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Study protocol: COmparison of the effect of treatment with NSAIDs added to anti-TNF therapy versus anti-TNF therapy alone on progression of StrUctural damage in the spine over two years in patients with ankylosing spondylitis (CONSUL) – a randomized controlled multicenter trial

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Manuscripts

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5 **Study protocol: COmparison of the effect of treatment with NSAIDs**
6 **added to anti-TNF therapy versus anti-TNF therapy alone on**
7 **progression of StrUctural damage in the spine over two years in**
8 **patients with ankylosing spondylitis (CONSUL) – a randomized**
9 **controlled multicenter trial**
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3 **Introduction:** There is some evidence that NSAIDs, in particular Celecoxib, might
4 possess not only a symptomatic efficacy but also disease modifying properties in AS,
5 retarding the progression of structural damage in the spine if taken continuously. In
6 contrast this could not been proven for TNF-inhibitors, despite their good clinical
7 efficacy on inflammatory aspects, pain and physical-function. The impact of a
8 combined therapy (a TNF-inhibitor plus an NSAID) on radiographic spinal
9 progression in AS remains unclear.
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11 **Methods and analysis:** The aim of this prospective, randomized, controlled
12 multicentre clinical trial is to evaluate the impact of treatment with an NSAID
13 (Celecoxib) when added to a TNF-inhibitor (Golimumab) as compared to TNF-
14 inhibitor (Golimumab) alone on progression of structural damage in the spine over
15 two years in patients with AS. The study consists of a 6-week screening period, a 12-
16 week period (Phase I: Run-in Phase) of treatment with Golimumab for all subjects
17 followed by a 96-week controlled treatment period (Phase II: Core-Phase) with
18 Golimumab plus Celecoxib versus Golimumab alone, and a safety follow-up period of
19 4 weeks. At week 108 the primary study endpoint (radiographic spinal progression as
20 assessed by the modified Stoke Ankylosing Spondylitis Spine Score – mSASSS) will
21 be evaluated.
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23 **Ethics and dissemination:** The study will be performed according to the ICH / GCP
24 guidelines and the German drug law. The written approval of the Central
25 Independent Ethics Committee, the German federal authority and the local Ethics
26 Committees of the study centres have been obtained. Study results upon study
27 completion are expected to be published in a peer-reviewed journal.
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29 **Registration details:** ClinicalTrials.gov ID: NCT02758782, EudraCT Number: 2016-
30 000615-33.
31

32 **Funding:** This work is supported by the German Federal Ministry of Education and
33 Research (BMBF), Grant No. FKZ 01KG1603. MSD Sharp & Dohme GmbH provides
34 the study drug Golimumab and financial support of the MRI sub-study.
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Article summary

Strengths and limitations of this study

Strengths:

- There is no treatment with proven efficacy against radiographic spinal progression in ankylosing spondylitis
- The effect of a combination of a TNF Blocker with an NSAID on radiographic spinal progression in ankylosing spondylitis has never been investigated so far
- multicentre, randomized, controlled, prospective design;
- Patient population consists of patients at high risk of radiographic spinal progression.

Limitations:

- Study is conducted only in one country (Germany) and the intervention is not masked / blinded and is taking place in a highly selected patient population.

Introduction

Ankylosing spondylitis (AS)[1] is a chronic inflammatory disease of unknown aetiology with primary involvement of the axial skeleton (sacroiliac joint [SIJ] and spine), starting in most of the cases in subjects under 45 years old and with a strong association with the MHC class I antigen HLA-B27, which is positive in 90-95% of the patients. AS patients can develop peripheral joint and entheses manifestations, as well as extra-articular manifestations such as anterior uveitis, psoriasis and inflammatory bowel disease[2]. The prevalence of AS is estimated to be between 0.1 and 1.4%[2]. The disease is characterized by the presence of active inflammation in the SIJ and the spine, which manifests as pain and stiffness, and by excessive new bone formation (leading to the development of syndesmophytes and ankylosis in the same areas). This will produce in up to 40% of the patients a significant functional impairment[4] and may occur with a close relationship between the grade of impairment and the duration of the disease[5]. At the same time, the disease has a relevant socio-economic impact due to disability and chronic therapies including biological drugs, generating high costs[6-7]. Reduction of clinical burden and prevention of disability can probably be best achieved by early and adequate treatment targeting both inflammation and new bone formation. According to the Assessment of SpondyloArthritis international Society (ASAS) and European League Against Rheumatism (EULAR) recommendations, the first-line therapy for patients with AS are nonsteroidal anti-inflammatory drugs (NSAIDs), including selective cyclooxygenase-2 (COX-2) antagonists, along with education and continuous exercise/physiotherapy[8]. Therapy with conventional disease-modifying anti-rheumatic drugs (DMARDs) such as methotrexate, leflunomide, and sulfasalazine may have some beneficial effect in patients with peripheral joint involvement, but in general are not effective for the treatment of axial involvement[9-11]. For those patients who had a poor response to NSAIDs, contraindications or intolerance for NSAIDs, the only effective treatment currently available is the therapy with tumour necrosis factor (TNF)-inhibitors[8, 12]; very recently secukinumab, a monoclonal antibody against interleukin (IL)-17, has been approved in the European Union (EU) for the treatment of active AS based on the positive results of two phase III studies[13]. There is some evidence that NSAIDs, in particular Celecoxib, might possess not only a symptomatic efficacy but also disease modifying properties in AS,

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3 retarding the progression of structural damage (syndesmophytes and ankylosis) in
4 the spine if taken continuously[14]. This might be explained by a direct inhibitory
5 effect on osteoblast genesis and activity[15]. This effect was especially evident in AS
6 patients with elevated C-reactive protein (CRP)[16], which is also considered a risk
7 factor for radiographic spinal progression in AS[17]. The data from the GESPIC study
8 (a non-interventional observational cohort) showed a similar protective effect against
9 radiographic spinal progression in those patients who had high NSAIDs intake
10 (defined as >50% of the maximum recommended dose) and who were at high risk for
11 radiographic spinal progression (presence of syndesmophytes and/or elevated CRP)
12 at baseline[18]. For diclofenac, a nonselective COX inhibitor, such effect was,
13 however, not proven in the recently published ENRADAS trial[19]. TNF-inhibitors are
14 used as a second line therapy in patients with AS, if NSAIDs demonstrate no or
15 insufficient clinical effect and have until now the best effect on inflammation signs and
16 symptoms[12]. Despite good clinical efficacy on inflammatory aspects, TNF-inhibitors
17 are not able to retard radiographic spinal progression in AS over a period of two[20-
18 22] or four[23] years. Many of the patients with AS treated with a TNF-inhibitor
19 discontinue their NSAIDs due to good symptom control with the anti-TNF agent
20 (including the 5-year GO-RAISE pivotal study on the efficacy of Golimumab in
21 AS[23]). Therefore, it has not been possible until now to answer the question of the
22 impact of a combined therapy (TNF blocker and NSAID) on radiographic spinal
23 progression. It is crucial to clarify whether adding an NSAID (especially a COX-2
24 selective one) to TNF-blocker treatment is able to stop or reduce radiographic
25 progression, especially in patients at high risk (i.e. with elevated CRP and/or with
26 already present syndesmophytes).

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The aim of this prospective study is to evaluate the impact of treatment with an
NSAID Celecoxib added to a TNF inhibitor Golimumab as compared to Golimumab
alone on progression of structural damage in the spine over two years in patients with
AS.

Methods and analysis:

Study design. This study is a randomized, controlled, multicenter, open-label clinical trial. The study consists of a 6-week screening period, a 12-week period (Phase I: Run-in Phase) of treatment with Golimumab for all subjects followed by a 96-week controlled treatment period (Phase II: Core-Phase) with Golimumab plus Celecoxib

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3 versus Golimumab alone, and a safety follow-up period of 4 weeks (figure 1). Only
4 subjects with a good clinical response to Golimumab in the Phase I (achievement of
5 a 50% improvement of the Bath Ankylosing Spondylitis Disease Activity Index
6 (BASDAI) score – BASDAI50-response or ≥ 2 absolute points on the BASDAI 0-10
7 scale response at Week 12) will be eligible for Phase II and will be randomized based
8 on a 1:1 ratio to receive Golimumab plus Celecoxib or Golimumab alone for 96
9 weeks. At week 108 the primary study endpoint (radiographic spinal progression as
10 assessed by the modified Stoke Ankylosing Spondylitis Spine Score – mSASSS[24])
11 will be evaluated. Magnetic resonance imaging (MRI) of the spine and sacroiliac
12 joints will be performed at baseline (Week 0), and at Week 108 (or in case of early
13 termination (ET) at Week 84 or later) in a sub-study with patients of study sites in
14 Berlin & Brandenburg having no contraindication for this investigation.

