Statistical Analysis Plan

Title	Treat and Train – A Post-Marketing-Observational Study (PMOS) to determine the effectiveness of combined adalimumab treatment and active supervised training in patients with axial spondyloarthritis
	P15-710
Version Identifier of the Final SAP	1.0
Date of Last Version of Final SAP	14-Feb-2019
EU PAS Register Number	The Study got no EU PAS Register Number. Instead the ClinicalTrials.gov Identifier: NCT03258814 leads to https://clinicaltrials.gov/ct2/show/NCT03258814?titles=Treat+and+Train&draw=1&rank=1
Active Substance	N/A
Medicinal Product	N/A
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Procedure Number	N/A
Marketing Authorisation Holder(s)	AbbVie Deutschland GmbH & Co. KG Knollstraße 67061 Ludwigshafen, Germany Germany
Joint PASS	NOT REQUIRED
Research Question and Objectives	This study was a non-confirmatory study to compare, in adalimumab (HUMIRA®) treated patients with axial spondyloarthritis, an active supervised and standardized training with standard of care physiotherapy in improving health-related outcomes. The primary objective was the improvement in spinal mobility after a 6-month training program. Further objectives were the improvement in physical function, health-related quality of life, disease activity, pain, psychosocial risk factors and workability.
Country(-ies) of Study	Germany
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Signatures:

Study Director

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Lead Medical Unit Rheumatology

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StatConsult GmbH

[redacted] Date

1 Documents

1.1 SAP versions

Version	Date	Author	Description
0.1	15-DEC-2017	[redacted]	Document creation
1.0	14-FEB-2019	[redacted]	Finalization

1.2 External documents

Document no.	Document
1	Study Protocol "P15-710_Treat and Train_PMOS study protocol_20170220_Amendment V02_final.docx"

Contents

2 Abbreviations

ADA	Adalimumab
AE	Adverse event
AMG	German Drug Law (*Arzneimittelgesetz*)
AS	Ankylosing spondylitis
ASAS	Assessment of Spondyloarthritis International Society
ASDAS	Ankylosing Spondylitis Disease Activity Score
AST	Active Supervised Training
axSpA	Axial Spondyloarthritis
BASDAI	Bath AS Disease Activity Index
BASFI	Bath AS Functional Index
BASMI	Bath Ankylosing Spondylitis Metrology Index
CA	Competent authorities
CRP	C-reactive protein
DMARD	Disease-Modifying Anti-Rheumatic Drug
eCRF	Electronic Case Report Form
EC	Ethics Committee
EDC	Electronic Data Capture
EOW	Every other week
ESR	Erythrocyte Sedimentation Rate
EULAR	European League Against Rheumatism
HI	Health Index
HLA-B27	Human Leukocyte Antigen B27
NIS	Non-Interventional Study
nr-axSpA	Non-radiographic axial spondyloarthritis
NRS	Numerical Rating Scale
NSAID	Non-Steroidal Anti-Inflammatory Drug
PAM-13	Patient Activation Measure 13 (patient activation questionnaire, 13 items)
PGA	Physician’s global assessment
PRO	Patient-reported outcomes
PTGA	Patient’s global assessment
QoL	Quality of life
SAE	Serious adverse event
SAP	Plan for statistical analysis
SOC	Standard of care
VAS	Visual analog scale
WAI	Work Ability Index

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4 Description of the study

4.1 Background

The term "axial spondyloarthritis" (axSpA) includes both non-radiographic axSpA (nr-axSpA) and ankylosing spondylitis (AS) with radiographic signs of disease. Axial spondyloarthritis is a chronic, degenerative and disabling rheumatic disease characterized by signs and symptoms including inflammatory back pain, significant functional limitation, reduced spinal mobility, and impaired quality of life.

