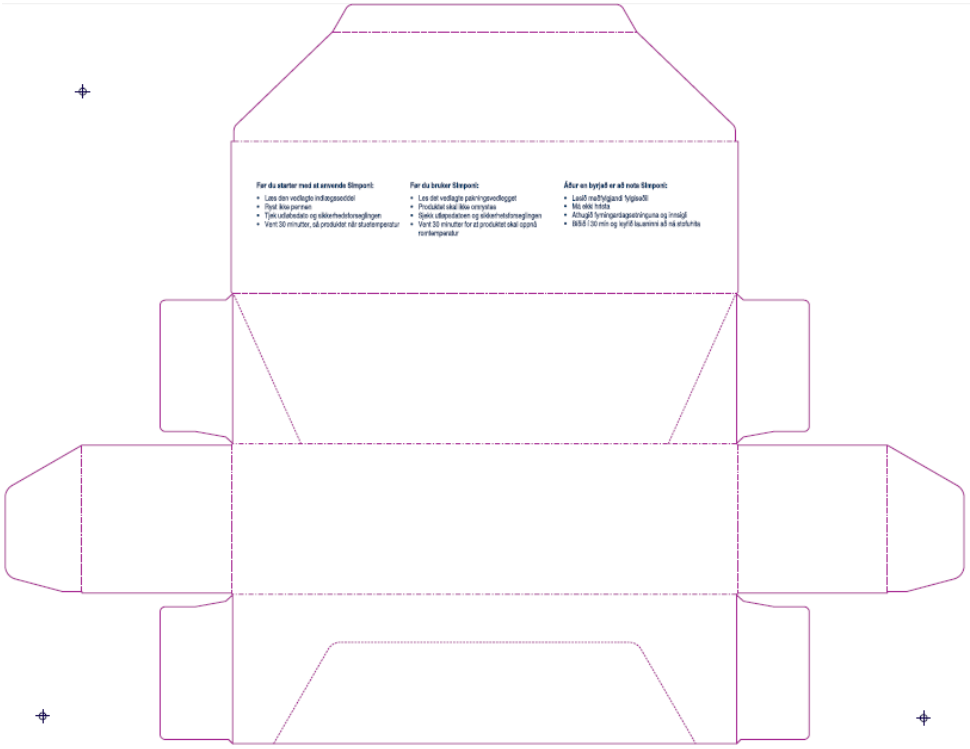
- Læg straks pennen i en nålebeholder. Sørg for at De skaffer Dem af med beholderen som instrueret af Deres læge eller sygeplejerske.

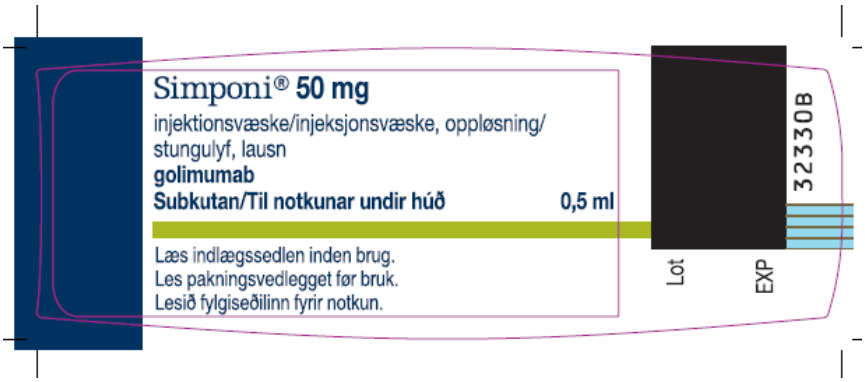
Tal med Deres læge eller apoteket, hvis De føler eller er usikker på, at der er noget der er gået galt med indsprøjtningen.



Figur 10

33 COPY OF IMP PACKAGE





34 LABEL ON PACKAGE

Sponsor Professor Mikkel Østergaard, Videncenter for Reumatologi og Rygsygdomme VRR, Glostrup Hospital. Tlf.: XXXXXXXX.
Investigator initieret forsøg.