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24 *Patients.* Patients of 18 years and older, diagnosed with AS due to the modified New
25 York Criteria¹, with an active disease (defined as an BASDAI-Score >4), history of an
26 inadequate response to two different NSAID's for at least 14 days each and one of
27 the two following risk factors for radiographic spinal progression: elevated CRP or
28 existing syndesmophytes at screening, who gave written informed consent are going
29 to be included in the study. Main inclusion and exclusion criteria are shown in table 1.
30 Study participants will be recruited from 21 rheumatologic centres throughout
31 Germany between September 2016 and presumably February 2018. 190 patients
32 shall be assessed for eligibility (assuming a 10% screening failure rate
33 approximately), so that 170 patients with active AS despite treatment with NSAIDs
34 alone will be included in the phase I of the trial and treated with Golimumab. Only
35 patients with good clinical response (achievement of BASDAI50 or reduction ≥ 2
36 absolute points (on a 0-10 scale) of the BASDAI) after 12 weeks of Golimumab
37 treatment will be enrolled in phase II of the trial. It is assumed that approximately
38 60% (n=100) of patients included in phase I will continue in to phase II of the study,
39 considering that elevated CRP at baseline is currently the best response predictor for
40 TNF-inhibitor therapy. So 100 patients (n=50 in each group) will enter phase II of the
41 trial (intention-to-treat population - ITT) after 1:1 randomization and going to be
42 analysed for the primary and secondary outcome parameters.

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Outcome parameters. The study outcome parameters are summarized in table 2.
The primary outcome parameter of the study is radiographic spinal progression
measured by the change in the modified Stoke Ankylosing Spondylitis Spine Score

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3 (mSASSS) between week 12 and week 108 (primary endpoint). Secondary outcome
4 parameters will include new syndesmophyte formation or progression of existing
5 syndesmophytes after 2 years of treatment, change of the bone and cartilage
6 biomarkers serum levels at week 108 in comparison to baseline, change of the
7 enteric microbiome profile at week 108 in comparison to baseline, change of osteitis
8 score and scores for the chronic post-inflammatory changes in the spine and
9 sacroiliac joints on MRI by Berlin MRI scoring method at week 108 in comparison to
10 baseline (in the MRI sub-study only) and the improvement of disease activity,
11 function, axial mobility and quality of life measures at week 12 and week 108 in
12 comparison to baseline. Safety outcome parameters will include evaluation of
13 adverse events (AE's), serious AE and events of interest: infections, malignancies,
14 gastrointestinal events (ulceration, bleeding, perforation, gastric outlet obstruction),
15 cardiovascular events (myocardial infarction, stroke, pulmonary artery embolism,
16 peripheral arterial or venous thrombosis), renal impairment (creatinine > 1.8 mg/dl or
17 increase > 0.5 mg/dl vs. Baseline) and substantial (>5-fold) liver enzyme elevation.

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28 *Data analysis plan.* The study consists of a 12-week run-in period, 96-week core
29 period (randomized treatment) and 4-week follow-up period. The primary efficacy
30 endpoint will be the absolute progression of the mSASSS score over two years of
31 therapy (phase II of the trial, week 12 – week 108) in both treatment groups. The
32 primary analysis will be based on the mean of the mSASSS scores evaluated by 2
33 trained readers for the spinal x-rays performed at Week 12 and at Week 108 in the
34 ITT population. A database lock will occur for the purposes of the efficacy and safety
35 analysis, once all data up to week 112 have been collected and cleaned.

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42 *Statistical analysis.* The primary analysis will be based on all patients who entered
43 phase II of the trial (ITT population). Multiple imputation methods with mSASSS score
44 at baseline as covariate will be applied to deal with missing radiographs in the
45 primary analysis. The Mann-Whitney test will be used to compare the primary
46 outcome (change in the mSASSS score) between the treatment groups. Cumulative
47 probability plots will be built to visualise the finding. In a secondary analysis the
48 Mann-Whitney test will be used to compare radiographic progression in the subgroup
49 of patients with complete sets of radiographs. A likelihood approach will be applied to
50 deal with missing data in secondary outcome parameters assessed at multiple time
51 points. For that reason, linear mixed models will be applied to compare means of
52 secondary outcome parameters over time. A non-responder imputation for missing
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3 response data and chi-square tests will additionally be applied to compare response
4 rates. Two-sided p values < 0.05 will be considered to be statistically significant.
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7 **Ethics and dissemination:**

8 The study will be performed according to the ICH / GCP guidelines and the German
9 drug law (Arzneimittelgesetz – AMG). The written approval of the Central
10 Independent Ethics Committee (Ethics Committee of the Federal State Berlin), of the
11 German federal authority (Paul-Ehrlich-Institut – PEI, Langen, Germany) and of the
12 local Ethics Committees of the study centres have been obtained. Study results upon
13 study completion are expected to be published in a peer-reviewed journal.
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18 **Registration details:**

19 The study has been registered; ClinicalTrials.gov ID: NCT02758782, EudraCT
20 Number: 2016-000615-33.
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24 **Author's contribution.**

25 Fabian Proft (FP), Burkard Muche (BM) and Valeria Rios Rodriguez (VRR) were
26 involved in drafting the study protocol. Joachim Listing (JL) was involved in statistical
27 planning and drafting the study protocol. Joachim Sieper (JS) has emerged the idea
28 for this trial and was involved in drafting and revising the study protocol. Denis
29 Poddubnyy (DP) has emerged the idea for this trial, was involved in drafting and
30 revising the study protocol and is the principal investigator of this trial.
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37 **Funding.**

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39 (Bundesministerium für Bildung und Forschung - BMBF), Grant No: FKZ 01KG1603.
40 MSD Sharp & Dohme GmbH provides study drug Golimumab and supports the MRI
41 sub-study.
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46 **Competing interests.**

47 FP: honoraria from Novartis-Sandoz

48 BM: none.

49 JL: honoraria from Novartis-Sandoz and Pfizer

50 VRR: none.

51 JS: research grants, honoraria, speaker fees and/or consultancy payments from
52 Abbvie, Bristol Myers Squibb, Janssen, Eli Lilly, MSD / Merck, Novartis, Pfizer,
53 Roche, and UCB
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3 DP: honoraria, speaker fees and/or consultancy payments from Abbvie, Bristol Myers
4 Squibb, Janssen, Eli Lilly, MSD / Merck, Novartis, Pfizer, Roche, and UCB.
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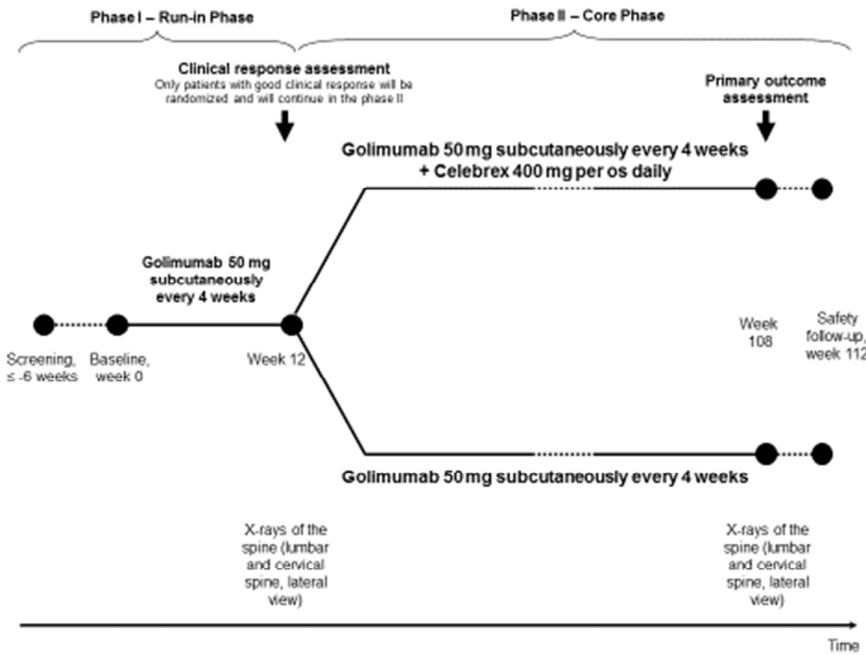
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For peer review only