The term "ankylosing" refers to bone neogenesis which, in end-stage disease, may result in osteophyte formation and fusion across vertebrae. "Spondylitis" refers to the inflammation of the vertebrae. In its severe form, the condition leads to new bone formation culminating in the fusion of vertebrae, bony parts of the sacroiliac joint and other axial skeletal bones, resulting in significant functional limitation and disability [1, 2]. While the disease duration is shorter in non-radiographic axSpA and there are no manifest radiographic changes, patients with this condition still have a major disease burden with self-reported disease activity, functional limitation and reduced quality of life similar to those of patients with the radiographic form of the condition [3]. The prevalence of axSpA is estimated at 0.2-1.9% and depends greatly on the HLA-B27 in the specific country. Specific details of the percentage share of nr-axSpA among the total axSpA patient population are unavailable, but calculations suggest it is approximately 50% in the first 10 years of the condition [4]. Current observations suggest that about 12% of patients with nr-axSpA will go on to develop radiographic lesions within the first two years after diagnosis.

This study is being done to investigate the efficacy of active supervised training (AST) versus standard-of-care physiotherapy (SOC) in patients with axSpA who are receiving treatment with Humira® (adalimumab).

The primary goal of treatment in axSpA patients in the first instance is to control symptoms and inflammation, prevent structural damage, and maintain or normalize major functional abilities and participation in social life and in that way achieve sustained improvement in health-related quality of life [5].

NSAIDs and biologics such as TNF blockers and anti-IL-17 antibodies are currently the only effective and approved therapeutic options for axSpA. The latter drugs are the treatment of choice for axSpA patients who have not responded to NSAIDs. TNF blockers neutralize a key mediator of inflammatory response, normalize acute-phase reactants and thus reduce acute inflammation of the sacroiliac joint and spine, as has been demonstrated in magnetic resonance imaging (MRI) [6].

In addition to joint problems people with inflammatory musculoskeletal conditions may also develop weak muscles and loss of muscle tissue. In combination with fatigue and anemia, other comorbidities and the actual disease symptoms, this can have negative effects on cardiovascular function, muscle function and mobility, resulting in a further reduction in physical activity [7]. As a consequence, many patients increasingly develop major disabilities, progressively limited spinal mobility and reduced quality of life despite effective treatment with a powerful drug [8, 9]. The 2013 basic dataset indicates that about 40% of axSpA patients have significantly reduced physical performance (70% or less of full performance measured using the Hanover Health Assessment Questionnaire Disability Index [FFbH]) [10]. In fact, around half had poor physical performance scores corresponding to less than 50% of full functional ability. Reduced physical functioning impairs work ability and may lead to permanent work disability [11]. An analysis of the socioeconomic implications by Huscher et al. [12] using data from the national database of regional cooperative rheumatology centers shows that poor functional ability is a significant health economics factor and cost driver. The percentage of patients drawing disability benefit differed by a factor of 5-10 between good and poor functional status [12]. Indirect costs attributable to workplace absenteeism and permanent work disability differed by a factor of 5 between good and poor functional status. This is evidently due to the fact that a very small percentage of patients scoring below 50% of normal on functional index scales are fit to work, while those still in the workplace have high rates of absenteeism and prolonged absenteeism [12]. Alongside the reduction in work ability, limited physical functioning also has detrimental effects on participation in social life and on quality of life [11, 13].

The guidelines explicitly recommend regular physical training as a mainstay of axSpA therapy in combination with anti-inflammatory drugs such as NSAIDs and biologics such as TNF blockers as a way to improve and maintain spinal ability and preserve physical functioning and muscle strength in general 5,14. Other objectives associated with regular exercise include relieving pain, improving posture and preventing falls. Supervised exercises – in an individual or group setting – are more effective than and therefore preferable to exercising at home [5, 14].

The best physical activity program for axSpA patients has not been pinpointed yet, however, and is not yet being administered to most patients [8, 9]. There are no specific recommendations to date concerning exercise type and intensity, and a standardized procedure for exercising has not been established in Germany [9].

Recently published recommendations by the American College of Rheumatology on the treatment of axSpA and nr-axSpA are more precise as regards the best type of physical activity to engage in during therapy. Patients with active axSpA are advised to engage in active physical therapy (supervised training) rather than passive physical therapy (massage, ultrasound, heat) [15]. The level of evidence is still limited, however, and further studies are required to investigate the effects of active supervised training in axSpA patients.

