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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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# 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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**Introduction:** 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 in the spine if taken continuously. In contrast this could not been proven for TNF-inhibitors, despite their good clinical efficacy on inflammatory aspects, pain and physical-function. The impact of a combined therapy (a TNF-inhibitor plus an NSAID) on radiographic spinal progression in AS remains unclear.

**Methods and analysis:** The aim of this prospective, randomized, controlled multicentre clinical trial 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 modified Stoke Ankylosing Spondylitis Spine Score – mSASSS) will be evaluated.

**Ethics and dissemination:** The study will be performed according to the ICH / GCP guidelines and the German drug law. The written approval of the Central Independent Ethics Committee, the German federal authority and the local Ethics Committees of the study centres have been obtained. Study results upon study completion 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.

## 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 cycloohygenases-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,

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

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

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 (achievement of a 50% improvement of the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score – BASDAI50-response or ≥2 absolute points on the BASDAI 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 plus Celecoxib or Golimumab alone for 96 weeks. At week 108 the primary study endpoint (radiographic spinal progression as assessed by the modified Stoke Ankylosing Spondylitis Spine Score – mSASSS[24]) 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 with patients of study sites in Berlin & Brandenburg having no contraindication for this investigation.

*Patients.* Patients of 18 years and older, diagnosed with AS due to the modified New York Criteria[1], with an active disease (defined as an BASDAI-Score>4), history of an inadequate response to two different NSAID's for at least 14 days each and one of the two following risk factors for radiographic spinal progression: elevated CRP or existing syndesmophytes at screening, who gave written informed consent are going to be included in the study. Main 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 approximately), 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 (achievement of BASDAI50 or reduction ≥2 absolute points (on a 0-10 scale) of the BASDAI) after 12 weeks of Golimumab treatment will be enrolled in phase II of the trial. It is assumed that approximately 60% (n=100) of patients included in phase I will continue in to phase II of the study, considering that elevated CRP at baseline is currently the best response predictor for TNF-inhibitor therapy. So 100 patients (n=50 in each group) will enter phase II of the trial (intention-to-treat population - ITT) after 1:1 randomization and going to be analysed for the primary and secondary outcome parameters.

*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

(mSASSS) between week 12 and week 108 (primary endpoint). Secondary outcome parameters will include new syndesmophyte formation or progression of existing syndesmophytes after 2 years of treatment, change of the bone and cartilage biomarkers serum levels at week 108 in comparison to baseline, 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 MRI by Berlin MRI scoring method at week 108 in comparison to baseline (in the MRI sub-study only) and the improvement of disease activity, function, axial mobility and quality of life measures at week 12 and week 108 in comparison to baseline. Safety outcome parameters will include evaluation of adverse events (AE's), serious AE and events of interest: infections, malignancies, gastrointestinal events (ulceration, bleeding, perforation, gastric outlet obstruction), cardiovascular events (myocardial infarction, stroke, pulmonary artery embolism, peripheral arterial or venous thrombosis), renal impairment (creatinine > 1.8 mg/dl or increase > 0.5 mg/dl vs. Baseline) and substantial (>5-fold) liver enzyme elevation.

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

*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

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

**Ethics and dissemination:**

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

**Registration details:**

The study has been registered; ClinicalTrials.gov ID: NCT02758782, EudraCT Number: 2016-000615-33.

**Author's contribution.**

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

**Funding.**

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**Competing interests.**

FP: honoraria from Novartis-Sandoz

BM: none.

JL: honoraria from Novartis-Sandoz and Pfizer

VRR: none.

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

DP: honoraria, speaker fees and/or consultancy payments from Abbvie, Bristol Myers Squibb, Janssen, Eli Lilly, MSD / Merck, Novartis, Pfizer, Roche, and UCB.