Inclusion criteria	Exclusion criteria
Age ≥ 18 years	Presence of total spinal ankylosis
Definite diagnosis of AS according to the modified New York criteria	History of primary non-response to previous anti-TNF therapy (if any)
Active disease (defined as an BASDAI-Score ≥ 4)	Contraindications for the treatment with Golimumab and/or Celecoxib
History of an inadequate response to ≥ 2 NSAIDs taken for at least 2 weeks each	
Risk factors for radiographic spinal progression (defined as elevated CRP or existing syndesmophytes) at screening	

Efficacy:	Safety:
<p><i>Primary endpoint:</i></p> <ul style="list-style-type: none"> • Radiographic spinal progression measured by the change in the modified Stoke Ankylosing Spondylitis Spine Score (mSASSS) between week 12 and week 108. <p><i>Secondary endpoints:</i></p> <ul style="list-style-type: none"> • New syndesmophyte formation or progression of existing syndesmophytes after 2 years of treatment. • Improvement of disease activity, function, axial mobility and quality of life measures at week 12 and week 108 in comparison to baseline according to: <ul style="list-style-type: none"> – BASDAI – ASDAS – CRP and erythrocyte sedimentation rate (ESR) – Bath AS Functional Index (BASFI) – Bath AS Metrology Index (BASMI) and chest expansion – Global assessment (patient/physician), general pain and nocturnal pain on the numeric rating scale (NRS) – ASAS Health Index – Physician Acceptable Symptom State (PhASS) – Patient Acceptable Symptom State (PASS) – Percentage of subjects who achieve an ASAS20, ASAS40, ASAS partial remission, BASDAI50 and ASDAS in comparison to baseline; • Change of the bone and cartilage biomarkers serum levels at week 108 in comparison to baseline and their relevance for the prediction of radiographic progression. • Change of the enteric microbiome profile at week 108 in comparison to baseline. • Change of osteitis score and scores for the chronic post-inflammatory changes in the spine and sacroiliac joints (SIJ) on magnetic resonance imaging (MRI) by Berlin MRI scoring method at week 12 and week 108 in comparison to baseline – for the MRI sub-study only. 	<p>Adverse events (AE), serious AE and AE of interest until Week 112.</p>

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Study protocol: COmparison of the effect of treatment with NSAIDs added to anti-TNF therapy versus anti-TNF therapy alone on progression of StrUctural damage in the spine over two years in patients with ankylosing spondylitis (CONSUL) – an open-Label, randomized controlled, multicenter trial

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3 **Study protocol: COmparison of the effect of treatment with NSAIDs**
4 **added to anti-TNF therapy versus anti-TNF therapy alone on**
5 **progression of StrUctural damage in the spine over two years in**
6 **patients with ankylosing spondylitis (CONSUL) – an open-label**
7 **randomized controlled multicenter trial**
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3 **Introduction:** There is some evidence that NSAIDs, in particular Celecoxib, might
4 possess not only a symptomatic efficacy but also disease modifying properties in AS,
5 retarding the progression of structural damage in the spine if taken continuously. In
6 contrast, this remains controversial for TNF inhibitors, despite their good clinical
7 efficacy on inflammatory aspects, pain and physical-function. The impact of a
8 combined therapy (a TNF inhibitor plus an NSAID) on radiographic spinal
9 progression in AS is unclear.
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11 **Methods and analysis:** The aim of this prospective, open-label, randomized,
12 controlled multicentre clinical trial is to evaluate the impact of treatment with an
13 NSAID (Celecoxib) when added to a TNF inhibitor (Golimumab) as compared to TNF
14 inhibitor (Golimumab) alone on progression of structural damage in the spine over
15 two years in patients with AS. The study consists of a 6-week screening period, a 12-
16 week period (Phase I: Run-in Phase) of treatment with Golimumab for all subjects
17 followed by a 96-week controlled treatment period (Phase II: Core Phase) with
18 Golimumab plus Celecoxib versus Golimumab alone, and a safety follow-up period of
19 4 weeks. At week 108 the primary study endpoint (radiographic spinal progression as
20 assessed by the modified Stoke Ankylosing Spondylitis Spine Score – mSASSS) will
21 be evaluated.
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23 **Ethics and dissemination:** The study will be performed according to the ICH / GCP
24 guidelines and the German drug law. The written approval of the Central
25 Independent Ethics Committee, the German federal authority and the local Ethics
26 Committees of the study centres have been obtained. Study results upon study
27 completion are expected to be published in a peer-reviewed journal.
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29 **Registration details:** ClinicalTrials.gov ID: NCT02758782, EudraCT Number: 2016-
30 000615-33.
31

32 **Funding:** This work is supported by the German Federal Ministry of Education and
33 Research (BMBF), Grant No. FKZ 01KG1603. MSD Sharp & Dohme GmbH provides
34 the study drug Golimumab and financial support of the MRI sub-study.
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Article summary

Strengths and limitations of this study

Strengths:

- This is the first prospective randomized controlled multicentre trial with the objective to investigate the effect of a combination of a TNF inhibitor with an NSAID on radiographic spinal progression in ankylosing spondylitis.
- The primary outcome measure (radiographic spinal progression) is not dependent on.
- Patient population consists of patients at high risk of radiographic spinal progression.

Limitations:

- Study is conducted only in one country (Germany)
- The intervention is not masked / blinded
- Highly selected patient population
- Assumptions made for the sample size calculation are based on data obtained separately for TNF inhibitors and NSAIDs.
- The sample size calculation are based on data obtained separately for TNF inhibitors and NSAIDs.

Introduction

Ankylosing spondylitis (AS) is a chronic inflammatory disease of unknown aetiology with primary involvement of the axial skeleton (sacroiliac joint [SIJ] and spine), starting in most of the cases in subjects under 45 years¹ of age (mean age onset about 26 years²), with a strong association with the MHC class I antigen HLA-B27, which is positive in 80-90% of the patients¹. AS patients can develop peripheral arthritis and enthesitis, as well as extra-articular manifestations such as anterior uveitis, psoriasis and inflammatory bowel disease³. The prevalence of AS is estimated to be between 0.1 and 1.4%⁴. The disease is characterized by the presence of active inflammation in the SIJ and the spine, which manifests as pain and stiffness, and by excessive new bone formation (leading to the development of syndesmophytes and ankylosis in the same areas). This results in a significant functional impairment in up to 40% of the patients⁵.⁶ Given young age at disease onset in the majority of patients, impairment of the functional status in AS causing disability has a relevant socio-economic impact⁷. Reduction of clinical burden and prevention of disability can probably be best achieved by early and adequate treatment targeting both inflammation and new bone formation. According to the Assessment of SpondyloArthritis international Society (ASAS) and European League Against Rheumatism (EULAR) recommendations, the first-line therapy for patients with AS are nonsteroidal anti-inflammatory drugs (NSAIDs), including selective cyclooxygenases-2 (COX-2) antagonists, along with education and continuous exercise/physiotherapy⁸. Therapy with conventional disease-modifying anti-rheumatic drugs (DMARDs) such as methotrexate, leflunomide, and sulfasalazine may have some beneficial effect in patients with peripheral joint involvement, but in general are not effective for the treatment of axial involvement⁹⁻¹¹. For those patients who had a poor response to NSAIDs, contraindications or intolerance for NSAIDs, the only effective treatment currently available is the therapy with tumour necrosis factor (TNF)-inhibitors⁸; or with a recently introduced monoclonal antibody against interleukin (IL)-17 secukinumab¹². There is some evidence that NSAIDs, in particular Celecoxib, might possess not only a symptomatic efficacy but also disease modifying properties in AS, retarding the progression of structural damage (syndesmophytes and ankylosis) in the spine if taken continuously¹³. This might be explained by a direct inhibitory effect on osteoblast genesis and activity¹⁴. This effect was especially