Extensive and robust evidence is now available on the treatment of patients with unspecific back pain, according to which intense active and – importantly – supervised training under the guidance of an instructor is extremely effective in the treatment of back pain and to improve physical impairment. Recent literature on the topic describing various treatment regimens for axSpA patients notes a measurable improvement in BASMI after structured training in addition to stable response to TNF blockers. Liang et al. (2015) assessed five studies to compare the efficacy of physical activity on disease outcomes in axSpA patients. The cited literature search included a study by Masiero et al. (2014) investigating various patient groups with an average BASMI of 4.6 to 5.2 prior to therapy with a TNF blocker. An average 0.97 point improvement in BASMI scores was observed after 9-month TNF blocker therapy. Following subsequent randomization to three treatment arms ("rehabilitation group" with intense training; "education group" with education about the disease; "control group" without intervention), an additional 1.3 point improvement in the BASMI score was established in the rehabilitation group. No difference was observed in the education group and BASMI scores worsened in the control group. These results indicate that structured training in individuals with a stable response to TNF blockers produces BASMI scores superior to those achieved with TNF blocker therapy alone.

In Germany, the Research and Prevention Center (FPZ) developed a concept for active supervised training for back pain patients that is administered in this study and compared as regards effectiveness with SOC physiotherapy. Intense active supervised training comprises 24 exercise units over a period of 20 weeks and focuses on strengthening the spine-stabilizing muscles of the back and general improvement of core muscle strength. Another objective is to reduce back pain and improve physical impairment, as these are often attributable to muscular insufficiencies and imbalances. Thus, the FPZ offers a standardized yet customized training concept administered at certified training / physiotherapy centers.

The axSpA patients receive Humira® (adalimumab) in accordance with the national Humira® label and the appropriate standard of care, including as regards medical consultation schedules, requisite lab tests, and all the other procedures required for proper therapy. Patients use a commercially available Humira® product prescribed in accordance with national prescription regulations and on-label. Humira® is prescribed as the doctor sees fit, regardless of the patient's inclusion in this study. Humira® treatment has a well-researched and extensively documented safety profile that is based on large non-interventional studies and a continuous program of clinical trials conducted since the drug was first approved and indicated for use in rheumatoid arthritis in the EU in 2003.

Study participants are instructed to contact their doctor in emergencies and if they have questions of any kind.

4.2 Research question and objectives of the project

The study is being conducted to investigate whether active supervised training is more effective in improving health-related outcomes than routine SOC physiotherapy for axSpA patients receiving Humira®.

To answer that question, a two-arm study is being done in axSpA patients who are responding to Humira® in their physician's judgment and are eligible for active physiotherapy. Patients were randomized to receive either active supervised training (AST group) or SOC physiotherapy (SOC group).

Active supervised training comprises 24 exercise units over a period of 20 weeks and takes place at certified FZP training centers. After the 20-week training program, AST group patients who still have stage II muscular deconditioning or worse will be offered the option to join an advanced training program consisting of 10 units over a period of 8 to 10 weeks.

The SOC physiotherapy administered in this instance includes both active and passive exercises and massages at the physiotherapist's discretion. The type of physiotherapy is documented in the eCRF. As the treatment recommendations do not provide structured specifications, the quality and scope of physiotherapy in the SOC group is not precisely defined. Instead, the SOC group reflects the status quo of physiotherapy as practiced in Germany, thus enabling comparison with the actual situation in order to generate real-world evidence.

The health-related results are assessed at the enrollment visit (initiation of Humira® treatment), baseline visit (after randomization) and during follow-up 3, 6, 9 and 12 months after baseline. A time window of ± 4 weeks is allowed for each follow-up visit.

This primary endpoint of this study is comparison of active supervised training against SOC physiotherapy in terms of improving spinal mobility 6 months after the baseline visit in axSpA patients who are receiving treatment with Humira®.

Secondary endpoints are improvements in physical ability and health-related quality of life, disease activity, pain, psychosocial risk factors and work ability.

Since there is no intervention in this study as regards the treatment administered to patients, all measures are based on medical estimation on the basis of analysis of axSpA patient data, which corresponds to real-world practice. No additional diagnostic or monitoring procedures are used.