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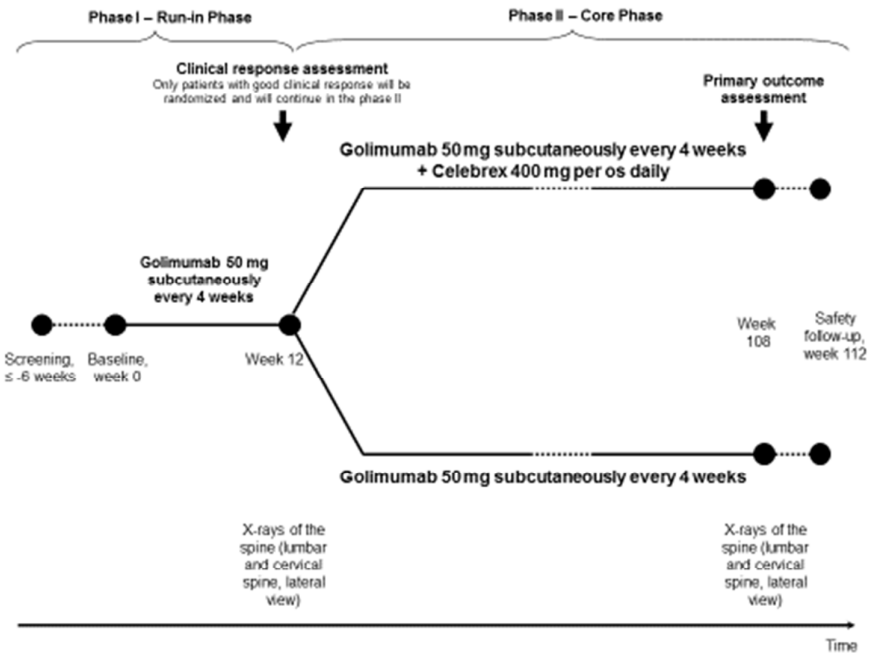
| Inclusion criteria | Exclusion criteria |
|---|---|
| Age ≥18 years | Presence of total spinal ankylosis |
| Definite diagnosis of AS according to the modified New York criteria | History of primary non-response to previous anti-TNF therapy (if any) |
| Active disease (defined as an BASDAI-Score>=4) | 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: |
|---|---|
| *Primary endpoint:*<br>• Radiographic spinal progression measured by the change in the modified Stoke Ankylosing Spondylitis Spine Score (mSASSS) between week 12 and week 108.<br><br>*Secondary endpoints:*<br>• New syndesmophyte formation or progression of existing syndesmophytes after 2 years of treatment.<br>• Improvement of disease activity, function, axial mobility and quality of life measures at week 12 and week 108 in comparison to baseline according to:<br>– BASDAI<br>– ASDAS<br>– CRP and erythrocyte sedimentation rate (ESR)<br>– Bath AS Functional Index (BASFI)<br>– Bath AS Metrology Index (BASMI) and chest expansion<br>– Global assessment (patient/physician), general pain and nocturnal pain on the numeric rating scale (NRS)<br>– ASAS Health Index<br>– Physician Acceptable Symptom State (PhASS)<br>– Patient Acceptable Symptom State (PASS)<br>– Percentage of subjects who achieve an ASAS20, ASAS40, ASAS partial remission, BASDAI50 and ASDAS in comparison to baseline;<br>• 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.<br>• Change of the enteric microbiome profile at week 108 in comparison to baseline.<br>• 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. | Adverse events (AE), serious AE and AE of interest until Week 112. |



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**Introduction:** 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 in the spine if taken continuously. In contrast, this remains controversial for TNF inhibitors, despite their good clinical efficacy on inflammatory aspects, pain and physical-function. 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 prospective, open-label, randomized, controlled multicentre clinical trial 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 modified Stoke Ankylosing Spondylitis Spine Score – mSASSS) will be evaluated.

**Ethics and dissemination:** The study will be performed according to the ICH / GCP guidelines and the German drug law. The written approval of the Central Independent Ethics Committee, the German federal authority and the local Ethics Committees of the study centres have been obtained. Study results upon study completion are expected to be published in a peer-reviewed journal.