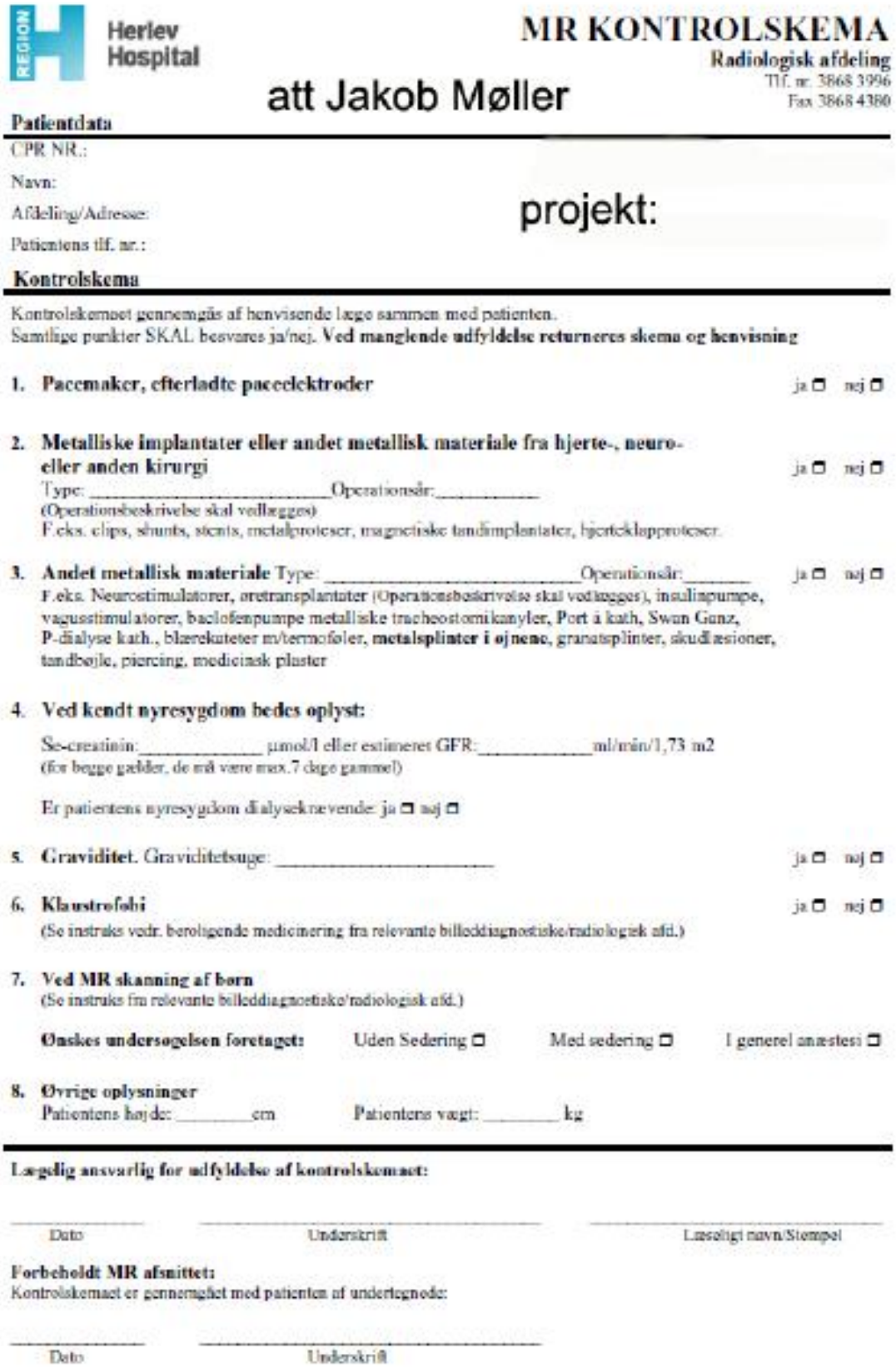
Initialer:_____ CRF nr.:_____

Dato for udlevering:_____
Skal ingives som anført på æsken.
Kun til brug i klinisk forsøg MANGO (H-1-2013-118)