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3 evident in AS patients with elevated C-reactive protein (CRP)¹⁵, which is also
4 considered a risk factor for radiographic spinal progression in AS¹⁶. The data from
5 the GESPIC study (a non-interventional observational cohort) showed a similar
6 protective effect against radiographic spinal progression in those patients who had
7 high NSAIDs intake (defined as >50% of the maximum recommended dose) and who
8 were at high risk for radiographic spinal progression (presence of syndesmophytes
9 and/or elevated CRP) at baseline¹⁷. For diclofenac, a nonselective COX inhibitor,
10 such effect was, however, not proven in the recently published ENRADAS trial¹⁸.
11 TNF-inhibitors are used as a second line therapy in patients with AS, if NSAIDs
12 demonstrate no or insufficient clinical effect¹⁹. Despite high anti-inflammatory
13 capacity, the existing data on the effect of TNF inhibitors on radiographic spinal
14 progression is controversial. While some studies could not show a retardation of
15 radiographic spinal progression in AS over a period of two²⁰⁻²² or four²³ years, there
16 are three observational studies suggesting that it may take more than four years to
17 detect such an effect²⁴⁻²⁶ and that early (within the first five or ten years of the
18 disease) initiation of anti-TNF therapy might play a key role^{25 26}. However, no
19 prospective controlled trials have been conducted so far to confirm these
20 observations.
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33 Many of the patients with AS treated with a TNF-inhibitor discontinue their NSAIDs
34 due to good symptom control with the anti-TNF agent (including the 5-year GO-
35 RAISE pivotal study on the efficacy of Golimumab in AS²³). Therefore, it has not
36 been possible until now to answer the question of the impact of a combined therapy
37 (TNF inhibitor and NSAID) on radiographic spinal progression. It is crucial to clarify
38 whether adding an NSAID (especially a COX-2 selective one) to TNF inhibitor
39 treatment is able to stop or reduce radiographic progression, especially in patients at
40 high risk (i.e. with elevated CRP and/or with already present syndesmophytes).
41 Recently, results of an observational study indicating inhibition of radiographic spinal
42 progression with a combination of a TNF inhibitor with a high dose NSAID were
43 presented²⁷ stressing a need for a prospective interventional trial.
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53 The aim of this prospective study is to evaluate the impact of treatment with an
54 NSAID Celecoxib added to a TNF inhibitor Golimumab as compared to Golimumab
55 alone on progression of structural damage in the spine over two years in patients with
56 AS.
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Methods and analysis:

Study design. This study is a randomized, controlled, multicenter, open-label clinical trial. The study consists of a 6-week screening period, a 12-week period (Phase I: Run-in Phase) of treatment with Golimumab 50 mg subcutaneously (sc) every four weeks for all subjects followed by a 96-week controlled treatment period (Phase II: Core-Phase) with Golimumab plus Celecoxib versus Golimumab alone, and a safety follow-up period of 4 weeks (figure 1). Only subjects with a good clinical response to Golimumab in the Phase I (improvement of the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score by ≥ 2 absolute points on a 0-10 scale response at Week 12) will be eligible for Phase II and will be randomized based on a 1:1 ratio to receive Golimumab 50mg sc every four weeks plus Celecoxib (in a daily dose of 400mg per day) or Golimumab 50 mg sc every four weeks alone for 96 weeks. At week 108 the primary study endpoint (radiographic spinal progression as assessed by the modified Stoke Ankylosing Spondylitis Spine Score – mSASSS²⁸) will be evaluated. Magnetic resonance imaging (MRI) of the spine and sacroiliac joints will be performed at baseline (Week 0), and at Week 108 (or in case of early termination (ET) at Week 84 or later) in a sub-study of approximately 60 patients with no contraindication for this investigation.

Patients. Patients of 18 years and older, diagnosed with AS due to the modified New York Criteria²⁹, with an active disease (defined as an BASDAI-Score > 4), history of an inadequate response to therapeutic trials of at least two NSAIDs taken in a maximal recommended or tolerated anti-inflammatory dose for at least four weeks in total and at least one of the two following risk factors for radiographic spinal progression: elevated CRP or already present syndesmophyte(s) at screening, and who gave written informed consent are going to be included in the study. Key inclusion and exclusion criteria are shown in table 1. Study participants will be recruited from 21 rheumatologic centres throughout Germany between September 2016 and presumably February 2018. 190 patients shall be assessed for eligibility (assuming a 10% screening failure rate), so that 170 patients with active AS despite treatment with NSAIDs alone will be included in the phase I of the trial and treated with Golimumab. Only patients with good clinical response (BASDAI-reduction by ≥ 2 absolute points (on a 0-10 scale) after 12 weeks of Golimumab treatment will be enrolled in phase II (Core Phase) of the trial. It is assumed that approximately 60%

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3 (n=100) of patients included in phase I will continue in to phase II of the study,
4 considering that elevated CRP at baseline is currently the best response predictor for
5 TNF-inhibitor therapy. Thus, 100 patients (n=50 in each group) will enter phase II of
6 the trial (intention-to-treat population - ITT) after 1:1 randomization and will be
7 analysed for the primary and secondary outcome parameters.
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11 *Outcome parameters.* The study outcome parameters are summarized in table 2.
12 The primary outcome parameter of the study is radiographic spinal progression
13 measured by the change in the modified Stoke Ankylosing Spondylitis Spine Score
14 (mSASSS) between week 12 and week 108 (primary endpoint). Secondary outcome
15 parameters include new syndesmophyte formation or progression of existing
16 syndesmophytes after 2 years of treatment, change of the bone and cartilage
17 biomarkers serum levels at week 108 in comparison to baseline, change of the
18 enteric microbiome profile at week 108 in comparison to baseline, change of osteitis
19 score and scores for the chronic post-inflammatory changes in the spine and
20 sacroiliac joints on MRI by Berlin MRI scoring method at week 108 in comparison to
21 baseline (in the MRI sub-study only) and the improvement of disease activity,
22 function, axial mobility and quality of life measures at week 12 and week 108 in
23 comparison to baseline. Safety outcome parameters include evaluation of adverse
24 events (AE's), serious AE and AEs of interest: infections, malignancies,
25 gastrointestinal events (ulceration, bleeding, perforation, gastric outlet obstruction),
26 cardiovascular events (myocardial infarction, stroke, pulmonary artery embolism,
27 peripheral arterial or venous thrombosis), renal impairment (creatinine > 1.8 mg/dl or
28 increase > 0.5 mg/dl vs. Baseline) and substantial (> 5-fold) liver enzyme elevation.
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32 *Data analysis plan.* The study consists of a 12-week run-in period, 96-week core
33 period (randomized treatment) and 4-week follow-up period. The primary efficacy
34 endpoint will be the absolute progression of the mSASSS score after two years of
35 therapy (phase II of the trial, week 12 – week 108) in both treatment groups. The
36 primary analysis will be based on the mean of the mSASSS scores obtained by 2
37 trained readers for the spinal x-rays performed at Week 12 and at Week 108 in the
38 ITT population. A database lock will occur for the purposes of the efficacy and safety
39 analysis, once all data up to week 112 have been collected and cleaned.
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43 *Statistical analysis.* The primary analysis will be based on all patients who entered
44 phase II of the trial (ITT population). Multiple imputation methods with mSASSS score
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3 at baseline as covariate will be applied to deal with missing radiographs in the
4 primary analysis. The Mann-Whitney test will be used to compare the primary
5 outcome (change in the mSASSS score) between the treatment groups. Cumulative
6 probability plots will be built to visualise the finding. In a secondary analysis the
7 Mann-Whitney test will be used to compare radiographic progression in the subgroup
8 of patients with complete sets of radiographs. A likelihood approach will be applied to
9 deal with missing data in secondary outcome parameters assessed at multiple time
10 points. For that reason, linear mixed models will be applied to compare means of
11 secondary outcome parameters over time. A non-responder imputation for missing
12 response data and chi-square tests will additionally be applied to compare response
13 rates. Two-sided p values < 0.05 will be considered to be statistically significant.
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21 *Sample Size Justification.* The sample size calculation is based on the findings of
22 Kroon et al.¹⁵ our own results from GESPIC Cohort¹⁷, and those of Braun et al²³. We
23 assume a worsening in the mSASSS score of 1.7 ± 2.8 in patients of the control group
24 and of 0.2 ± 1.6 in patients with continuous NSAIDs intake. We considered such a
25 difference of 1.5 mSASSS units as clinically relevant and planned the sample size of
26 this study by means of a two-sided ($\alpha=0.05$) Welch-Satterthwaite t-test accordingly.
27 To detect the mentioned difference with an 80% power, the sample size of $n=38$ in
28 each group is needed in the phase II of the trial. This is also true if the Mann-Whitney
29 test is applied. However, the power will decrease by the application of multiple
30 imputations to deal with missing radiographs of dropouts in the ITT population. We
31 estimated this decrease by: a) an estimation of dropout rates and b) the use of own
32 mSASSS data. Considering that all subjects enrolled in the phase II will be
33 responders to Golimumab therapy receiving this same treatment for the whole period
34 of the trial, along with our experience in conducting randomized controlled trials, we
35 presume dropout rates of less than 20% during phase II. For this reason and based
36 on our own mSASSS data, we expect an increase in the variance of mSASSS
37 progression because of multiple imputation by less than 25%. Considering this
38 possible increase, a sample size of $n = 100$ patients is needed for phase II of the trial
39 to detect the expected and clinically relevant difference of on average 1.5 mSASSS
40 points with an 80% power in the ITT population. In addition we assumed that 60% of
41 the subjects enrolled in phase I of the study would be eligible for randomization and
42 participation in phase II (based on the rate of the BASDAI50 response in AS patients
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3 with elevated CRP), giving a total n=170 subjects to be included in the phase I of the
4 trial.
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8 9 **Ethics and dissemination:**