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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 years[1] of age (mean age onset about 26 years[2]), with a strong association with the MHC class I antigen HLA-B27, which is positive in 80-90% of the patients[1]. AS patients can develop peripheral arthritis and enthesitis, as well as extra-articular manifestations such as anterior uveitis, psoriasis and inflammatory bowel disease[3]. 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 patients[5] [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 impact[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 cycloohygenases-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]; or with a recently introduced monoclonal antibody against interleukin (IL)-17 secukinumab[12]. 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 continuously[13]. This might be explained by a direct inhibitory effect on osteoblast genesis and activity[14]. This effect was especially

evident in AS patients with elevated C-reactive protein (CRP)[15], which is also considered a risk factor for radiographic spinal progression in AS[16]. The data from the GESPIC study (a non-interventional observational cohort) showed a similar protective effect against radiographic spinal progression in those patients who had high NSAIDs intake (defined as >50% of the maximum recommended dose) and who were at high risk for radiographic spinal progression (presence of syndesmophytes and/or elevated CRP) at baseline[17]. For diclofenac, a nonselective COX inhibitor, such effect was, however, not proven in the recently published ENRADAS trial[18]. TNF-inhibitors are used as a second line therapy in patients with AS, if NSAIDs demonstrate no or insufficient clinical effect[19] . Despite high anti-inflammatory capacity, the existing data on the effect of TNF inhibitors on radiographic spinal progression is controversial. While some studies could not show a retardation of radiographic spinal progression in AS over a period of two[20-22] or four[23] years, there are three observational studies suggesting that it may take more than four years to detect such an effect[24-26] and that early (within the first five or ten years of the disease) initiation of anti-TNF therapy might play a key role[25 26]. However, no prospective controlled trials have been conducted so far to confirm these observations.

Many of the patients with AS treated with a TNF-inhibitor discontinue their NSAIDs due to good symptom control with the anti-TNF agent (including the 5-year GO-RAISE pivotal study on the efficacy of Golimumab in AS[23]). Therefore, it has not been possible until now to answer the question of the impact of a combined therapy (TNF inhibitor and NSAID) on radiographic spinal progression. It is crucial to clarify whether adding an NSAID (especially a COX-2 selective one) to TNF inhibitor treatment is able to stop or reduce radiographic progression, especially in patients at high risk (i.e. with elevated CRP and/or with already present syndesmophytes). Recently, results of an observational study indicating inhibition of radiographic spinal progression with a combination of a TNF inhibitor with a high dose NSAID were presented[27] stressing a need for a prospective interventional trial.

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 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 – mSASSS[28]) 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 Criteria[29], 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%

(n=100) of patients included in phase I will continue in to phase II of the study, considering that elevated CRP at baseline is currently the best response predictor for TNF-inhibitor therapy. Thus,100 patients (n=50 in each group) will enter phase II of the trial (intention-to-treat population - ITT) after 1:1 randomization and will be analysed for the primary and secondary outcome parameters.

*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 (mSASSS) between week 12 and week 108 (primary endpoint). Secondary outcome parameters include new syndesmophyte formation or progression of existing syndesmophytes after 2 years of treatment, change of the bone and cartilage biomarkers serum levels at week 108 in comparison to baseline, 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 MRI by Berlin MRI scoring method at week 108 in comparison to baseline (in the MRI sub-study only) and the improvement of disease activity, function, axial mobility and quality of life measures at week 12 and week 108 in comparison to baseline. Safety outcome parameters include evaluation of adverse events (AE's), serious AE and AEs of interest: infections, malignancies, gastrointestinal events (ulceration, bleeding, perforation, gastric outlet obstruction), cardiovascular events (myocardial infarction, stroke, pulmonary artery embolism, peripheral arterial or venous thrombosis), renal impairment (creatinine > 1.8 mg/dl or increase > 0.5 mg/dl vs. Baseline) and substantial (> 5-fold) liver enzyme elevation.

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

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

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

with elevated CRP), giving a total n=170 subjects to be included in the phase I of the trial.

**Ethics and dissemination:**

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

**Registration details:**

The study has been registered; ClinicalTrials.gov ID: NCT02758782, EudraCT Number: 2016-000615-33.