35 PATIENT CARD

FORSØGSDELTAGER ID-KORT I nødstilfælde kontakt: Overlæge, Hospital Afdeling Gadenavn, nr., postnr. og by Tlf. (eller vagthavende) Protokol: MANGO (H-1-2013-118) Forsøgsdeltagernummer: _____ **Sponsor: Mikkel Østergaard, Glostrup Hospital, Tlf. 3863 3863 (dagtid)**	**DE BEDES VENLIGST BÆRE DETTE KORT PÅ DEM DØGNET RUNDT UNDER DIN DELTAGELSE I MANGE STUDIET** Forsøgsmedicinen er Golimumab (Simponi) 50 mg/0.5 ml, der injiceres subkutant en gang månedlig (på den samme dato). Forsøgspersonen har rygsøjlegigt. I tilfælde af problemer eller forespørgsler, kontakt venligst lægen, angivet på forsiden af dette kort.
Subject Identification Card In case of emergency please contact: Doctor, Investigator Hospital name Department name Address Telephone Protocol: MANGO (H-1-2013-118) Subject identification number: _____ **Sponsor: Mikkel Østergaard, Glostrup Hospital, Tlf. 3863 3863 (dagtid)**	**PLEASE CARRY THIS CARD AT ALL TIMES DURING THE MANGO STUDY** The investigational medicinal product is Golimumab (Simponi) 50 mg/0.5 ml, which is injected subcutanously every month (on the same date). The subject suffers from axial spondyloarthritis. Any problems or queries should be referred to the investigator contact name at the front page of this card.

36 CONTRAINDICATIONS MRI



Herlev Hospital

MR KONTROLSKEMA

Radiologisk afdeling
Tlf. nr. 3868 3996
Fax 3868 4380

att Jakob Møller

projekt:

Patientdata

CPR NR.:

Navn:

Afdeling/Adresse:

Patientens tlf. nr.:

Kontrolskema

Kontrolskemaet gennemgås af henvisende læge sammen med patienten.
Samtlige punkter SKAL besvares ja/nej. **Ved manglende udfyldelse returneres skema og henvisning**

1. **Pacemaker, efterladte paceelektroder** ja ☐ nej ☐

2. **Metalliske implantater eller andet metallisk materiale fra hjerte-, neuro- eller anden kirurgi** ja ☐ nej ☐
   Type: _____Operationsår:_____
   (Operationsbeskrivelse skal vedlægges)
   F.eks. clips, shunts, stents, metalproteser, magnetiske tandimplantater, hjerteklapproteser.

3. **Andet metallisk materiale** Type: _____Operationsår:_____ ja ☐ nej ☐
   F.eks. Neurostimulatorer, øretransplantater (Operationsbeskrivelse skal vedlægges), insulinpumpe, vagusstimulatorer, baclofenpumpe metalliske tracheostomikanyler, Port à kath, Swan Ganz, P-dialyse kath., blærekuteter m/termoføler, **metalsplinter i øjnene**, granatsplinter, skudlæsioner, tandbøjle, piercing, medicinsk plaster

4. **Ved kendt nyresygdom bedes oplyst:**
   Se-creatinin:_____ µmol/l eller estimeret GFR:_____ml/min/1,73 m2
   (for begge gælder, de må være max.7 dage gammel)

   Er patientens nyresygdom dialysekrævende: ja ☐ nej ☐

5. **Graviditet.** Graviditetsuge: _____ ja ☐ nej ☐

6. **Klaustrofobi** ja ☐ nej ☐
   (Se instruks vedr. beroligende medicinering fra relevante billeddiagnostiske/radiologisk afd.)

7. **Ved MR skanning af børn**
   (Se instruks fra relevante billeddiagnostiske/radiologisk afd.)