4.3 Study design

The axSpA patients receive Humira® in accordance with the national Humira® label and the appropriate SOC, including as regards medical consultation schedules, requisite lab tests, and all the other procedures required for proper therapy. Patients receiving Humira® therapy have been given the German package leaflet, informed by their doctor about the benefits and risks of Humira®, and trained in the injection technique. Humira® is sourced as a commercially available medicine. AbbVie provides no medication for this study.

This SAP describes the methods of analysis used for exploratory investigation of the effects of active supervised training versus SOC physiotherapy during Humira® treatment.

Adult axSpA patients starting Humira® therapy based on the criteria employed in routine clinical practice are informed about the study. Subjects are enrolled into the study at the enrollment visit after providing their written consent. Patients who respond adequately to Humira® within 12 ± 4 weeks (based on their rheumatologist's individual assessment) and are eligible for active physiotherapy (in the estimation of their rheumatologist and physiotherapist) are randomized at a ratio of 1:1. Patients are randomized to receive either active supervised training (AST group) or SOC physiotherapy (SOC group) (see Figure 1). Patients are randomized in equal proportions following stratification by age (<=40 years / >40 years), disease duration (<3 years / >= 3 years) and disease activity (BASMI <=3 / >3).

Patients who are not eligible for FPZ training will be excluded from the study. Eligibility for participation in the study depends on whether the patient is capable in principle of performing physical activities (ascertainment of basic trainability). The rheumatologist treating the patient and the physiotherapist make this decision.

The observational part of the study comprises a follow-up period of 12 months after the baseline visit. The baseline visit is preceded by a 3- to 5-month enrollment period during which treatment is initiated and response is assessed (see Figure 1).

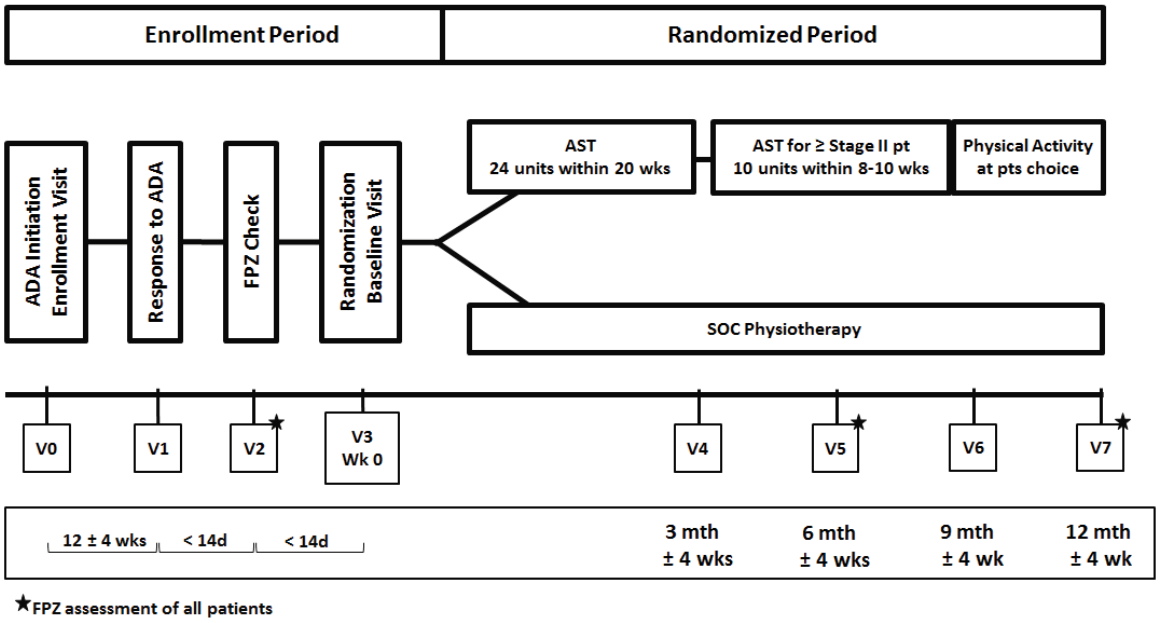

Figure 1 Study design diagram

4.4 Study endpoints

4.4.1 Primary study endpoint

(1) Spinal mobility measured using the Bath Ankylosing Spondylitis Metrology Index (BASMI), 6 months after the baseline visit (a time window of ± 4 weeks is allowed)

4.4.2 Secondary study endpoints

The following secondary study endpoints, which concern changes from baseline, are assessed at all visits (after 3, 6, 8 and 12 months).