10 The study will be performed according to the ICH / GCP guidelines and the German
11 drug law (Arzneimittelgesetz – AMG). The written approval of the Central
12 Independent Ethics Committee (Ethics Committee of the Federal State Berlin), of the
13 German federal authority (Paul-Ehrlich-Institut – PEI, Langen, Germany) and of the
14 local Ethics Committees of the study centres have been obtained. Study results upon
15 study completion are expected to be published in a peer-reviewed journal.
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20 21 **Registration details:**

22 The study has been registered; ClinicalTrials.gov ID: NCT02758782, EudraCT
23 Number: 2016-000615-33.
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26 27 **Author's contribution.**

28 Fabian Proft (FP), Burkard Muche (BM) and Valeria Rios Rodriguez (VRR) were
29 involved in drafting the study protocol. Joachim Listing (JL) was involved in statistical
30 planning and drafting the study protocol. Joachim Sieper (JS) has emerged the idea
31 for this trial and was involved in drafting and revising the study protocol. Denis
32 Poddubnyy (DP) has emerged the idea for this trial, was involved in drafting and
33 revising the study protocol and is the principal investigator of this trial.
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39 40 **Funding.**

41 This work is supported by the German Federal Ministry of Education and Research
42 (Bundesministerium für Bildung und Forschung - BMBF), Grant No: FKZ 01KG1603.
43 MSD Sharp & Dohme GmbH provides study drug Golimumab and supports the MRI
44 sub-study.
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48 49 **Competing interests.**

50 FP: consultancy payments from Novartis. BM: consultancy payments from Novartis
51 and UCB.
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53 JL: honoraria from Novartis and Pfizer.
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55 VRR: none.
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3 JS: research grants from Abbvie, Bristol Myers Squibb, Janssen, MSD, Pfizer, and
4 Roche; speaker fees and/or consultancy payments from Abbvie, Bristol Myers
5 Squibb, Janssen, Eli Lilly, MSD / Merck, Novartis, Pfizer, Roche, and UCB
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8 DP: research grants from Abbvie, MSD, and Novartis; speaker fees and/or
9 consultancy payments from Abbvie, Bristol Myers Squibb, Janssen, Eli Lilly, MSD /
10 Merck, Novartis, Pfizer, Roche, and UCB.
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14 **Figure legend:**
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18 Figure 1: Study design.
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Tables:

Inclusion criteria	Exclusion criteria
Age ≥ 18 years	Presence of total spinal ankylosis
Definite diagnosis of AS according to the modified New York criteria	History of primary non-response to previous anti-TNF therapy (if any)
Active disease (defined as BASDAI ≥ 4)	Contraindications for the treatment with Golimumab and/or Celecoxib
History of an inadequate response to a therapeutic trials of at least two NSAIDs	
Risk factors for radiographic spinal progression (defined as elevated CRP or existing syndesmophytes) at screening	

Table 1: Main inclusion and exclusion criteria.

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<u>Efficacy:</u>	<u>Safety:</u>
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Table 2: Study outcome parameters.

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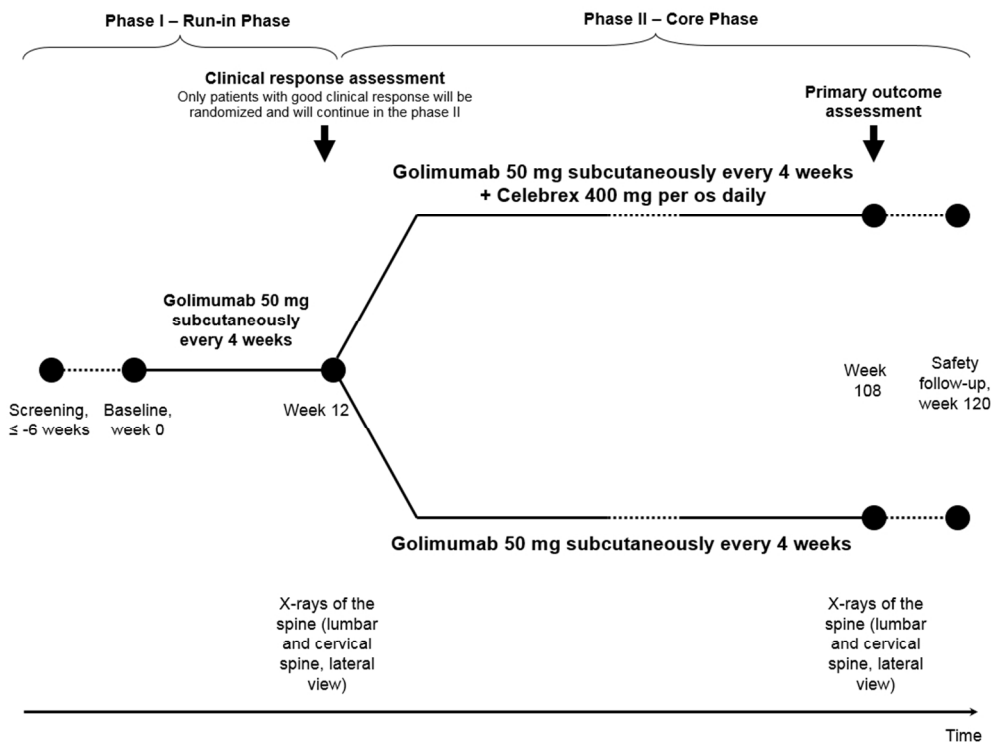


Figure 1: Study design.
Figure 1
92x69mm (300 x 300 DPI)



SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1 of 61
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	https://clinicaltrials.gov/ct2/show/NCT02758782
	2b	All items from the World Health Organization Trial Registration Data Set	yes
Protocol version	3	Date and version identifier	1 of 61
Funding	4	Sources and types of financial, material, and other support	12 of 61
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1 of 61
	5b	Name and contact information for the trial sponsor	1 of 61
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	N/A

1 2 3 4 5 6 7 8 9 10	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	N/A
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Introduction

11 12 13 14 15 16 17 18 19 20 21 22 23	Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	15-17 of 61
		6b	Explanation for choice of comparators	20-21 of 61
	Objectives	7	Specific objectives or hypotheses	18-19 of 61
	Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	20-35 of 61

Methods: Participants, interventions, and outcomes

24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45	Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	https://clinicaltrials.gov/ct2/show/NCT02758782
	Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	23-26 of 61
	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	27-29 of 61
		11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	30 of 61
		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	30 of 61

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3		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	27 of 61
4	Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	18-19 of 61
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10	Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	20 of 61
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13	Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	49-50 of 61
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16	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	N/A
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19	Methods: Assignment of interventions (for controlled trials)			
20	Allocation:			
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22	Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	49 of 61
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28	Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	49 of 61
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32	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	49 of 61
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36	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	N/A
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39		17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
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3 **Methods: Data collection, management, and analysis**
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5 Data collection	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	13-14 of 61
6 methods			
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11	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	21, 31 and 35 of 61
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14 Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	51-52 of 61
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18 Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	46-53 of 61
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22	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	48 of 61
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24	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	48 of 61
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27 **Methods: Monitoring**
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29 Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	https://clinicaltrials.gov/ct2/show/NCT02758782
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35	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	31-32 of 61
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38 Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	36-39 of 61
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41 Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	54 of 61
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49**Ethics and dissemination**

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	45 of 61
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	46 of 61
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	IRB
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	55
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	N/A
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	PI, SI and Study biostatistician
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	44 of 61
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	https://clinicaltrials.gov/ct2/show/NCT02758782
	31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	https://clinicaltrials.gov/ct2/show/NCT02758782

Appendices

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	N/A
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "[Attribution-NonCommercial-NoDerivs 3.0 Unported](#)" license.