   Ønskes undersøgelsen foretaget: Uden Sedering ☐ Med sedering ☐ I generel anæstesi ☐

8. **Øvrige oplysninger**
   Patientens højde: _____cm Patientens vægt: _____ kg

Lægelig ansvarlig for udfyldelse af kontrolskemaet:

_____ _____ _____
Dato Underskrift Læsetigt navn/Stempel

Forbeholdt MR afsnittet:
Kontrolskemaet er gennemgået med patienten af undertegnede:

_____ _____
Dato Underskrift

37 ASAS KRITERIERNE FOR AKSIAL SPONDYLARTRITIS

ASAS 2009 kriterierne for spondylartritis omfatter såvel patienter med som uden sikre radiologiske tegn på sacroilitis. I henhold til kriterierne vil en patient med kroniske rygsmerter (varighed >3 mdr.) og smertedebut <45 års alderen blive klassificeret ved tilstedeværelse af:

1) sacroilitis (enten sikker tilstedeværelsen på konventionel røntgenoptagelse af sacroiliacaled eller ved aktive inflammatoriske forandringer på MRI, der er forenelig med SpA) og opfyldelse af 1 klinisk kriterium
2) HLA-B27 positiv vævstype og opfyldelse af 2 kliniske kriterier

Kliniske kriterier	**Definition**
Inflammatoriske rygsmerter (IBP)	Inflammatoriske rygsmerter vurderet af en ekspert. Mindst 4 af 5 af følgende skal være opfyldt: Debutalder <45 år, 2. "Snigende" debut, 3. Lindring ved fysisk aktivitet, 4. Ingen lindring i hvile, 5. Natlige smerter (der mindskes når patienten er stået op)
Arthritis	Tidligere eller nuværende aktiv synovitis diagnosticeret af læge
Enthesitis (hæl)	Hæl enthesitis: Tidligere eller nuværende spontan smerte eller ømhed hvor Achillessene eller fascia plantaris insererer på calcaneus
Uveitis	Tidligere eller nuværende uveitis anterior diagnosticeret af øjenlæge
Dactylitis	Tidligere eller nuværende dactylitis diagnosticeret ved læge
Psoriasis	Tidligere eller nuværende psoriasis diagnosticeret ved læge
Inflammatorisk tarmsygdom	Tidligere eller nuværende Crohn's sygdom eller colitis ulcerative diagnosticeret ved læge
God effekt af NSAID	24-48 timer efter en fuld dosis NSAID er rygsmerterne enten forbedret eller helt forsvundet
Dispositioner til SpA	Tilstedeværelse af en af følgende: a) Ankyloserende spondylitis b) Psoriasis c) Akut anterior uveitis d) Reaktiv arthritis e) Inflammatorisk tarmsygdom hos førstegradsslægtninge (mor, far, søstre, brødre, børn) eller andengrads slægtninge (bedsteforældre, forældres søskende, fætter, kusine)
Forhøjet CRP	C-reaktiv protein koncentration over øvre normal grænse efter at andre årsager hertil udelukket
HLA-B27	Positiv test i henhold til standard laboratorie teknikker
Sacroiliitis på konvnetionel røntgenundersøgelse	Bilateral grad 2-4 eller unilateral grad 3-4 sacroiliitis på konventionel røntgenundersøgelse i henhold til de modificerede New York kriterier
Sacroiliitis på MRI	Aktive inflammatoriske forandringer i sacroiliacaled med sikker knoglemarvsødem/osteitis forenelig med SpA

38 LABORATORIEMANUAL FOR MANGO STUDIET

Videnskabeligt studie af nye MR- og biokemiske metoder til af følge og forudsige klinisk respons og sygdomsforløb hos patienter med rygsøjlegigt der påbegynder behandling med Golimumab

Udarbejdet af:
Læge, ph.d. Susanne Juhl Pedersen og forskningsbioanalytiker, Teresa Rozenfeld, Videncenter for Reumatologi og Rygsygdomme, Glostrup Hospital

Formål
Studiet har til formål at undersøge om nye typer af MR-skanning og cirkulerende biomarkører for inflammation, brusk-, bindevævs- og knogleomsætning kan anvendes til at forudsige klinisk behandlingsrespons og sygdomsforløb hos patienter med rygsøjlegigt (axial spondylartritis herunder Mb. Bechterew og visse former for psoriasisgigt).

Hyppighed
Patienten afgiver blod-og urinprøver til forsøget 7 gange over 52 uger, såfremt de gennemfører studiet. Ved alle besøg tages rutineprøver. Ved 4 af de 6 besøg (uge 0, 4, 16 og 52) tages desuden blod- og urinprøver til senere analyse af eksperimentelle biomarkører.
Rutinekontrolblodprøver: Hæmoglobin, CRP, leukocytter inkl. differentialtælling, trombocytter, albumin, ALAT eller ASAT, LDH, alkalisk phosphatase, kreatinin. Desuden foretages der ved uge 0 og 52 analyse af ANA.