(2) Improvement in spinal mobility – BASMI

(3) Improvement in physical functioning – BASFI NRS score (0 to 10)

(4) Improvement in quality of life – general functioning assessed by ASAS-HI

(5) Reduction in disease activity

a. Disease activity assessed by BASDAI

b. Percentage of study participants achieving a 50% improvement in BASDAI score (BASDAI50 response)

c. Change in disease activity from baseline assessed by ASDAS (Ankylosing Spondylitis Disease Activity Score)

d. Percentage of study participants achieving ASAS major improvement

e. Percentage of study participants achieving ASDAS clinically important improvement

f. Percentage of study participants in ASDAS inactive disease (ASDAS < 1.3)
g. Percentage of study participants with low disease activity (ASDAS < 2.1)
h. Percentage of study participants with moderate disease activity (ASDAS ≥ 1.3 to < 2.1)
i. Percentage of study participants with high disease activity (ASDAS ≥ 2.1 to < 3.5)
j. Percentage of study participants with very high disease activity (ASDAS ≥ 3.5)
k. Percentage of study participants achieving ASAS20
l. Percentage of study participants achieving ASAS40
m. Percentage of study participants achieving partial ASAS remission
n. Change from baseline in physician's global assessment of disease activity
o. Change from baseline in patient's global assessment of disease activity

(6) Reduction in pain
   a. Change from baseline in patient's global assessment of pain
   b. Change from baseline in patient's assessment of total back pain
   c. Change from baseline in patient's assessment of nocturnal back pain

(7) Improvement in other PROs
   a. Fatigue (BASDAI Question 1)
   b. Duration and severity of morning stiffness (mean of BASDAI Questions 5 and 6)

(8) Psychosocial risk factors – FABQ

(9) Other variables proposed for assessment:
   a. Comorbidities (screening only)
   b. Comedication:
      i. previous and concomitant non-biologic DMARDs
      ii. concomitant systemic glucocorticoids
      iii. concomitant pain medication: analgesics, NSAIDs, cyclooxygenase-2 (COX-2) inhibitors

4.5 Inclusion and exclusion criteria

Patients agreeing to take part in the study are observed for a period of 12 months from baseline. Physicians are instructed to treat enrolled axSpA patients like their other axSpA patients in accordance with normal clinical practice. Patients can stop their Humira® treatment or stop participating in the study at any time without giving a reason. Subjects who stop Humira® will receive treatment based on the rheumatologist's best judgment.

If an adverse event is the reason for stopping treatment, the event must be reported as follows:

- SAE: To be reported to AbbVie within 24 hours after the physician becomes aware of the event
- Non-SAE: To be reported to AbbVie within 24 hours after the physician becomes aware of the event

Patients who stop Humira® treatment or start treatment with another biologic sold in the EU are dropped from the study and not included in the primary assessment population.

If a patient drops out of the study or is lost to follow-up, every effort must be made to document this along with the reason for the dropout in the electronic case report form (eCRF).

4.5.1 Inclusion criteria

Patients meeting the following criteria are eligible for participation in the study:

- axSpA diagnosis (radiographic or non-radiographic) meeting the ASAS classification
- Age at least 18 years
- Prescribed Humira® (adalimumab) for the treatment of axSpA according to the local product label
- Eligible for active physiotherapy according to the rheumatologist and physiotherapist
- Participants must have signed written informed consent before starting any study-related assessments or procedures.

4.5.2 Exclusion criteria

Patients meeting any of the following criteria are not eligible for participation in the study:

- total spinal ankylosis based on the physician's assessment of available radiographs
- not eligible for active supervised training or active physiotherapy at the discretion of the rheumatologist and/or the physiotherapist
- poorly controlled medical condition(s), which in the physician's opinion would put the participant at risk by participation in the protocol
- prior treatment with a biologic DMARD

4.6 Patient Population

Approximately 510 axSpA patients (ASAS criteria 2009 [16]), treated with Humira® according to the local product label and who meet the inclusion criteria for the study will be enrolled. A population of 510 patients treated with Humira® is estimated to be sufficient to achieve the endpoints of this study. Approximately 50 rheumatologists will be involved in enrolling eligible patients into the study.