**Author's contribution.**

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

**Funding.**

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**Competing interests.**

FP: consultancy payments from Novartis.BM: consultancy payments from Novartis and UCB.

JL: honoraria from Novartis and Pfizer.

VRR: none.

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

DP: research grants from Abbvie, MSD, and Novartis; speaker fees and/or consultancy payments from Abbvie, Bristol Myers Squibb, Janssen, Eli Lilly, MSD / Merck, Novartis, Pfizer, Roche, and UCB.

**Figure legend:**

Figure 1: Study design.

**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.

| Efficacy: | Safety: |
| --- | --- |
| | |

| | |
|---|---|
| *Primary endpoint:*<br>• Radiographic spinal progression measured by the change in the modified Stoke Ankylosing Spondylitis Spine Score (mSASSS) between week 12 and week 108.<br><br>*Secondary endpoints:*<br>• New syndesmophyte formation or progression of existing syndesmophytes after 2 years of treatment.<br>• Improvement of disease activity, function, axial mobility and quality of life measures at week 12 and week 108 in comparison to baseline according to:<br>– BASDAI<br>– ASDAS<br>– CRP and erythrocyte sedimentation rate (ESR)<br>– Bath AS Functional Index (BASFI)<br>– Bath AS Metrology Index (BASMI) and chest expansion<br>– Global assessment (patient/physician), general pain and nocturnal pain on the numeric rating scale (NRS)<br>– ASAS Health Index<br>– Physician Acceptable Symptom State (PhASS)<br>– Patient Acceptable Symptom State (PASS)<br>– Percentage of subjects who achieve an ASAS20, ASAS40, ASAS partial remission, BASDAI50 and ASDAS in comparison to baseline;<br>• 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.<br>• Change of the enteric microbiome profile at week 108 in comparison to baseline.<br>• 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. | Adverse events (AE), serious AE and AE of interest until Week 112. |

Table 2: Study outcome parameters.



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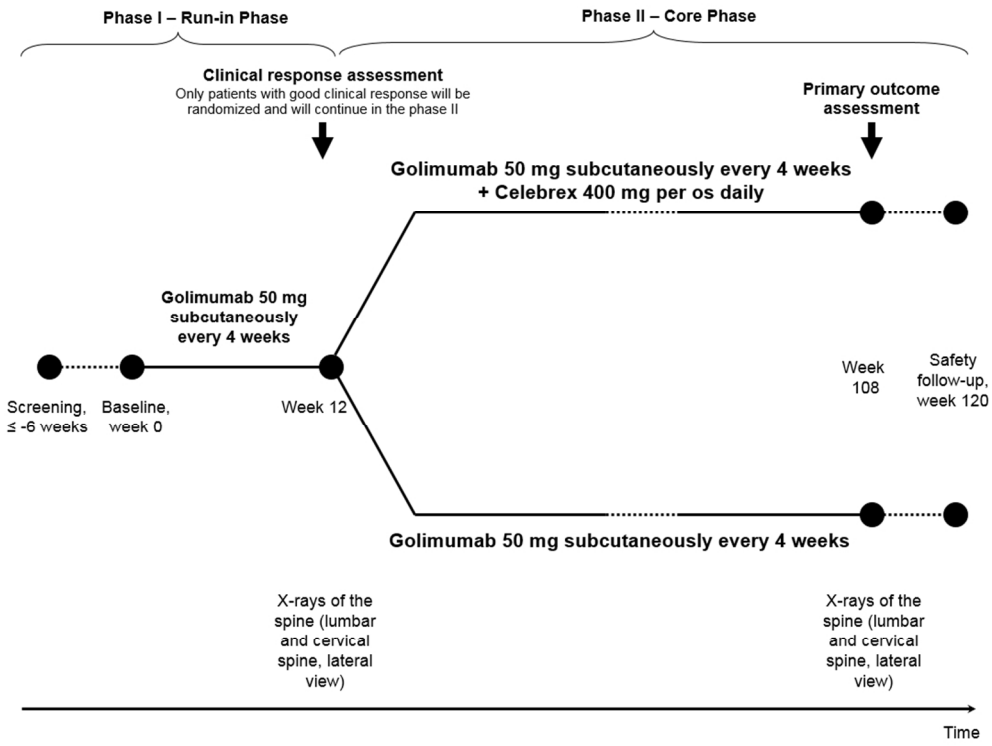