Patienten vil blive bedt om at afgive projektblod- og urinprøver på følgende tider:

Besøg 1 (uge 0)	Rutineblodprøver og eksperimentelle blod- og urinprøver
Besøg 2 (uge 4)	Rutineblodprøver og eksperimentelle blod- og urinprøver
Besøg 3 (uge 16)	Rutineblodprøver og eksperimentelle blod- og urinprøver
Besøg 4 (uge 28)	Rutineblodprøver
Besøg 5 (uge 40)	Rutineblodprøver
Besøg 6 (uge 52)	Rutineblodprøver og eksperimentelle blod- og urinprøver
Besøg 7 Eksklusionsbesøg	Rutineblodprøver og eksperimentelle blod- og urinprøver

De undersøgelser, der er angivet i denne laboratorievejledning for ”Eksklusionsbesøg” udføres hurtigst muligt efter eksklusion ("eksklusionsbesøg").

Anvendelse
Blod- og urinprøverne mærkes og opbevares i pseudo-anonymiseret form. Anvendelse kan kun ske efter godkendelse fra MANGO-styregruppen. Anvendelse af prøvematerialet til undersøgelser for specifikke biomarkører skal godkendes af Videnskabsetiske Komité.

Blod- og urinprøver
Den afgivne mængde blod til eksperimentelle biomarkører per gang er 58 ml fraset ved besøg 1, hvor der vil blive udtaget 76 ml. Den afgivne mænge urin er 10 ml. Patienten er ikke fastende.

Der tages følgende projektrelaterede blodprøver (fra perifer vene)
a) 2 x 9 ml blod i tørglas til serum
b) 3 x 6 ml blod i EDTA glas til EDTA-plasma
c) 1 x 9 ml blod i citrat glas til citrat-plasma
d) 2 x 4 ml blod i heparin glas til heparin-plasma
e) 5 ml fuldblod fordeles i to PAXgene RNA-rør
f) kun ved "Besøg 1" 3 x 6 ml fuldblod i EDTA glas.
g) 10 ml urin.

Der udfyldes MANGO flow-skema ved hvert besøg (se nedenfor).

Mærkning
Alle fryserør skal mærkes med **MANGO**, hospitalsnavn, patient nr., patient-initialer, visit nr., dato (dag-måned-årstal) og hvad rørene indeholder (serum, EDTA-plasma, citrat-plasma, heparin-plasma, fuldblod, buffy coat, urin, PAXgene RNA). Det er ikke et krav, at der anvendes farvekoder på rørene. Der anvendes fortrykte mærkater, således, at der kun skal anføres dato (dato-måned-årstal) med hånden (brug vandbestandig tusch eller kuglepen). Etiketterne fremstilles på de enkelte centre efter elektronisk "master". Prøverne vil på senere aftalte tidspunkter blive transporteret til de laboratorier, der skal foretage de enkelte analyser.

Pakning
Cryorørenes position i fryseæskerne noteres på flowskemaet. F.eks. K1, P1-5, hvor "K1" angiver kasse nr. 1 og "P1-5" beskriver position 1-5. Hver fryseæske mærkes med **MANGO**, hospitals navn, patient nr., patient-initialer, kasse nr. og materiale (mærkes på låg (nederste venstre hjørne), på siden af låg (nederste venstre hjørne) og på kassen (nederste venstre hjørne).
Blodprøver (dvs. serum, EDTA-, citrat- og heparin plasma samt buffy coat) fra hver patient gemmes samlet i en kasse (dvs. blodprøver fra kun en patient i en kasse).
Paxgene RNA rør opbevares i separate kasser, alle patienter i en kasse.
Urin opbevares i separate kasser, alle patienter i en kasse. Fryses ubehandlet ved –20^{o}C.
Fuldblod fra "Besøg 1" opbevares ubehandlet i separate kasser ved –20^{o}C (alle patienter i en kasse).