Peer review only

BMJ Open

Study protocol: Comparison of the effect of treatment with NSAIDs added to anti-TNF therapy versus anti-TNF therapy alone on progression of structural damage in the spine over two years in patients with ankylosing spondylitis – an open-label randomized controlled multi-centre trial

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Manuscript ID	bmjopen-2016-014591.R2
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Primary Subject Heading:	Rheumatology
Secondary Subject Heading:	Radiology and imaging
Keywords:	Ankylosing spondylitis, radiographic progression, TNF inhibitors, NSAIDs, mSASS

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Manuscripts

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3 **Study protocol: Comparison of the effect of treatment with NSAIDs**
4 **added to anti-TNF therapy versus anti-TNF therapy alone on**
5 **progression of structural damage in the spine over two years in**
6 **patients with ankylosing spondylitis – an open-label randomized**
7 **controlled multi-centre trial**
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Article summary

Introduction: There is some evidence that non-steroidal anti-inflammatory drugs (NSAIDs), in particular Celecoxib, might possess not only a symptomatic efficacy but also disease modifying properties in ankylosing spondylitis (AS), retarding the progression of structural damage in the spine if taken continuously. In contrast, this remains controversial for tumour necrosis factor (TNF) α inhibitors, despite their good clinical efficacy. The impact of a combined therapy (a TNF inhibitor plus an NSAID) on radiographic spinal progression in AS is unclear.

Methods and analysis: The aim of this study is to evaluate the impact of treatment with an NSAID (Celecoxib) when added to a TNF inhibitor (Golimumab) as compared to TNF inhibitor (Golimumab) alone on progression of structural damage in the spine over two years in patients with AS. The study consists of a 6-week screening period, a 12-week period (Phase I: Run-in Phase) of treatment with Golimumab for all subjects followed by a 96-week controlled treatment period (Phase II: Core Phase) with Golimumab plus Celecoxib versus Golimumab alone, and a safety follow-up period of 4 weeks. At week 108 the primary study endpoint radiographic spinal progression (as assessed by the change in the modified Stoke Ankylosing Spondylitis Spine Score – mSASSS after two years) will be evaluated.

Ethics and dissemination: The study will be performed according to the principles of good clinical practice (GCP) and the German drug law. The written approval of the independent ethics committee and of the German federal authority have been obtained. Upon study completion, results are expected to be published in a peer-reviewed journal.

Registration details: ClinicalTrials.gov ID: NCT02758782, EudraCT Number: 2016-000615-33.

Funding: This work is supported by the German Federal Ministry of Education and Research (BMBF), Grant-No. FKZ 01KG1603. MSD Sharp & Dohme GmbH provides the study drug Golimumab and financial support of the MRI sub-study.

Strengths and limitations of this study

Strengths:

- This is the first prospective randomized controlled multi-centre trial with the objective to investigate the effect of a combination of a TNF inhibitor with an NSAID on radiographic spinal progression in ankylosing spondylitis.
- The primary outcome measure (radiographic spinal progression) will be evaluated by two independent readers blinded for the time-point and all clinical data including treatment allocation, and is therefore, not affected by the open-label study design.
- Patient population consists of patients at high risk of radiographic spinal progression.

Limitations:

- Study is conducted only in one country (Germany).
- The intervention is not masked / blinded.
- Highly selected patient population.
- Assumptions made for the sample size calculation are based on data obtained separately for TNF inhibitors and NSAIDs.

Introduction

Ankylosing spondylitis (AS) is a chronic inflammatory disease of unknown aetiology with primary involvement of the axial skeleton (sacroiliac joint (SIJ) and spine), starting in most of the cases in subjects under 45 years of age (mean age onset about 26 years), with a strong association with the MHC class I antigen HLA-B27, which is positive in 80-90% of the patients¹. AS patients can develop peripheral arthritis and enthesitis, as well as extra-articular manifestations such as anterior uveitis, psoriasis and inflammatory bowel disease². The prevalence of AS is estimated to be between 0.1 and 1.4%³. The disease is characterized by the presence of active inflammation in the SIJ and the spine, which manifests as pain and stiffness, and by excessive new bone formation (leading to the development of syndesmophytes and ankylosis in the same areas). This results in a significant functional impairment in up to 40% of the patients^{4 5}. Given the young age at disease onset in the majority of patients, impairment of the functional status in AS causing disability has a relevant socio-economic impact⁶. Reduction of clinical burden and prevention of disability can probably be best achieved by early and adequate treatment targeting both inflammation and new bone formation. According to the Assessment of SpondyloArthritis international Society (ASAS) and European League Against Rheumatism (EULAR) recommendations, the first-line therapy for patients with AS are nonsteroidal anti-inflammatory drugs (NSAIDs), including selective cyclooxygenase-2 (COX-2) antagonists, along with education and continuous exercise/physiotherapy⁷. Therapy with conventional disease-modifying anti-rheumatic drugs (DMARDs) such as sulfasalazine or methotrexate may have some beneficial effect in patients with peripheral joint involvement, but in general is not effective for the treatment of axial involvement⁸⁻¹⁰. For those patients who have a poor response to NSAIDs, contraindications or intolerance for NSAIDs, the only effective treatment currently available is the therapy with tumour necrosis factor (TNF) α inhibitors⁷ or with a recently introduced monoclonal antibody against interleukin (IL)-17 secukinumab¹¹. There is some evidence that NSAIDs, in particular Celecoxib, might possess not only a symptomatic efficacy but also disease modifying properties in AS, retarding the progression of structural damage (syndesmophytes and ankylosis) in the spine if taken continuously¹². This might be explained by a direct inhibitory effect on osteoblast genesis and activity¹³. This effect was especially evident in AS patients with elevated C-reactive protein (CRP)¹⁴, which is also considered a risk factor for

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3 radiographic spinal progression in AS¹⁵. The data from the German Spondyloarthritis
4 Inception Cohort (GESPIC) showed a similar protective effect against radiographic
5 spinal progression in those patients who had high NSAIDs intake (defined as >50%
6 of the maximum recommended dose) and who were at high risk for radiographic
7 spinal progression (due to presence of syndesmophytes and/or elevated CRP) at
8 baseline¹⁶. For diclofenac, a nonselective COX inhibitor, such effect was, however,
9 not proven in a recently published trial¹⁷.

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15 The data on the effect of TNF inhibitors on radiographic spinal progression in
16 ankylosing spondylitis – despite their high anti-inflammatory efficacy – remains
17 controversial. While some studies could not show a retardation of radiographic spinal
18 progression in AS over a period of two¹⁸⁻²⁰ or four²¹ years, there are three
19 observational studies suggesting that it may take more than four years to detect such
20 an effect²²⁻²⁴ and that early (within the first five or ten years of the disease) initiation
21 of anti-TNF therapy might play a key role^{23 24}. However, no prospective controlled
22 trials have been conducted so far to confirm these observations.

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29 Many patients with AS treated with a TNF inhibitor discontinue their NSAIDs due to
30 good symptom control²⁵. Therefore, it has not been possible until now to answer the
31 question of the impact of a combined therapy (TNF inhibitor and NSAID) on
32 radiographic spinal progression. It is crucial to clarify whether adding an NSAID
33 (especially a COX-2 selective one) to TNF inhibitor treatment is able to stop or
34 reduce radiographic progression, especially in patients at high risk (i.e. with elevated
35 CRP and/or with already present syndesmophytes). Recently, results of an
36 observational study indicating inhibition of radiographic spinal progression with a
37 combination of a TNF inhibitor with a high dose NSAID were presented²⁶ stressing a
38 need for a prospective interventional trial.