Figure 1: Study design.
Figure 1
92x69mm (300 x 300 DPI)


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 |

| | | | |
|---|---|---|---|
| | 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 |
| **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 | 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** | | | |
| 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 |

| | | | |
|---|---|---|---|
| | 11d | Relevant concomitant care and interventions that are permitted or prohibited during the trial | 27 of 61 |
| 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 |
| 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 |
| 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 |
| Recruitment | 15 | Strategies for achieving adequate participant enrolment to reach target sample size | N/A |
| **Methods: Assignment of interventions (for controlled trials)** | | | |
| Allocation: | | | |
| 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 |
| 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 |
| Implementation | 16c | Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions | 49 of 61 |
| Blinding (masking) | 17a | Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how | N/A |
| | 17b | If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial | N/A |

**Methods: Data collection, management, and analysis**

| | | | |
|---|---|---|---|
| Data collection methods | 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 |
| | 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 |
| 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 |
| 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 |
| | 20b | Methods for any additional analyses (eg, subgroup and adjusted analyses) | 48 of 61 |
| | 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 |

**Methods: Monitoring**

| | | | |
|---|---|---|---|
| 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 |
| | 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 |
| 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 |
| 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 |

**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. 

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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| | |

# 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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## 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 patients[1]. AS patients can develop peripheral arthritis and enthesitis, 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%[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 impact[6]. 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[7]. 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 involvement[8-10]. 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 inhibitors[7] or with a recently introduced monoclonal antibody against interleukin (IL)-17 secukinumab[11]. 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 continuously[12]. This might be explained by a direct inhibitory effect on osteoblast genesis and activity[13]. This effect was especially evident in AS patients with elevated C-reactive protein (CRP)[14], which is also considered a risk factor for

radiographic spinal progression in AS[15]. The data from the German Spondyloarthritis Inception Cohort (GESPIC) showed a similar protective effect against radiographic spinal progression in those patients who had high NSAIDs intake (defined as >50% of the maximum recommended dose) and who were at high risk for radiographic spinal progression (due to presence of syndesmophytes and/or elevated CRP) at baseline[16]. For diclofenac, a nonselective COX inhibitor, such effect was, however, not proven in a recently published trial[17].

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

Many patients with AS treated with a TNF inhibitor discontinue their NSAIDs due to good symptom control[25]. Therefore, it has not been possible until now to answer the question of the impact of a combined therapy (TNF inhibitor and NSAID) on radiographic spinal progression. It is crucial to clarify whether adding an NSAID (especially a COX-2 selective one) to TNF inhibitor treatment is able to stop or reduce radiographic progression, especially in patients at high risk (i.e. with elevated CRP and/or with already present syndesmophytes). Recently, results of an observational study indicating inhibition of radiographic spinal progression with a combination of a TNF inhibitor with a high dose NSAID were presented[26] stressing a need for a prospective interventional trial.

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, multi-centre, 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 50 mg sc every four weeks plus Celecoxib (in a daily dose of 400 mg per day) or Golimumab 50 mg sc every four weeks alone for another 96 weeks. At week 108 the primary study endpoint (radiographic spinal progression defined as the change in the modified Stoke Ankylosing Spondylitis Spine Score – mSASSS[27] after two years) 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.* Included Patients will be 18 years and older with AS fulfilling the modified New York Criteria[28] with an active disease (BASDAI ≥4), history of an inadequate response to at least two NSAIDs and at least one of the two following risk factors for radiographic spinal progression: elevated CRP or already present syndesmophyte(s) at screening, and give written informed consent. 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 the phase II (Core Phase) of the trial. Based on the efficacy results from a phase-III study with Golimumab in AS[29], we assume that approximately 60% (n=100) of the patients included in phase I will continue in to phase II of the study. Thus, 100 patients (n=50 in each group) will enter phase II of the trial (intention-to-treat population - ITT) after 1:1 randomization and will be analysed for the primary and secondary outcome parameters.