4.7 Randomization

Subjects were randomized after stratification by the categories age (<=40 years / >40 years), disease duration (<3 years / >= 3 ears) and disease activity (BASMI <=3 / >3) using SAS 9.4 statistical software (SAS Institute Inc., Cary, NY, USA). Patients are assigned to receive either active supervised training (AST group) or SOC physiotherapy (SOC group) at a ratio of 1:1 via block randomization with varying block length.
A sufficiently comprehensive randomization list was prepared and implemented in the database. Once a new patient has responded to Humira at V1, the correct stratum is selected based on the categories, and assignment is made known at V3. The use of block randomization achieves balance in the allocation of treatment within the strata regardless of occupancy.

4.8 Safety

Safety data are described on the basis of the safety population. The data are broken down by severity, intensity, required treatment, system organ class, causal relationship, treatment outcome, and action taken.

4.9 Data management

The database is run by e.factum GmbH. Database hardlock will be followed by exportation of all the data to StatConsult GmbH for analysis using SAS 9.4 (SAS Institute Inc., Cary, NY, USA).

4.10 Changes from planned analyses

Not applicable.

5 Study evaluation

5.1 Schedule

Part 1: Study measures	**Initiation of ADA treatment (Enrollment visit) V0**	**Assessment of response V1**	**FPZ assessment V2**	**Randomization (baseline visit) V3**	**Follow-up 3 months after baseline V4**
Subject's informed consent obtained	X				
Inclusion/exclusion criteria	X[1]	X[2]	X[3]		
Age, sex, weight, height, smoking status	X				
Social background, education	X				
Non-axSpA-related medical/surgical history	X				
AxSpA-related medical/surgical history	X				
Disease duration	X				
Family history	X				
HLA-B27	X				
Comorbidities	X				
Former axSpA medication	X				
Current axSpA medication	X	X		X	X
Comedication	X	X		X	X
Type of regular exercise	X				
Type of physical activity	X	X		X	X
SAE/AE	X	X	X	X	X
CRP or ESR/routine blood draw	X	X		X	X
BASMIlin	X	X		X	X
BASFI	X	X		X	X
ASAS-HI	X	X		X	X
ASDAS	X	X		X	X
BASDAI	X	X		X	X
Physician's global assessment of disease activity	X	X		X	X
Patient's global assessment of disease activity	X	X		X	X
Modified WAI	X	X		X	X
Patient's global assessment of pain	X	X		X	X
Patient's assessment of total back pain	X	X		X	X
Patient's assessment of nocturnal back pain	X	X		X	X
FABq	X	X		X	X

Table 1 Part 1: Study measures

[1] Inclusion criteria: diagnosed with axSpA, at least 18 years of age; prescribed Humira® (adalimumab) for the treatment of axSpA according to the local product label; participants must have signed written informed consent before starting any study-related assessments or procedures; poorly controlled medical condition(s), which in the physician's opinion would put the participant at risk by participation in the protocol; total spinal ankylosis based on the physician's assessment of available radiographs; prior treatment with a biologic DMARD

[2] Inclusion criteria: adequate response to Humira® within 12 ± 4 weeks (no increase or change of treatment regimen required according to the rheumatologist); eligible for active physiotherapy according to the rheumatologist

[3] Inclusion criteria: eligible for active physiotherapy in the physiotherapist's estimation (as per FPZ requirements)

Part 2: Study measures Follow-ups	**Follow-up 6 months after baseline V5**	**Follow-up 9 months after baseline V6**	**Follow-up 12 months after baseline V7**
Comorbidities	X	X	X
Current axSpA medication	X	X	X
Comedication	X	X	X
Type of regular exercise	X	X	X
Type of physiotherapy	X	X	X
SAE/AE	X	X	X
CRP or ESR/routine blood draw	X	X	X
$BASMI_{lin}$	X	X	X
BASFI	X	X	X
ASAS-HI	X	X	X
ASDAS calculation	X	X	X
BASDAI	X	X	X
Physician's global assessment of disease activity	X	X	X
Patient's global assessment of disease activity	X	X	X
Modified WAI	X	X	X
Patient's global assessment of pain (NRS)	X	X	X
Patient’s assessment of total back pain (NRS)	X	X	X
Patient's assessment of nocturnal back pain (NRS)	X	X	X
FABq	X	X	X