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46 The aim of this prospective study is to evaluate the impact of treatment with an
47 NSAID Celecoxib added to a TNF inhibitor Golimumab as compared to Golimumab
48 alone on progression of structural damage in the spine over two years in patients with
49 AS.
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52 53 54 55 **Methods and analysis:**

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57 *Study design.* This study is a randomized, controlled, multi-centre, open-label clinical
58 trial. The study consists of a 6-week screening period, a 12-week period (Phase I:
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3 Run-in Phase) of treatment with Golimumab 50 mg subcutaneously (sc) every four
4 weeks for all subjects followed by a 96-week controlled treatment period (Phase II:
5 Core-Phase) with Golimumab plus Celecoxib versus Golimumab alone, and a safety
6 follow-up period of 4 weeks (**figure 1**). Only subjects with a good clinical response to
7 Golimumab in the Phase I (improvement of the Bath Ankylosing Spondylitis Disease
8 Activity Index (BASDAI) score by ≥ 2 absolute points on a 0-10 scale response at
9 Week 12) will be eligible for Phase II and will be randomized based on a 1:1 ratio to
10 receive Golimumab 50 mg sc every four weeks plus Celecoxib (in a daily dose of 400
11 mg per day) or Golimumab 50 mg sc every four weeks alone for another 96 weeks.
12 At week 108 the primary study endpoint (radiographic spinal progression defined as
13 the change in the modified Stoke Ankylosing Spondylitis Spine Score – mSASSS²⁷
14 after two years) will be evaluated. Magnetic resonance imaging (MRI) of the spine
15 and sacroiliac joints will be performed at baseline (Week 0), and at Week 108 (or in
16 case of early termination (ET) at Week 84 or later) in a sub-study of approximately 60
17 patients with no contraindication for this investigation.

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28 *Patients.* Included Patients will be 18 years and older with AS fulfilling the modified
29 New York Criteria²⁸ with an active disease (BASDAI ≥ 4), history of an inadequate
30 response to at least two NSAIDs and at least one of the two following risk factors for
31 radiographic spinal progression: elevated CRP or already present syndesmophyte(s)
32 at screening, and give written informed consent. Key inclusion and exclusion criteria
33 are shown in **table 1**. Study participants will be recruited from 21 rheumatologic
34 centres throughout Germany between September 2016 and presumably February
35 2018. 190 patients shall be assessed for eligibility (assuming a 10% screening failure
36 rate), so that 170 patients with active AS despite treatment with NSAIDs alone will be
37 included in the phase I of the trial and treated with Golimumab. Only patients with
38 good clinical response (BASDAI reduction by ≥ 2 absolute points (on a 0-10 scale)
39 after 12 weeks of Golimumab treatment will be enrolled in the phase II (Core Phase)
40 of the trial. Based on the efficacy results from a phase-III study with Golimumab in
41 AS²⁹, we assume that approximately 60% (n=100) of the patients included in phase I
42 will continue in to phase II of the study. Thus, 100 patients (n=50 in each group) will
43 enter phase II of the trial (intention-to-treat population - ITT) after 1:1 randomization
44 and will be analysed for the primary and secondary outcome parameters.

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57 *Outcome parameters.* The study outcome parameters are summarized in table 2.
58 The primary outcome parameter of the study is radiographic spinal progression
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3 measured by the change in the modified Stoke Ankylosing Spondylitis Spine Score
4 (mSASSS) after two years of treatment (primary endpoint). Secondary outcome
5 parameters include new syndesmophyte formation or progression of existing
6 syndesmophytes after two years of treatment, change of the bone and cartilage
7 biomarkers serum levels change of the enteric microbiome profile, change of osteitis
8 score and scores for the chronic post-inflammatory changes in the spine and
9 sacroiliac joints on MRI by Berlin MRI scoring method (in the MRI sub-study only)
10 and improvement of disease activity, function, axial mobility and quality of life. Safety
11 outcome parameters include evaluation of adverse events (AEs), serious AE and
12 AEs of interest: infections, malignancies, gastrointestinal events (ulceration, bleeding,
13 perforation, gastric outlet obstruction), cardiovascular events (myocardial infarction,
14 stroke, pulmonary artery embolism, peripheral arterial or venous thrombosis), renal
15 impairment (creatinine >1.8 mg/dl or increase >0.5 mg/dl vs. baseline) and
16 substantial (>5-fold) liver enzyme elevation.
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27 *Data analysis plan.* The study consists of a 12-week run-in period, 96-week core
28 period (randomized treatment) and 4-week follow-up period. The primary efficacy
29 endpoint will be the absolute progression of the mSASSS score after two years of
30 therapy in both treatment groups. The primary analysis will be based on the mean of
31 the mSASSS scores obtained by 2 trained readers for the spinal X-rays performed at
32 inclusion in the study and at Week 108 in the ITT population. For the purposes of the
33 efficacy and safety analysis, a database lock will occur, once all data up to week 112
34 has been collected and cleaned.
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Statistical analysis. The primary analysis will be based on all patients who entered
phase II of the trial (ITT population). Multiple imputation methods with mSASSS score
at baseline as covariate will be applied to deal with missing radiographs in the
primary analysis. The Mann-Whitney test will be used to compare the primary
outcome (change in the mSASSS score) between the treatment groups. Cumulative
probability plots will be built to visualise the finding. In a secondary analysis the
Mann-Whitney test will be used to compare radiographic progression in the subgroup
of patients with complete sets of radiographs. A likelihood approach will be applied to
deal with missing data in secondary outcome parameters assessed at multiple time
points. For that reason, linear mixed models will be applied to compare means of
secondary outcome parameters over time. A non-responder imputation for missing

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3 response data and chi-square tests will additionally be applied to compare response
4 rates. Two-sided p values < 0.05 will be considered to be statistically significant.

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6 *Sample Size Justification.* The sample size calculation is based on the findings of
7 Kroon et al.¹⁴ our own results from GESPIC Cohort¹⁶, and those of Braun et al²¹. We
8 assume a worsening in the mSASSS score of 1.7±2.8 in patients of the control group
9 and of 0.2±1.6 in patients with continuous NSAIDs intake. We considered such a
10 difference of 1.5 mSASSS units as clinically relevant and planned the sample size of
11 this study by means of a two-sided ($\alpha=0.05$) Welch-Satterthwaite t-test accordingly.
12 To detect the mentioned difference with an 80% power, the sample size of n=38 in
13 each group is needed in the phase II of the trial. This is also true if the Mann-Whitney
14 test is applied. However, the power will decrease by the application of multiple
15 imputations to deal with missing radiographs of dropouts in the ITT population.
16 Considering that all subjects enrolled in the phase II will be responders to Golimumab
17 therapy receiving this same treatment for the whole period of the trial, along with our
18 experience in conducting randomized controlled trials, we presume dropout rates of
19 less than 20% during phase II. For this reason and based on our own mSASSS data,
20 we expect an increase in the variance of mSASSS progression because of multiple
21 imputation by less than 25%. Considering this possible increase, a sample size of
22 n=100 patients is needed for phase II of the trial to detect the expected and clinically
23 relevant difference of an average 1.5 mSASSS points with an 80% power in the ITT
24 population. In addition we assumed that 60% of the subjects enrolled in phase I of
25 the study would be eligible for randomization and participation in phase II (based on
26 the rate of the BASDAI50 response in AS patients with elevated CRP), giving a total
27 n=170 subjects to be included in the phase I of the trial.

28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 **Ethics and dissemination:**

45 The study will be performed according to the International Conference of
46 Harmonisation Good Clinical Practice (ICH / GCP) guidelines and the German drug
47 law (Arzneimittelgesetz – AMG). The written approval of the central independent
48 ethics committee (Ethics Committee of the Federal State Berlin), of the German
49 federal authority (Paul-Ehrlich-Institut – PEI, Langen, Germany) and of the local
50 ethics committees of the study centres have been obtained. Upon study completion,
51 results are expected to be published in a peer-reviewed journal.