*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 (mSASSS) after two years of treatment (primary endpoint). Secondary outcome parameters include new syndesmophyte formation or progression of existing syndesmophytes after two years of treatment, change of the bone and cartilage biomarkers serum levels change of the enteric microbiome profile, change of osteitis score and scores for the chronic post-inflammatory changes in the spine and sacroiliac joints on MRI by Berlin MRI scoring method (in the MRI sub-study only) and improvement of disease activity, function, axial mobility and quality of life. Safety outcome parameters include evaluation of adverse events (AEs), serious AE and AEs of interest: infections, malignancies, gastrointestinal events (ulceration, bleeding, perforation, gastric outlet obstruction), cardiovascular events (myocardial infarction, stroke, pulmonary artery embolism, peripheral arterial or venous thrombosis), renal impairment (creatinine >1.8 mg/dl or increase >0.5 mg/dl vs. baseline) and substantial (>5-fold) liver enzyme elevation.

*Data analysis plan.* The study consists of a 12-week run-in period, 96-week core period (randomized treatment) and 4-week follow-up period. The primary efficacy endpoint will be the absolute progression of the mSASSS score after two years of therapy in both treatment groups. The primary analysis will be based on the mean of the mSASSS scores obtained by 2 trained readers for the spinal X-rays performed at inclusion in the study and at Week 108 in the ITT population. For the purposes of the efficacy and safety analysis, a database lock will occur, once all data up to week 112 has been collected and cleaned.

*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

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

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

**Ethics and dissemination:**

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

**Registration details:**

The study has been registered in the ClinicalTrials.gov register (registration ID: NCT02758782) and in the European Union Clinical Trials Register (EudraCT Number: 2016-000615-33).

**Author's contribution.**

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

**Funding.**

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

**Competing interests.**

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

BM: consultancy payments from Novartis and UCB.

JL: honoraria from Novartis and Pfizer.

VRR: none.

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

DP: research grants from Abbvie, MSD, and Novartis; speaker fees and/or consultancy payments from Abbvie, Bristol Myers Squibb, Janssen, Eli Lilly, MSD / Merck, Novartis, Pfizer, Roche, and UCB.

**Figure legend.**

**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.

| 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 of the CONSUL study.

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Table 2: Main outcome parameters of the CONSUL study.

| Efficacy: | Safety: |
|---|---|
| *Primary endpoint:*<br>• Radiographic spinal progression measured by the change in the modified Stoke Ankylosing Spondylitis Spine Score (mSASSS) after 2 years of treatment.<br><br>*Secondary endpoints:*<br>• New syndesmophyte formation or progression of existing syndesmophytes after 2 years of treatment.<br>• Improvement of disease activity, function, axial mobility and quality of life measures at week 12 and week 108 in comparison to baseline according to:<br>– Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)<br>– Ankylosing Spondylitis Disease Activity Score (ASDAS)<br>– C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR)<br>– Bath Ankylosing Spondylitis Functional Index (BASFI)<br>– Bath Ankylosing Spondylitis Metrology Index (BASMI) and chest expansion<br>– Global assessment (patient/physician), general pain and nocturnal pain on the numeric rating scale (NRS)<br>– Assessment of SpondyloArthritis international Society (ASAS) Health Index<br>– Physician Acceptable Symptom State (PhASS)<br>– Patient Acceptable Symptom State (PASS)<br>– Percentage of subjects who achieve an ASAS20, ASAS40, ASAS partial remission, BASDAI50 responses and ASDAS inactive disease state in comparison to baseline;<br>• 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.<br>• Change of the enteric microbiome profile at week 108 in comparison to baseline.<br>• 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). | Adverse events (AE), serious AE and AE of interest until Week 112. |