Table 2 Part 2: Study measures

5.2 Specific measuring instruments

The health-related results are assessed at the enrollment visit (initiation of Humira® treatment), baseline visit (after randomization) and during follow-up 3, 6, 9 and 12 months after baseline. A time window of ± 4 weeks is allowed for each follow-up visit.

The primary outcome measure is improvement in spinal mobility 6 months after the baseline visit as measured by BASMI score in the AST group versus SOC group.

The BASMI is an objective scale for comprehensive investigation of range of motion (RoM) and spinal mobility. Its sensitivity has been demonstrated as a measure of limitation of spinal mobility in the various

stages of axSpA. In addition, the BASMI delivers objective scores as it is not based on PRO parameters and therefore not influenced by psychosocial factors.

The main criterion for selecting the BASMI score as a relevant metric to assess the outcome measure is that the relevant exercises of the FPZ physiotherapy training concept developed by the AST provider correlate directly with four of the five BASMI parameters. On those grounds, BASMI is considered the most appropriate, objective and validated metric of choice to observe spinal mobility in the AST group and compare it with that of the SOC group.

PROs have not been chosen as primary outcome measure because they are less objective because of possibly already developed psychosocial factors. Research work has shown that patients with a high risk of depression and anxiety score higher on BASDAI, BASFI, EQ-5D and ASDAS-CRP, overall pain (VAS) and ASQoL. Nonetheless, precise assessment of psychosocial risk factors using the relevant questionnaires mentioned above is hugely important in addition to considering the somatic parameters. The selected metrics are being used for that reason.

The secondary health-related outcome measures are:

- Spinal mobility assessed by BASDAI
- Physical function assessed on the basis of BASFI-NRS score (0-10)
- General functioning assessed by ASAS-HI
- Disease activity assessed by BASDAI
- Percentage of study participants achieving a 50% improvement in BASDAI score (BASDAI50 response)
- Disease activity assessed by ASDAS
- Percentage of study participants in ASDAS inactive disease (ASDAS < 1.3)
- Percentage of study participants with low disease activity (ASDAS < 2.1)
- Percentage of study participants with moderate disease activity (ASDAS ≥ 1.3 to < 2.1)
- Percentage of study participants with high disease activity (ASDAS ≥ 2.1 to < 3.5)
- Percentage of study participants with very high disease activity (ASDAS ≥ 3.5)
- Major ASDAS improvement (Δ ≥ 2.0)
- ASDAS clinically important improvement (Δ ≥ 1.0)
- ASAS20, ASAS40 and partial ASAS remission
    - ASAS20 response: ≥ 20% improvement and an absolute improvement by ≥ 1 unit (scale from 0-10) from baseline in ≥ 3 of the following 4 domains, with no worsening of the remaining domain (defined as a worsening of ≥ 20% and average worsening of ≥ 1 unit)
    - Patient's global assessment of disease activity (NRS) based on PTGA-NRS score (0-10)
    - Pain based on patient’s assessment of total back pain, NRS score (0-10)
    - Functioning based on BASFI-NRS score (0-10)
    - Inflammation based on mean of two BASDAI-NRS morning stiffness scores (mean of BASDAI Questions 5 and 6 [0-10])
    - ASAS40 response: ≥ 40% improvement and an absolute improvement by ≥ 2 units (scale from 0-10) from baseline in ≥ 3 of the 4 domains described above for ASAS20, with no worsening of the potential 5th domain of functioning assessed by BASFI-NRS
    - Partial ASAS remission: absolute score of < 2 units in each of the 4 domains described under ASAS20 above
- Patient's global assessment of pain

- Patient's assessment of total back pain
- Patient's assessment of nocturnal back pain
- Work ability (modified WAI, Work Ability Index)
- Fatigue (BASDAI Question 1)
- Duration and severity of morning stiffness (mean of BASDAI Questions 5 and 6)