MANGO flow-skema: Blod- og urinprøver

Hospital:_____; Patient nr.:_____; Patient initialer:_____

Måned	**0**	**4**	**16**	**52**	**Eksklusion**
Visit	**1**	**2**	**3**	**6**	**7**
Dato for blodprøvetagning					
2 x 9 ml blod i tørglas til serum. Fordeles i 5 stk Cryorør rør. **RØD**					
3 x 6 ml blod i EDTA-glas til EDTA plasma. Fordeles i 5 stk. Cryorør. **BLÅ**					
9 ml blod i Na-Citrat-glas 3,2 % til CITRAT plasma. Fordeles i 3 stk. Cryorør. **HVID**					
2 x 4 ml blod i LH-Heparin-glas til HEPARIN plasma. Fordeles i 3 stk. Cryorør. **GRØN**					
Buffycoat fra EDTA glas. Fordeles i 3 stk. Cryorør rør. **GUL**					
5 ml blod fordeles i 2 Paxgene RNA-rør					
3 x 6 ml EDTA-glas til fuldblod					
Urin 10 ml					
Tidspunkt for urinafgivelse					
Signatur					

MANGO Håndtering af blodprøver for projekt

VIGTIGT: Prioritering af glas: **LILLA** EDTA glas – **RØDT** tørglas – **PAXgene** rør – **BLÅT** citrat glas – **GRØNT** Li-heparin glas

OPSAMLING ALLE BESØG	2 x 9 ml **RØDT** TØRGLAS	3 x 6 ml **LILLA** EDTA GLAS (**Ekstra 3 X 6 ML ved BESØG 1)**	**BUFFY COAT** (Brug glassene fra EDTA-plasma rørene)	9 ml **BLÅT Na-**CITRAT 3,2 % GLAS	2 x 4 ml **GRØNT** Lithium-HEPARIN GLAS	**2 X PAX-gene RNA RØR**	3 x 6 ml LILLA EDTA GLAS (**KUN BESØG 1)**	Urin 10 ml i 10 ml rør
PREPARERING	Henstår mindst 30 min. og max. 2 timer Centrifugeres ved 2330g 10 min 4° C Serum, undtagen det nederste ca. 5 mm serumlag over cellelag overføres til 5 x cryorør med **rødt** låg minimum 500 µl	Henstår mindst 30 min. og max. 2 timer Centrifugeres ved 2330g 10 min 4° C Fjern plasma til ca. 5 mm over cellelag. Plasma overføres til 5 x cryorør med **blåt** låg minimum 500 µl **<u>Gem rør til Buffy coat</u>**	Tag alle de hvide blodlegemer fra 1 glas og kom dem i 1 cryorør med **gult** låg 1 glas = 1 cryorør Så man i alt har 3 cryorør.	Henstår mindst 30 min. og max. 2 timer Centrifugeres ved 2330g 10 min 4° C Plasma overføres til 3 x cryorør med **<u>hvidt</u>** låg minimum 500 µl	Henstår mindst 30 min. og max. 2 timer Centrifugeres ved 2330g 10 min 4° C Plasma overføres til 3 x cryorør med **grønt** låg minimum 500 µl	Vendes **STRAKS** 10 gange efter blodprøvetagningen. Henstår i 2-24 timer ved stue tempe-ratur. Vendes godt inden røret fryses.		
OPBEVARING	-80°C fryser					Fryses ved -20°C i 24-72 timer. Derefter flyttes glasset over til -80°C fryser.	Fryses ved -20°C	

DATO NOTERES I FLOWSKEMA + ANTAL AF RØR

PLACERING AF RØR, SE NEDENSTÅENDE

73	**74**	**75**	**76**	**77**	**78**	**79**	**80**	**81**
64	**65**	**66**	**67**	**68**	**69**	**70**	**71**	**72**
55	**56**	**57**	**58**	**59**	**60**	**61**	**62**	**63**
46	**47**	**48**	**49**	**50**	**51**	**52**	**53**	**54**
37	**38**	**39**	**40**	**41**	**42**	**43**	**44**	**45**
28	**29**	**30**	**31**	**32**	**33**	**34**	**35**	**36**
19	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**
10	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**
1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**

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