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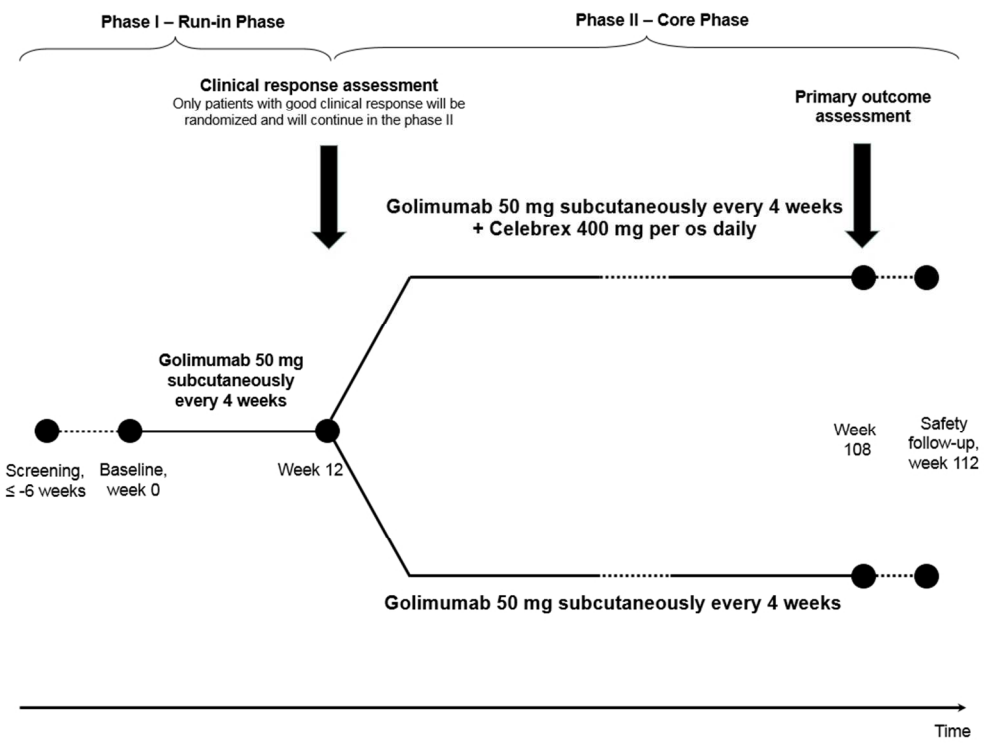


Figure 1: Design of the COmparison of the effect of treatment with NSAIDs added to anti-TNF therapy versus anti-TNF therapy alone on progression of StrUctural damage in the spine over two years in patients with ankylosing spondylitis (CONSUL) study.
figure 1
88x66mm (300 x 300 DPI)


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 |
| **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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| | 11d | Relevant concomitant care and interventions that are permitted or prohibited during the trial | 25 of 59 |
| 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 |
| 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 |
| 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 |
| Recruitment | 15 | Strategies for achieving adequate participant enrolment to reach target sample size | N/A |
| **Methods: Assignment of interventions (for controlled trials)** | | | |
| Allocation: | | | |
| 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 |
| 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 |
| Implementation | 16c | Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions | 47 of 59 |
| Blinding (masking) | 17a | Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how | N/A |
| | 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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| **Methods: Data collection, management, and analysis** | | | |
| Data collection methods | 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 |
| | 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<br>12-13 of 59 |
| 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 |
| 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 |
| | 20b | Methods for any additional analyses (eg, subgroup and adjusted analyses) | 46 of 59 |
| | 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 |
| **Methods: Monitoring** | | | |
| 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 |
| | 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. |
| 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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| 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 |
| **Ethics and dissemination** | | | |
| Research ethics approval | 24 | Plans for seeking research ethics committee/institutional review board (REC/IRB) approval | 43 of 59 |
| 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 |
| 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 |
| | 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 | 53 of 59 |
| 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 | 38, 42 of 59 |
| 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 |

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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 |
| **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. 