Psychosocial risk factors

- FABQ

Other variables proposed for assessment:

- Comorbidities
- Comedication:
    - previous and concomitant non-biologic DMARDs
    - concomitant systemic glucocorticoids
    - concomitant pain medication: analgesics, NSAIDs, cyclooxygenase-2 (COX-2) inhibitors

6 Statistical methods

6.1 Analysis populations

Safety population: all patients enrolled into the study who received at least one dose of Humira® (adalimumab)

ITT population: all randomized patients

Per-protocol (PP) population: all randomized patients who underwent AST or SOC physiotherapy for 6 months with no major protocol deviations.

6.2 Descriptive statistics

The number of valid and missing values, means, standard deviations, minimum, lower quartile (Q1), median, upper quartile (Q3) and maximum are reported for distributions of (quasi) continuous variables.

Absolute and relative frequencies are given for categorical variables.

6.3 General principles and test methods

All analyses are deliberately performed at the full level of significance of $\alpha = 0.05$, i.e. with no correction for multiple testing.

All treatment effects are indicated with their 95% confidence interval.

Sensitivity analyses (see section 6.4) are run with inclusion of covariates (see section 6.5) for verification of initially univariate investigated effects, in particular for the primary outcome measure.

(1) Primary outcome measure/endpoint

Primary assessment is based on the ITT population.

BASMI at 6 months (V5) is determined by analysis of covariance with treatment as fixed coefficient and baseline BASMI (V3) as covariate. The treatment effect is indicated with its 95% confidence interval. If the criteria for analysis of covariance are not met, suitable methods may be used (transformation of the data).

Note: BASMI (BASMIlin) is a continuous variable because it is the mean of 5 analogous assessments on a scale of 0-10.

(2) Secondary outcome measures/endpoints

Continuous variables for which baseline data are available will be assessed in the same way as the primary outcome variable. Assessments take place at all follow-up visits (after 3, 6, 9 and 12 months).

In the absence of baseline data, the robust t-test for independent samples will be used.

Discrete outcome variables depending on treatment are assessed using contingency tables. Simple analyses for the presence of an association will be performed using a chi square test (possible Fisher's exact test in the presence of small sample sizes), and studies for associations with ordinal variables will be done using the Cochrane-Armitage test for trend.

6.4 Missing values and sensitivity analyses

(1)

Missing values in questionnaires (single items are missing) will be completed by applying questionnaire-specific rules. If no such rules exist, missing individual values will be replaced by the median of the other items for the respective patient from the visit concerned, unless more than 25% of items are missing. If more than 25% of the items are missing, the entire score qualifies as missing.

(2)

There are various reasons for assuming why patients complete the AST or SOC physiotherapy.

If less than 10% of values are missing for the primary outcome variable, complete case analysis is effective. If more values are missing, various approaches meeting the criteria of sensitivity analyses are employed that cover a worst-case and a best-case scenario.

6.5 Investigation of covariates

Additional potential variables are included in the primary covariance model as fixed factors. This applies to baseline data describing the response to treatment between enrollment and baseline visit.

A mixed model is also implemented for the primary outcome measure in which the sites are included as random effects in order to address any patient-site dependencies.

6.6 Safety data

Safety data are described on the basis of the safety population. The data are broken down by severity, intensity, required treatment, system organ class, causal relationship, treatment outcome, and action taken.

6.7 Sample size planning

Ciprian et al. (2013), Masiero et al. (2014) and Ygrit et al. (2013) have shown that populations receiving structured physiotherapy improve their BASMI score by one point versus control groups (Liang et al. 2015). A detectable difference of one BASMI point, a power of 80% and a standard deviation of 3.7 gives a calculated population size of 216 patients in the active arm (432 patients in total).

In view of the complex enrollment process, relatively long study duration, and physical activity/participation on the part of patients, we expect a dropout rate of 15%. All this gives a final sample size of 510 patients (216 * 2 * 1/0.85) for the study.

6.8 Interim analysis

An interim analysis is not planned.

6.9 Statistical software

All analyses will be run using SAS 9.4® software (SAS Institute Inc. Cary, NY, USA) on Windows 10.

7 List of Tables and Lists