52 53 54 55 56 57 58 **Registration details:**

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3 The study has been registered in the ClinicalTrials.gov register (registration ID:
4 NCT02758782) and in the European Union Clinical Trials Register (EudraCT
5 Number: 2016-000615-33).
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8 **Author's contribution.**

9
10 Fabian Proft (FP), Burkard Muche (BM) and Valeria Rios Rodriguez (VRR) were
11 involved in drafting the study protocol. Joachim Listing (JL) was involved in statistical
12 planning and drafting the study protocol. Joachim Sieper (JS) developed the idea for
13 this trial and was involved in drafting and revising the study protocol. Denis
14 Poddubnyy (DP) conceived the idea for this trial, was involved in drafting and revising
15 the study protocol and is the principal investigator of this trial.
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19

20 **Funding.**

21 This work is supported by the German Federal Ministry of Education and Research
22 (Bundesministerium für Bildung und Forschung - BMBF), Grant No: FKZ 01KG1603.
23 MSD Sharp & Dohme GmbH provides study drug Golimumab and supports the MRI
24 sub-study.
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29 **Competing interests.**

30 FP: speaker fees and/or consultancy payments from Novartis, UCB and Roche.
31

32 BM: consultancy payments from Novartis and UCB.
33

34 JL: honoraria from Novartis and Pfizer.
35

36 VRR: none.
37

38 JS: research grants from Abbvie, Bristol Myers Squibb, Janssen, MSD, Pfizer, and
39 Roche; speaker fees and/or consultancy payments from Abbvie, Bristol Myers
40 Squibb, Janssen, Eli Lilly, MSD / Merck, Novartis, Pfizer, Roche, and UCB
41

42 DP: research grants from Abbvie, MSD, and Novartis; speaker fees and/or
43 consultancy payments from Abbvie, Bristol Myers Squibb, Janssen, Eli Lilly, MSD /
44 Merck, Novartis, Pfizer, Roche, and UCB.
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3 **Figure legend.**
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6 **Figure 1:** Design of the COmparison of the effect of treatment with NSAIDs added to
7 anti-TNF therapy versus anti-TNF therapy alone on progression of StrUctural
8 damage in the spine over two years in patients with ankylosing spondylitis (CONSUL)
9 study.
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Inclusion criteria	Exclusion criteria
Age \geq 18 years	Presence of total spinal ankylosis
Definite diagnosis of AS according to the modified New York criteria	History of primary non-response to previous anti-TNF therapy (if any)
Active disease (defined as BASDAI \geq 4)	Contraindications for the treatment with Golimumab and/or Celecoxib
History of an inadequate response to a therapeutic trials of at least two NSAIDs	
Risk factors for radiographic spinal progression (defined as elevated CRP or existing syndesmophytes) at screening	

Table 1: Main inclusion and exclusion criteria of the CONSUL study.

Table 2: Main outcome parameters of the CONSUL study.

Efficacy:	Safety:
<p><i>Primary endpoint:</i></p> <ul style="list-style-type: none"> • Radiographic spinal progression measured by the change in the modified Stoke Ankylosing Spondylitis Spine Score (mSASSS) after 2 years of treatment. <p><i>Secondary endpoints:</i></p> <ul style="list-style-type: none"> • New syndesmophyte formation or progression of existing syndesmophytes after 2 years of treatment. • Improvement of disease activity, function, axial mobility and quality of life measures at week 12 and week 108 in comparison to baseline according to: <ul style="list-style-type: none"> – Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) – Ankylosing Spondylitis Disease Activity Score (ASDAS) – C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) – Bath Ankylosing Spondylitis Functional Index (BASFI) – Bath Ankylosing Spondylitis Metrology Index (BASMI) and chest expansion – Global assessment (patient/physician), general pain and nocturnal pain on the numeric rating scale (NRS) – Assessment of SpondyloArthritis international Society (ASAS) Health Index – Physician Acceptable Symptom State (PhASS) – Patient Acceptable Symptom State (PASS) – Percentage of subjects who achieve an ASAS20, ASAS40, ASAS partial remission, BASDAI50 responses and ASDAS inactive disease state in comparison to baseline; • Change of the bone and cartilage biomarkers serum levels at week 108 in comparison to baseline and their relevance for the prediction of radiographic progression. • Change of the enteric microbiome profile at week 108 in comparison to baseline. • Change of osteitis score and scores for the chronic post-inflammatory changes in the spine and sacroiliac joints on magnetic resonance imaging (MRI) by Berlin MRI scoring method at week 12 and week 108 in comparison to baseline (MRI sub-study only). 	<p>Adverse events (AE), serious AE and AE of interest until Week 112.</p>

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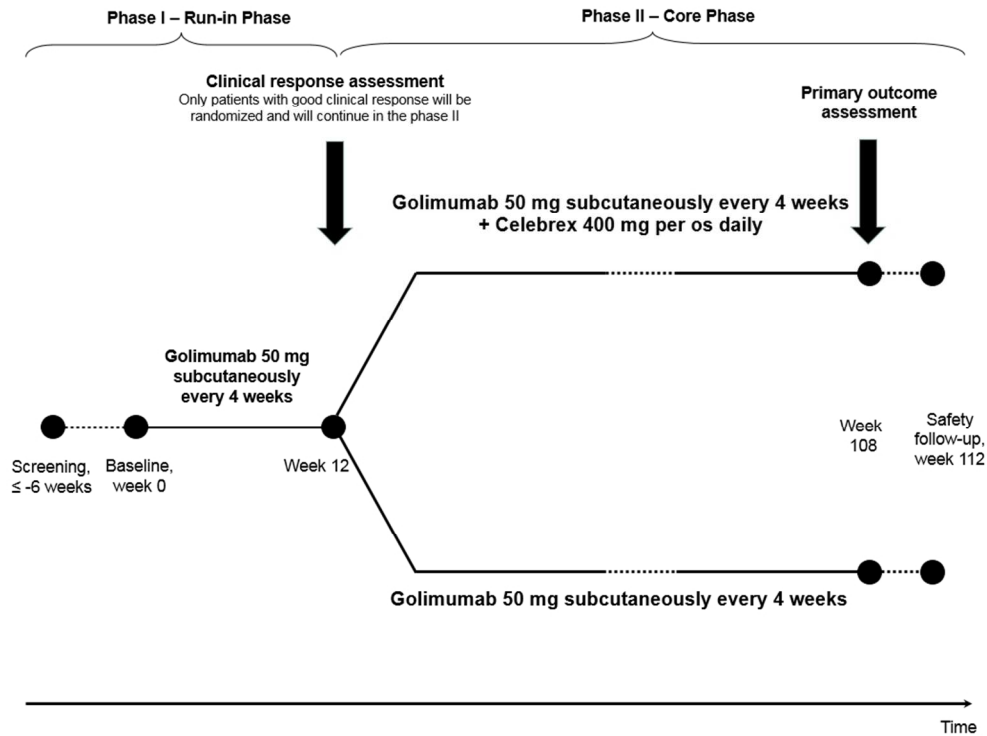


Figure 1: Design of the COMparison of the effect of treatment with NSAIDs added to anti-TNF therapy versus anti-TNF therapy alone on progression of StrUctural damage in the spine over two years in patients with ankylosing spondylitis (CONSUL) study.

figure 1
88x66mm (300 x 300 DPI)



SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1 of 59
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	ClinicalTrials.gov: NCT02758782 EU Clinical Trial Register: 2016-000615-33
	2b	All items from the World Health Organization Trial Registration Data Set	yes
Protocol version	3	Date and version identifier	1 of 59
Funding	4	Sources and types of financial, material, and other support	12 of 59
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1 of 59
	5b	Name and contact information for the trial sponsor	1 of 59
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	N/A

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	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	N/A
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Introduction

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	14-16 of 59
	6b	Explanation for choice of comparators	20-21 of 59
Objectives	7	Specific objectives or hypotheses	17-18 of 59
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	20-33 of 59

Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	https://clinicaltrials.gov/ct2/show/NCT02758782
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	22-25 of 59
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	26-28 of 59
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	28-30 of 59
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	28 of 59

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3		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	25 of 59
4	Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	17-18 of 59
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10	Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	19 of 59
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13	Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	47-48 of 59
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16	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	N/A
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19	Methods: Assignment of interventions (for controlled trials)			
20	Allocation:			
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22	Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	47 of 59
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28	Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	47 of 59
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32	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	47 of 59
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36	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	N/A
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39		17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
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3 **Methods: Data collection, management, and analysis**
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5 Data collection	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	12-13 of 59
6 methods			
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	20 of 59 12-13 of 59
14 Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	49-51 of 59
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18 Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	45-46 of 59
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21	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	46 of 59
22			
23	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	46 of 59
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27 **Methods: Monitoring**
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29 Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	https://clinicaltrials.gov/ct2/show/NCT02758782
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34	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	Interim analysis not planned. Trial discontinuation - see p. 30 of 59.
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40 Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	34-37 of 59
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3	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	52 of 59
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6	Ethics and dissemination			
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8	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	43 of 59
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11	Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	42, 44 of 59
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15	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	41-42 of 59
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19		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
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22	Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	53 of 59
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25	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	N/A
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28	Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	PI, SI and Study biostatistician
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31	Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	38, 42 of 59
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34	Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	https://clinicaltrials.gov/ct2/show/NCT02758782
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38		31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
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	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	https://clinicaltrials.gov/ct2/show/NCT02758782
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Appendices

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	N/A (only available in German language)
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "[Attribution-NonCommercial-NoDerivs 3.0 Unported](https://creativecommons.org/licenses/by-nc-nd/3.0/)" license.